Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and Safety of Amphotericin B Colloidal Dispersion via Nebulized Inhalation Combined with Intravenous Therapy for Invasive Pulmonary Fungal Disease: A Single-Center, Retrospective Cohort Study

Zhanjiang Li[1], Feng Li[2], Tengfei Chen[1], Rui Yang[1]

[1]Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, People's Republic of China; [2]Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, People's Republic of China

Correspondence: Rui Yang, Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Erqi District, Zhengzhou, 450052, People's Republic of China, Tel +86-18203693330, Email yrain2012@126.com

Purpose: To investigate the efficacy and safety of amphotericin B colloidal dispersion (ABCD) in treating invasive pulmonary fungal disease (IPFD) through nebulized inhalation combined with intravenous therapy.

Methods: Patients diagnosed with IPFD who received ABCD from October 2023 to March 2024 were retrospectively enrolled. The treatment protocol for patient was determined by clinicians according to the patient's condition and clinical practice. According to the treatment protocol, patients were divided into two groups: the ABCD nebulized inhalation combined with intravenous injection (combined therapy group) and the ABCD intravenous injection (intravenous therapy group). Clinical characteristics, ABCD administration (dose and duration), treatment outcomes (favorable response rate), and adverse events (AEs) were compared between the two groups.

Results: Thirty-two patients were included, with 16 in each group. No significant differences were observed in the clinical characteristics between the two groups. In the combined therapy group, the numbers of proven, probable, and possible cases were 4 (25.00%), 7 (43.75%), and 5 (31.25%), respectively. In the intravenous injection treatment group, 1 (6.25%), 11 (68.75%), and 4 (25.00%) patients were proven, probable, and possible, respectively. The total dose of ABCD was slightly lower in the combined therapy group than in the intravenous therapy group (1675 vs 1800, P=0.611), although the difference was not statistically significant. The duration of combined therapy group was significantly shorter than that of the intravenous therapy group (8 vs 12, P=0.032), indicating that combination therapy can decrease the risk of hospital-acquired infections. The favorable response rate of the combined therapy group was significantly higher than that of the intravenous therapy group (93.75% vs 62.50%, P=0.033). Elevated urea levels emerged as the most common AE in the combined therapy group (68.75%) and intravenous therapy group (50.00%), no statistically significant difference was observed in the incidence of AEs between the two groups. All 32 patients (100%) completed the prescribed treatment regimen, and no patients withdrew from the study due to AEs.

Conclusion: The efficacy of ABCD nebulized inhalation combined with intravenous injection was superior to intravenous injection of ABCD alone in the treatment of IPFD, with comparable safety and shortened medication time.

Keywords: amphotericin B colloidal dispersion, invasive pulmonary fungal disease, nebulized inhalation, intravenous therapy

Introduction

Invasive fungal diseases (IFD) are infectious diseases caused by the invasion of fungi into deep organs or blood. The clinical manifestations of IFD are diverse and predominantly occur in immunocompromised patients.[1] *Aspergillus* is the most common pathogen associated with IFD, and the lungs are the most frequently affected organs.[2] In recent years, the incidence of invasive pulmonary fungal diseases (IPFD) has increased, resulting in approximately 3 million cases of

Received: 8 February 2025
Accepted: 20 June 2025
Published: 10 July 2025

pulmonary aspergillosis annually.[1,3] As the most prevalent fungal infection among lung transplant recipients, invasive aspergillosis has a mortality rate exceeding 80% in the intensive care unit (ICU).[4] Furthermore, the management of invasive pulmonary aspergillosis frequently necessitates extended treatment duration. The adverse events (AEs) associated with antifungal therapy and the emergence of drug resistance further compromise the prognosis.[5] Therefore, selecting an effective and safe antifungal treatment regimen is crucial for controlling fungal infections.[6]

Currently available systemic antifungal agents include triazoles, polyenes, pyrimidine analogues, and echinocandins. The cardiotoxicity of itraconazole and voriconazole necessitates limitations to their utilization, with up to 30% of cases necessitating discontinuation.[7] Furthermore, the emergence of azole-resistant aspergillosis precludes the long-term utilization of azole medications.[8,9] Moreover, due to the relatively narrow spectrum of action and limited clinical efficacy, echinocandins (anidulafungin and caspofungin) are rarely used as monotherapy for IFD.[10] Conversely, amphotericin B and its lipid formulations continue to demonstrate a broad spectrum of antibacterial properties, and are also recommended by both international and domestic guidelines as the preferred or alternative treatment for IFD.[11] The main formulations of amphotericin B include amphotericin B deoxycholate (AmB-D) and Amphotericin B lipid formulations, including amphotericin B colloidal dispersion (ABCD), liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC). The adverse reaction associated with AmB-D, particularly nephrotoxicity, limit its clinical application.[12] In a real-world study, nephrotoxicity was reported in 28% of patients during AmB-D treatment, of which 12% were moderate to severe.[13] In contrast, amphotericin B lipid formulations serve as drug delivery systems by penetrating the target fungal cell wall while remaining closely associated with circulating liposomes, thereby greatly reducing the incidence of nephrotoxicity.[14]

Furthermore, considering the serious adverse reactions such as hypokalemia and infusion reactions caused by systemic application of antifungal drugs, as well as the low blood drug concentrations in lung lesions, many scholars have begun to investigate the potential for topical application of antifungal agents. Several case reports have documented successful treatments of invasive pulmonary aspergillosis and penicilliosis marneffei through bronchoscopic local perfusion and nebulized inhalation of AmB-D.[15,16] Notably, an increasing number of studies have confirmed that prophylactic nebulized inhalation of AmB-D, L-AmB or ABLC is associated with a lower incidence of invasive pulmonary fungal infections.[17,18] Previous study has demonstrated that the nebulized inhalation of amphotericin B not only exerts a local antifungal effect but also reduces the adverse effects caused by the interactions between systemically administered drugs.[19] The intravenous injection of ABCD has been demonstrated to be both efficacious and safe for patients suffering from *mucormycosis* and *talaromycosis*.[20,21] The primary lesion site of IPFD is in the lungs, thus emphasizing the necessity to augment the local drug concentration in lung tissue for treatment purposes. However, there are limited reports regarding the treatment of IPFD using nebulized ABCD in combination with intravenous injection.

This study is the first to retrospectively analyze the clinical data of patients with IPFD who were treated with ABCD nebulized inhalation combined with intravenous injection, as well as those receiving ABCD intravenous injection alone. The aim was to evaluate the efficacy and safety of ABCD nebulized inhalation in combination with intravenous injection for the treatment of IPFD, and to provide evidence for the clinical application of ABCD.

Materials and Methods

Study Design

This retrospective exploratory study analyzed the clinical data of patients with proven, probable and possible IPFD at the First Affiliated Hospital of Zhengzhou University from October 2023 to March 2024. The analysis included demographic characteristics, clinical symptoms, laboratory and imaging examinations, treatment, and AEs. Based on the treatment regimen, the enrolled patients were divided into ABCD nebulized inhalation combined with intravenous injection group (combined therapy group) and ABCD intravenous injection group (intravenous therapy group). This study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics committee of the First Affiliated Hospital of Zhengzhou University (2024-KY-0493-001). Due to the retrospective nature of this investigation, written informed consent was waived and approved by our ethics committee.

Eligibility for Patients

The inclusion criteria for this study were as follows: (1) ≥ 18 years old; (2) Proven, probable and possible diagnosis of invasive pulmonary mycoses following the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) diagnostic criteria;[22] (3) Patients received ABCD nebulized inhalation combined with intravenous injection or ABCD intravenous injection. The exclusion criteria included: (1) Pregnant or lactating individuals; (2) Patients diagnosed with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus); (3) Patients with refractory bacterial infections (including multidrug-resistant bacteria) or confirmed infections with Epstein-Barr virus or parasites; (4) Patients experiencing severe cardiac insufficiency (New York Heart Association Class III/IV), liver dysfunction (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ 5 times the upper limit of normal (ULN)), or renal impairment requiring or currently undergoing hemodialysis or peritoneal dialysis; (5) Patients with incomplete data or other variables that could influence the assessment of efficacy and safety; (6) Patients deemed unsuitable for enrollment by the investigators based on their clinical conditions.

Drug Administration

All eligible patients were treated with ABCD (50 mg/bottle, CSPC Ouyi Pharmaceutical Group Co., Ltd.) upon admission and completed the treatment according to the treatment regimen. Dexamethasone (with or without promethazine) was used to prevent infusion reactions. The initial dose of ABCD in the intravenous therapy group was 0.5–1.0 mg/k/d, which was increased to a therapeutic dose of 3.0–4.0 mg/k/d according to the situation on the third day.[23] In the combined therapy group, on the basis of intravenous injection, 50 mg ABCD was dissolved in 10 mL sterile water for injection and nebulized for inhalation using a compressed atomization pump.[24] Nebulization was performed 1–2 times a day, and each nebulization was completed within 10–15 min. The treatment protocol and dose for patient was determined by clinicians according to the patient's condition and clinical practice.

Efficacy and Safety Analysis

An efficacy evaluation was conducted on all patients prior to their discharge from hospital. Treatment response was comprehensively evaluated by clinical symptoms, signs, imaging and microbiology.[25,26] Complete response (CR) and partial response (PR) were classified as favorable response, whereas stable disease (SD) and treatment failure were classified as unfavorable response. CR was defined as the complete resolution of IPFD-related symptoms and signs, normalization of imaging abnormalities, and confirmed fungal clearance through microbiological examination. The imaging response in CR was defined as complete or very near complete disappearance of the lesion or abnormality. PR was defined as a significant improvement in IPFD-related symptoms, signs, and imaging abnormalities. The significant improvement in imaging abnormalities in PR was defined as a reduction in lesion size percentage of ≥ 50%. SD was characterized by the absence of improvement in IPFD-related symptoms and signs, along with no evidence of disease progression based on comprehensive clinical, imaging, and microbiological evaluations. The imaging response in SD was defined as a percentage reduction in lesion size of < 50% or no improvement but no deterioration. Treatment failure was defined as disease progression or death from various causes directly or indirectly related to IPFD. The safety was evaluated by AEs and laboratory abnormalities that occurred during the administration. AEs were recorded according to the National Cancer Institute's Common Adverse Reaction Evaluation Criteria version 5.0. Laboratory abnormalities were defined as laboratory test results that transition from normal to abnormal during antifungal treatment or values that deviate from baseline values.

Statistical Analysis

This exploratory study employed a simple random sampling method for patient selection. Statistical analyses of data were performed using SPSS 25. Categorical variables were presented as frequencies (%), and χ^2 test was used for comparison between groups. Quantitative variables that followed a normal distribution were represented by mean ± standard deviation (SD), and the independent samples *t*-test was utilized for group comparisons. Quantitative variables without normal distribution were expressed as median (interquartile range P25, P75), and non-parametric Mann Whitney *U*-test was employed for group comparisons. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 32 patients with IPFD were enrolled in this study, including 16 patients in the combined therapy group and 16 patients in the intravenous therapy group. No statistically significant differences was observed between the two groups in terms of age, respiratory rate, pulse rate, platelet count, neutrophil count, liver function, renal function, serum potassium levels, and CT thorax findings (P>0.05, Table 1). Both groups had 11 patients (68.75%) with various underlying lung disease. The three most prevalent lung diseases in the combination therapy group were chronic obstructive pulmonary disease (25.00%), pulmonary nodules (18.75%), and bronchiectasis (12.50%), whereas the three most prevalent diseases in the intravenous therapy group were bronchiectasis (18.75%), pulmonary fibrosis (12.50%), and old pulmonary tuberculosis (12.50%). No significant difference was observed in the incidence of underlying lung diseases between the two groups of patients (P=0.999). Aspergillus was identified as the predominant bacterial species in both cohorts, with 14 patients (87.50%) in the combined therapy group and 15 patients (93.75%) in the intravenous therapy group diagnosed with aspergillus infection. Additionally, mixed infections involving different genera were observed in 6 cases

Table 1 The Demographic and Clinical Characteristics of Patients

Characteristics	Combined Therapy Group (n=16)	Intravenous Therapy Group (n=16)	*P* value
Age (years), Median (IQR)	59.50 (45.50, 73.25)	56.50 (50.25, 75.25)	0.850
Gender, n (%)			0.127
Male	13 (81.25)	9 (56.25)	
Female	3 (18.75)	7 (43.75)	
Respiratory rate (time/ min), Median (IQR)	20.00 (20.00, 21.75)	21.00 (19.25, 22.00)	0.546
Pulse rate (time/ min), Median (IQR)	86.50 (79.00, 93.75)	88.00 (83.25, 93.50)	0.657
Underlying lung disease, n (%)			
No	5 (31.25)	5 (31.25)	
Yes	11 (68.75)	11 (68.75)	0.999
Chronic obstructive pulmonary disease	4 (25.00)	1 (6.25)	
Pulmonary nodule	3 (18.75)	0 (0)	
Bronchiectasis	2 (12.50)	3 (18.75)	
Lung tumor	3 (18.75)	1 (6.25)	
Pulmonary emphysema	1 (6.25)	1 (6.25)	
Pulmonary fibrosis	0 (0)	2 (12.50)	
Pulmonary embolism	0 (0)	1 (6.25)	
Old tuberculosis	0 (0)	2 (12.50)	
Other underlying disease, n (%)			
Hypertension	5 (31.25)	2 (12.50)	0.200
Diabetes	2 (12.50)	3 (18.75)	0.626
Coronary heart disease	1 (6.25)	3 (18.75)	0.285
B cell lymphoma	0 (0.00)	1 (6.25)	0.310
Chronic kidney disease	1 (6.25)	0 (0.00)	0.310
Infectious organism*, n (%)			0.671
Aspergillus	14 (87.50)	15 (93.75)	
Candida	4 (25.00)	3 (18.75)	
Mucor	3 (18.75)	2 (12.50)	
Cryptococcus	0 (0)	1 (6.25)	
Uncertain	1 (6.25)	0 (0)	
Diagnose, n (%)			0.247
Possible	5 (31.25)	4 (25.00)	
Probable	7 (43.75)	11 (68.75)	
Proven	4 (25.00)	1 (6.25)	

(*Continued*)

Table 1 (Continued).

Characteristics	Combined Therapy Group (n=16)	Intravenous Therapy Group (n=16)	*P* value
Laboratory index, Median (IQR)			
Blood platelet (10^9/L)	247.00 (170.00, 361.00)	273.50 (245.25, 294.50)	0.844
Hemoglobin (g/L)	130.00 (117.00, 139.00)	118.30 (101.25, 130.25)	0.085
Neutrophil (10^9/L)	5.57 (4.65, 9.12)	5.54 (4.20, 8.47)	0.662
Lymphocyte (10^9/L)	1.23 (0.73, 1.97)	0.76 (0.42, 1.44)	0.198
Glutamic-pyruvic transaminase (U/L)	22.50 (15.00, 31.75)	14.00 (8.00, 26.00)	0.052
Glutamic oxaloacetic transaminase (U/L)	21.50 (16.50, 24.50)	18.00 (15.00, 20.00)	0.227
Total bilirubin (μmol/L)	9.15 (7.13, 11.49)	10.40 (6.90, 12.30)	0.678
Urea (mmol/L)	5.69 (3.94, 7.43)	4.50 (3.47, 5.45)	0.138
Serum creatinine (μmol/L)	69.50 (58.25, 76.00)	61.00 (52.00, 71.00)	0.304
Serum potassium (mmol/L)	4.07 (3.65, 4.55)	4.03 (3.62, 4.48)	0.953
CT thorax findings, n (%)			
Ground-glass opacity	12 (75.00)	10 (62.50)	0.446
Consolidation	11 (68.75)	11 (68.75)	>0.999
Multiple nodule	6 (37.50)	4 (25.00)	0.446
Cavity	4 (25.00)	5 (31.25)	0.694
Halo signs	4 (25.00)	1 (6.25)	0.333
Air crescent sign	0	1 (6.25)	>0.999
Bronchiectasis	2 (12.50)	4 (25.00)	0.654

Notes: *In the combined therapy group, six patients presented with mixed infections: two patients exhibited co-infection with Aspergillus and Mucor, three patients had Aspergillus and Candida co-infections, and one patient had a mixed infection of Mucor and Candida. In the intravenous therapy group, four patients exhibited mixed infections: two patients had co-infections with Aspergillus and Candida, one patient had a mixed infection of Aspergillus and Mucor, and one patient exhibited co-infection with Aspergillus, Mucor, and Cryptococcus.

(37.50%) within the combined therapy group and 4 cases (25.00%) within the intravenous therapy group. In the combined therapy group, the proven, probable and possible cases were 4 (25.00%), 7 (43.75%) and 5 (31.25%), respectively. In the intravenous therapy group, the most patients were probable IPFD (68.75%, 11/16), and the remaining 5 patients were proven IPFD (6.25%, 1/16) and possible IPFD (25.00%, 4/16), respectively.

Administration of ABCD

As shown in Table 2, the total dose of ABCD administered was marginally lower in the combined therapy group compared to the intravenous therapy group (1675.00 vs 1800.00, *P*=0.611), Nevertheless, the difference was not statistically significant. The duration of medication administration was significantly reduced in the combined therapy group than in the intravenous therapy group (8 vs 12, *P*=0.032). The total dose of intravenous medication in the combined therapy group was also significantly lower than that in the intravenous therapy group (1125.00 vs 1800.00, *P*=0.014). Additionally, the median duration of nebulized medication administration in the combined therapy group was 8.00 (6.25, 10.75) days, and the total dose of nebulized medication was 400.00 (312.50, 537.50) mg.

Table 2 The Administration of ABCD for Combined Therapy and Intravenous Therapy

Variables, Median (IQR)	Combined Therapy Group (n=16)	Intravenous Therapy Group (n=16)	*P* value
Total dose (mg)	1675.00 (1237.50, 1900.00)	1800.00 (1125.00, 2512.50)	0.611
Duration of medication (d)	8.00 (7.25, 10.75)	12.00 (8.50, 17.00)	0.032
Total intravenous dose (mg)	1125.00 (912.50, 1475.00)	1800.00 (1125.00, 2512.50)	0.014
Duration of intravenous medication (d)	8.00 (7.00, 9.75)	12.00 (8.50, 17.00)	0.005
Total dose of nebulised medication (mg)	400.00 (312.50, 537.50)	–	–
Duration of nebulised medication (d)	8.00 (6.25, 10.75)	–	–

Table 3 The Efficiency of Treatment in Patients for Combined Therapy and Intravenous Therapy

	Combined Therapy Group (n=16)	Intravenous Therapy Group (n=16)	*P* value
Favorable response, no. (%)	15 (93.75)	10 (62.50)	0.033
CR	2 (12.50)	0 (0)	
PR	13 (81.25)	10 (62.50)	
SD, no. (%)	1 (6.25)	6 (37.5)	

Abbreviations: CR, Complete response; PR, partial response; SD, stable disease.

Efficacy Analysis

Following treatment, the favorable response rate of the combined therapy group was significantly higher than that of the intravenous therapy group (93.75% vs 62.50%, *P*=0.033). In the combined therapy group, 2 (12.50%) patients achieved CR and 13 (81.25%) patients achieved PR. In the intravenous therapy group, all 10 patients achieved PR (Table 3). In particular, Figure 1 illustrates the chest CT of three typical patients in the combined therapy group with notable absorption of lung lesions and significant improvement in imaging signs. Additionally, the remaining patients were observed to be in a state of SD.

Safety Analysis

Details of AEs that occurred during the treatment are presented in Table 4. Elevated urea levels emerged as the most common AE in the combined therapy group and intravenous therapy group, with incidence of 68.75% and 50.00%, respectively. Nephrotoxicity was evaluated according to serum creatinine levels during the administration. There were 2 (12.50%) and 1 (6.25%) cases of increased creatinine in both groups, respectively. In the combined therapy group, the incidence of hypokalemia was 31.25% (5/16), and most of them were grade 1–2 (80%). The incidence of anemia, bronchospasm, and gastrointestinal reactions were all 6.25% (1/16) in the combined therapy group. In the intravenous therapy group, the incidence of hypokalemia was 37.50% (6/16), and 66.7% of them were grade 1–2. The incidence of fever and chills were 31.25% (5/16)

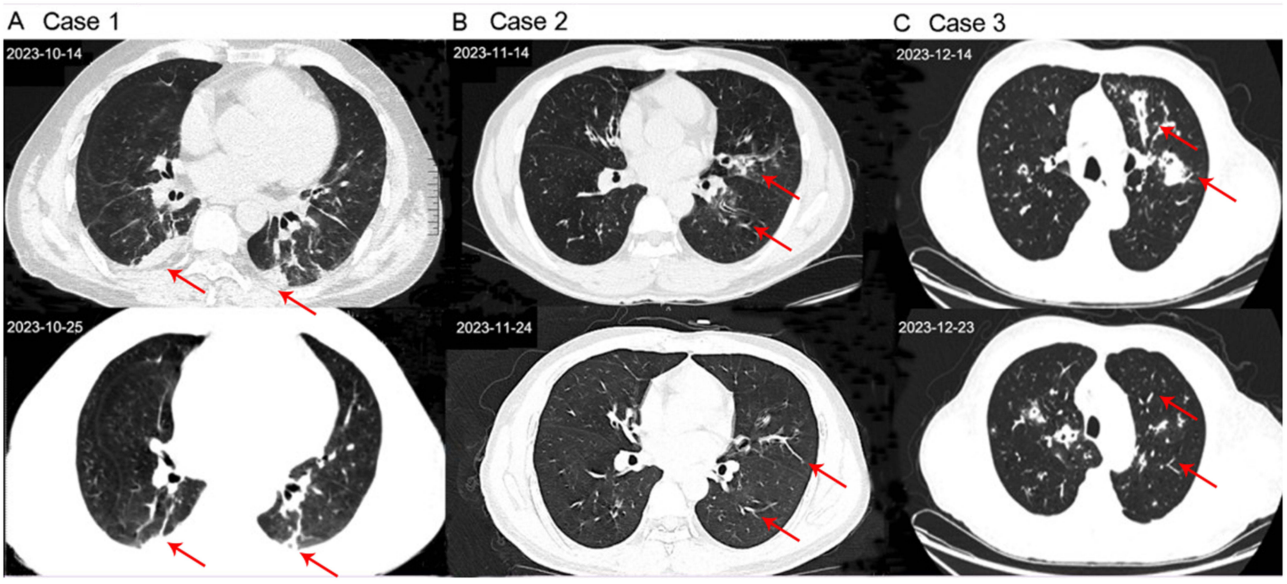

Figure 1 Chest CT before and after treatment of three typical patients in the ABCD nebulized inhalation combined with intravenous injection regimen. (**A**) CT imaging revealed linear shadow and consolidation in the bilateral lower lobes. Following a 9-day combination therapy, there was marked resolution of the lesions, with only minor fibrotic changes persisting. The red arrow refers to the lesion location. (**B**) CT imaging demonstrated thickening of the bronchial walls in the left lingual and left lower lobes, associated with peribronchial exudation shadow and mild bronchiectasis. Following a 10-day course of combination therapy, a substantial reduction in bronchial wall thickening was observed, accompanied by the absorption of the peribronchial exudate shadow. The red arrow refers to the lesion location. (**C**) The CT scan showed bronchial wall thickening in the left upper lobe along with nodular opacities. After a 9-day combination therapy, the bronchial wall thickening in the left upper lobe was completely resolved, and the nodular opacities had entirely disappeared. The red arrow refers to the lesion location.

Table 4 AEs Associated with Combined Therapy and Intravenous Therapy

	Combined Therapy Group (n=16)	Intravenous Therapy Group (n=16)	*P* value
AEs, n (%)			
Fever (elevated body temperature ≥ 1.0°C)	3 (18.75)	5 (31.25)	0.414
Chills	4 (25.00)	6 (37.50)	0.446
Hypokalemia[a]	5 (31.25)	6 (37.50)	0.476
Elevated alanine aminotransferase[b]	10 (62.50)	3 (18.75)	0.012
Elevated aspartate aminotransferase[c]	2 (12.50)	1 (6.25)	0.544
Increased creatinine[d]	2 (12.50)	1 (6.25)	0.544
Increased urea[e]	11 (68.75)	8 (50.00)	0.280
Decreased lymphocyte count[f]	1 (6.25)	2 (12.05)	0.544
Decreased eosinophil count[j]	1 (6.25)	1 (6.25)	0.999
Decreased monocyte count[h]	0 (0)	1 (6.25)	0.310
Hypoalbuminemia[i]	0 (0)	3 (18.75)	0.069
Anemic	1 (6.25)	4 (25.00)	0.144
Gastrointestinal reactions	1 (6.25)	0 (0)	0.310
Dyspnea	1 (6.25)	0 (0)	0.310
Sudden cough	1 (6.25)	0 (0)	0.310
Wheezing	1 (6.25)	0 (0)	0.310

Notes: [a]Hypokalemia is defined as a serum potassium concentration of less than 3.5 mmol/L. [b]Elevated alanine aminotransferase (ALT) is defined as ALT > upper limit of normal (50 U/L) (baseline normal) or ALT > 1.5 times baseline (baseline abnormal) Increased glutamic-pyruvic transaminase. [c]Elevated aspartate aminotransferase (AST) is defined as AST > upper limit of normal (50 U/L) (baseline normal) or AST > 1.5 times baseline (baseline abnormal) Increased glutamic-pyruvic transaminase. [d]Increased creatinine is defined as serum creatinine > 133 μmol/L. [e]Increased urea is defined as urea > 7.5 mmol/L. [f]Decreased lymphocyte count is defined as lymphocyte count < 0.8×10^9/L. [g]Decreased eosinophil count is defined as eosinophil count < 0.05×10^9/L. [h]Decreased monocyte count is defined as monocyte count < 0.12×10^9/L. [i]Hypoalbuminemia was defined as albumin concentration < 35 g/L.

and 37.50% (6/16), respectively. Additionally, bronchospasm was reported in one patient within the combined therapy group, predominantly manifesting as dyspnea, sudden cough, and wheezing. Following the implementation of appropriate symptomatic treatment, the symptoms demonstrated a notable improvement. All patients successfully completed the prescribed treatment regimen, and no patients discontinued treatment due to AEs.

Discussion

To the best of our knowledge, this is the first study to compare the antifungal effects of ABCD nebulized inhalation combined with intravenous injection and ABCD injection alone in the treatment of IPFD patients. Our findings demonstrated that the combination of ABCD nebulized inhalation and intravenous injection was superior to intravenous injection of ABCD alone in the treatment of IPFD. This new combination therapy demonstrated a favourable safety profile and reduced drug duration. This study proposes a novel framework for the personalized clinical management of IPFD.

Previous research has confirmed the favorable efficacy and safety profile of ABCD intravenous injection in the treatment of IFD.[27–30] Specifically, two open-label studies reported clinical response rates of 49% (48/97) and 67.2% (39/58) for ABCD intravenous injection in treating fungal infections.[27,28] Additionally, evidence suggests that ABCD is both effective and safe for patients who have previously experienced nephrotoxicity as a result of amphotericin B treatment.[29,30] A study with a small sample size demonstrated that among patients with mucormycosis in conjunction with hematological malignancies, the clinical response rates of ABCD treatment at 2 weeks, 4 weeks, and at the conclusion of treatment were 100% (9/9), 77.8% (7/9), and 77.8% (7/9), respectively, achieving satisfactory therapeutic outcomes.[20] The present study employed a retrospective collection of clinical data from IPFD patients who presented to the respiratory department, encompassing immunocompetent patients. Among the 16 patients in the intravenous therapy group, 10 achieved PR, with a favorable response rate of 62.5%, which is consistent with previous studies and once again proves the reliable efficacy of ABCD intravenous treatment for IPFD. Despite its definite clinical advantages, the use of ABCD is limited by high costs and AEs such as infusion reactions.

Theoretically, nebulized inhalation of antifungal agents can enhance pulmonary drug concentrations, thereby avoiding or alleviating the adverse reactions associated with intravenous therapy to a certain degree. This potential has garnered significant interest among researchers in the use of inhaled antifungal drugs.[31–34] Several studies have reported that inhaled amphotericin B, L-AmB, or ABLC are typically used as prophylactic antifungal treatments or targeted therapy regimens for lung transplant recipients.[35–39] These formulations show promise in preventing IPFD secondary to various viral infections.[40–42] It is widely acknowledged that conventional amphotericin B is associated with high levels of nephrotoxicity, while the liposomal formulation L-AmB exhibits low toxicity; however, its high cost constraints its utilization among economically disadvantaged patients or in regions. Moreover, due to the delisting of ABLC in certain countries, its accessibility is restricted.[43] In contrast, ABCD has been demonstrated to reduce free drug release and decrease nephrotoxicity through its cholesterol sulfate complex structure. It is noteworthy that ABCD nebulized has the potential to generate a higher concentration in the lungs, which is conducive to the management of local fungal infections. Furthermore, compared to L-AmB and ABLC, ABCD has a relatively lighter economic burden and is suitable for areas with limited long-term management and financial resources.

To date, there is a paucity of reports on the efficacy of nebulized amphotericin B and its lipid preparations in the treatment of IPFD. The study by Cui et al demonstrated that among 27 patients diagnosed with respiratory infections who received AmB nebulization therapy, 17 patients (62.96%) exhibited an improvement in their health condition following treatment.[19] Additionally, another single-center retrospective cohort study evaluated the efficacy of systemic antifungal therapy combined or not combined with nebulized L-AmB in patients with proven or probable invasive pulmonary aspergillosis. The findings indicated that the inclusion of nebulized L-AmB significantly reduced the 12-month mortality rate (HR 0.258; 95% CI 0.072–0.922; P=0.037).[44] In this study, we evaluated the efficacy of ABCD nebulized inhalation in combination with intravenous administration compared to ABCD intravenous administration alone. The baseline characteristics, including the proportions of patients classified as proven, probable, and possible, exhibited no significant differences between the two groups. However, among the 16 IPFD patients treated with the combined ABCD nebulization and intravenous injection regimen, 2 cases (12.5%) achieved CR, and 13 cases (81.25%) achieved PR, resulting in a favorable response rate of 93.75%. This favorable response rate was significantly higher than that observed with the intravenous administration alone (P=0.033). These results strongly demonstrate that, with a comparable total dose of medication, the combination of ABCD nebulization and intravenous injection exhibit outstanding therapeutic effects in the treatment of patients with IPFD. The nebulization of ABCD allows the drug to reach the lesion rapidly with a high local concentration.[19] In comparison with intravenous ABCD alone, the regimen combining ABCD nebulization with intravenous injection ensures a high alveolar concentration and limited systemic exposure of ABCD. This approach offers several advantages, including effective diffusion in the injured lung, good tolerance, and reduced drug toxicity. Furthermore, it is noteworthy that the total dose of ABCD in the combination therapy group was numerically lower than that in the intravenous therapy group, which suggests that the ABCD nebulized inhalation combined with intravenous injection regimen may reduce patient costs while maintaining efficacy. Furthermore, the combination therapy group significantly shortened the treatment duration, indicating that ABCD nebulized inhalation combined with intravenous injection regimen can control the condition more rapidly, improve prognosis, increase patient confidence in the treatment, reduce hospitalization duration, and decrease the risk of hospital-acquired infections.

Hypokalemia and infusion reactions are common AEs associated with the intravenous therapy of amphotericin B and its lipid formulations. Studies have reported that in the treatment of hematologic malignancies complicated by mucormycosis, over 30% of patients experienced hypokalemia when treated with ABCD.[20] Similarly, in this study, the incidence of hypokalemia in the combined therapy and intravenous therapy groups was 31.25% and 37.50%, respectively. It is recommended that during systemic antifungal treatment with ABCD, whether combined with nebulization therapy or not, patients' serum potassium levels should be closely monitored, and routine oral potassium supplements should be provided. A randomized, double-blind, multicenter study demonstrated that the use of L-AmB (343 cases) and AmB (344 cases) for the treatment of patients with fever and neutropenia resulted in an incidence of infusion-related fever of 17% and 44%, respectively. Additionally, the incidence of infusion-related chills was observed to be 18% for L-AmB and 54% for AmB.[45] In this study, the incidence of infusion-related AEs was marginally higher in the intravenous therapy group compared to the combined therapy group, with the primary manifestations being fever

(31.25% vs 18.75%, $P>0.05$) and chills (37.50% vs 25.00%, $P>0.05$). These AEs predominantly occurred during the initial infusion period and typically resolved promptly following steroid administration. Nephrotoxicity has been identified as an adverse reaction associated with ABCD.[46] This study closely monitored the nephrotoxicity through regular assessment of serum creatinine levels of patients. Our findings suggested that elevated creatinine levels were observed in 2 cases (12.50%) and 1 case (6.25%) in the combination therapy and intravenous therapy groups, respectively. Ultimately, all patients successfully completed the prescribed treatment regimen by taking the requisite measures in a timely manner, and no patients discontinued treatment due to AEs. Overall, these findings indicated the ABCD nebulization combined with the intravenous injection regimen is safe for the treatment of IPFD.

Furthermore, AEs such as cough, bronchospasm, and dyspnea warrant particular attention during nebulization therapy. Research conducted by Rijnders and Alexander has demonstrated that the incidence of cough in patients receiving nebulized ABLC or L-AmB ranges from 2.2% to 11.51%.[18,47] Additionally, two observational studies from Spain have reported the incidence of bronchospasm in patients undergoing nebulized ABLC or L-AmB for prophylactic antifungal treatment to be 8.8% (4/45) and 1.92% (2/104), respectively.[42,48] Bronchospasms primarily presents clinically as dyspnea, sudden cough, and wheezing. In this study, only one patient (6.25%) in the combination therapy group experienced bronchospasm, which was effectively managed with symptomatic treatment, allowing the patient to continue with the original therapeutic protocol. Regarding drug tolerance, a prospective, randomized, double-blind trial showed that among lung transplant recipients receiving nebulized AmB-D and ABLC for prophylactic antifungal treatment post-surgery, 6 out of 49 (12.2%) patients and 3 out of 51 (5.9%) patients, respectively, discontinued treatment due to intolerance ($P=0.313$).[17] In this study, all patients completed the prescribed treatment regimen without any discontinuations attributable to AEs.

Our study has several limitations. Firstly, this study is a single center retrospective study, which may limit the generalizability of our research findings. Secondly, given the exploratory nature of this study, the sample size was relatively small, and no sample size calculation was performed earlier, which may have led to selection bias. However, for subsequent high-quality studies, a detailed sample size calculation will be conducted and the sample size will be expanded further to improve the study's accuracy and power. Thirdly, due to the retrospective design, this study had some uncontrolled confounding factors such as differences in underlying lung diseases between groups. Ultimately, the present study did not undertake long-term follow-up and thus was unable to evaluate long-term efficacy and safety such as relapse rates or survival outcomes. Notwithstanding the limitations mentioned above, our present study has provided preliminary confirmation of the efficacy and safety of ABCD nebulization combined with intravenous injection regimen as a treatment for IPFD. In the future, a high-quality, prospective, multi-center, large-sample, randomized controlled trial will be conducted to comprehensively evaluate the clinical efficacy of ABCD nebulization combined with intravenous injection regimen.

In conclusion, the regimen combining ABCD nebulization with intravenous injection is a promising option for patients with IPFD, demonstrating both favourable efficacy and manageable safety. Furthermore, this combined treatment regimen can significantly reduce the duration of medication required for patients, potentially facilitating a more rapid recovery. At the same time, the combined therapy regimen has potential advantages in mitigating the incidence of AEs such as hypokalemia and infusion reactions. However, caution is warranted concerning the risk of bronchospasm and dyspnea.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics committee of the First Affiliated Hospital of Zhengzhou University (2024-KY-0493-001). The study guarantees that the identities of the participants and other related data have been kept anonymous and confidential. Due to the retrospective nature of this investigation, written informed consent was waived and approved by our ethics committee.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Henan Province Medical Science and Technology Public Relations Plan Province Department joint construction project (LHGJ20190209).

Disclosure

All authors declare that they have no conflict of interest.

References

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. *J Fungi*. 2017;3(4):57. doi:10.3390/jof3040057
2. Zarif A, Thomas A, Vayro A. Chronic pulmonary aspergillosis: a brief review. *Yale J Biol Med*. 2021;94(4):673–679. doi:10.1186/s13256-021-02721-9
3. Gow NA, Netea MG. Medical mycology and fungal immunology: new research perspectives addressing a major world health challenge. *Philos Trans R Soc Lond B Biol Sci*. 2016;371(1709):20150462. doi:10.1098/rstb.2015.0462
4. Colombo AL, de Almeida Júnior JN, Slavin MA, et al. Candida and invasive mould diseases in non-neutropenic critically ill patients and patients with haematological cancer. *Lancet Infect Dis*. 2017;17(11):e344–e356. doi:10.1016/S1473-3099(17)30304-3
5. Gunzer M, Thornton CR, Beziere N. Advances in the In vivo molecular imaging of invasive aspergillosis. *J Fungi*. 2020;6(4):338. doi:10.3390/jof6040338
6. Vergidis P, Sendi P, Alkhateeb HB, et al. How do I manage refractory invasive pulmonary aspergillosis. *Clin Microbiol Infect*. 2024;30(6):755–761. doi:10.1016/j.cmi.2024.01.015
7. Olum R, Baluku JB, Kazibwe A, et al. Tolerability of oral itraconazole and voriconazole for the treatment of chronic pulmonary aspergillosis: a systematic review and meta-analysis. *PLoS One*. 2020;15(10):e0240374. doi:10.1371/journal.pone.0240374
8. Verweij PE, Ananda-Rajah M, Andes D, et al. International expert opinion on the management of infection caused by azole-resistant Aspergillus fumigatus. *Drug Resist Updat*. 2015;21–22:30–40. doi:10.1016/j.drup.2015.08.001
9. Formanek PE, Dilling DF. Advances in the diagnosis and management of invasive fungal disease. *Chest*. 2019;156(5):834–842. doi:10.1016/j.chest.2019.06.032
10. Boyer J, Feys S, Zsifkovits I, et al. Treatment of invasive aspergillosis: how it's going, where it's heading. *Mycopathologia*. 2023;188(5):667–681. doi:10.1007/s11046-023-00727-z
11. Bupha-Intr O, Butters C, Reynolds G, et al. Consensus guidelines for the diagnosis and management of invasive fungal disease due to moulds other than Aspergillus in the haematology/oncology setting, 2021. *Intern Med J*. 2021;Suppl 51(S7):177–219. doi:10.1111/imj.15592
12. Zhang J, Liu H, Xi L, et al. Antifungal susceptibility profiles of olorofim (Formerly F901318) and currently available systemic antifungals against mold and yeast phases of Talaromyces marneffei. *Antimicrob Agents Chemother*. 2021;65(6):e00256–00221. doi:10.1128/AAC.00256-21
13. Gursoy V, Ozkalemkas F, Ozkocaman V, et al. Conventional amphotericin B associated nephrotoxicity in patients with hematologic malignancies. *Cureus*. 2021;13(7):e16445. doi:10.7759/cureus.16445
14. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. 2002;137(2):105–109. doi:10.7326/0003-4819-137-2-200207160-00008
15. Tan C, Qiu Y, Zhang J, et al. Nebulized inhalation combined with intravenous amphotericin B in the treatment of three cases of tracheo-bronchopulmonary Penicilliosis marneffei. *Chinese Med J*. 2015;95(46):3778–3781.
16. Wang H, Wu Y, Feng J, et al. Clinical study of bronchoscopic local perfusion of amphotericin B in the treatment of pulmonary fungal infection. *Chin J Pract Med*. 2013;40(20):3.
17. Drew RH, Dodds Ashley E, Benjamin DK, et al. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation*. 2004;77(2):232–237. doi:10.1097/01.TP.0000101516.08327.A9
18. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2008;46(9):1401–1408. doi:10.1086/586739
19. Cui N, Zhao J. Application and evaluation of topical amphotericin B for the treatment of respiratory fungal infections. *BMC Infect Dis*. 2024;24(1):439. doi:10.1186/s12879-024-09342-9
20. Liu J, Ma X. Amphotericin B colloidal dispersion: an effective drug for the treatment of mucormycosis in China. *Front Cell Infect Microbiol*. 2023;13:1147624
21. Liu M, Yang H, Liu Q, et al. Amphotericin B colloidal dispersion is efficacious and safe for the management of talaromycosis in HIV-infected patients: results of a retrospective cohort study in China. *Infect Drug Resist*. 2024;17:5581–5593. doi:10.2147/IDR.S481856
22. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020;71(6):1367–1376. doi:10.1093/cid/ciz1008

23. Brüggemann RJ, Jensen GM, Lass-Flörl C. Liposomal amphotericin B-the past. *J Antimicrob Chemother*. 2022;77(Suppl_2):ii3–ii10. doi:10.1093/jac/dkac351
24. Godet C, Couturaud F, Marchand-Adam S, et al. Nebulised liposomal amphotericin-B as maintenance therapy in allergic bronchopulmonary aspergillosis: a randomised, multicentre trial. *Eur Respir J*. 2022;59(6):2102218. doi:10.1183/13993003.02218-2021
25. Society of Hematology CMDA, Infections CWGoIF. Diagnostic criteria and treatment principles of invasive fungal disease in patients with hematological or malignant tumors (the sixth revision). *Chinese J Int Med*. 2020;59(10):754–763. doi:10.3760/cma.j.cn112138-20200627-00624
26. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391–1402. doi:10.1056/NEJMoa040446
27. Oppenheim BA, Herbrecht R, Kusne S. The safety and efficacy of amphotericin B colloidal dispersion in the treatment of invasive mycoses. *Clin Infect Dis*. 1995;21(5):1145–1153. doi:10.1093/clinids/21.5.1145
28. Anaissie EJ, Mattiuzzi GN, Miller CB, et al. Treatment of invasive fungal infections in renally impaired patients with amphotericin B colloidal dispersion. *Antimicrob Agents Chemother*. 1998;42(3):606–611. doi:10.1128/AAC.42.3.606
29. Zhu X, Wang Z, Ferrari MW, et al. Management of anticoagulation in patients with infective endocarditis. *Thromb Res*. 2023;229:15–25. doi:10.1016/j.thromres.2023.06.010
30. Mycoses Committee CMEA. Multidisciplinary expert consensus on rational clinical application of different dosage forms of amphotericin B (2024 edition). *Chinese J Int Med*. 2024;63(03):230–257. doi:10.3760/cma.j.cn112138-20231122-00332
31. Suttle AB, Grossmann KF, Ouellet D, et al. Assessment of the drug interaction potential and single- and repeat-dose pharmacokinetics of the BRAF inhibitor dabrafenib. *J Clin Pharmacol*. 2015;55(4):392–400. doi:10.1002/jcph.437
32. Short NJ, Kantarjian H, Ravandi F, et al. Emerging treatment paradigms with FLT3 inhibitors in acute myeloid leukemia. *Therap Adv Hematol*. 2019;10:2040620719827310. doi:10.1177/2040620719827310
33. Cronin S, Chandrasekar PH. Safety of triazole antifungal drugs in patients with cancer. *J Antimicrob Chemother*. 2010;65(3):410–416. doi:10.1093/jac/dkp464
34. Swaisland HC, Ranson M, Smith RP, et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet*. 2005;44(10):1067–1081. doi:10.2165/00003088-200544100-00005
35. Husain S, Camargo JF. Invasive aspergillosis in solid-organ transplant recipients: guidelines from the American Society of Transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13544. doi:10.1111/ctr.13544
36. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;63(4):e1–e60. doi:10.1093/cid/ciw326
37. Peghin M, Monforte V, Martin-Gomez MT, et al. 10 years of prophylaxis with nebulized liposomal amphotericin B and the changing epidemiology of Aspergillus spp. infection in lung transplantation. *Transpl Int*. 2016;29(1):51–62. doi:10.1111/tri.12679
38. Nihtinen A, Anttila V-J, Ruutu T, et al. Low incidence of invasive aspergillosis in allogeneic stem cell transplant recipients receiving amphotericin B inhalation prophylaxis. *Transpl Infect Dis*. 2012;14(1):24–32. doi:10.1111/j.1399-3062.2011.00661.x
39. Chong GL, Broekman F, Polinder S, et al. Aerosolised liposomal amphotericin B to prevent aspergillosis in acute myeloid leukaemia: efficacy and cost effectiveness in real-life. *Int J Antimicrob Agents*. 2015;46(1):82–87. doi:10.1016/j.ijantimicag.2015.02.023
40. Van Ackerbroeck S, Rutsaert L, Roelant E, et al. Inhaled liposomal amphotericin-B as a prophylactic treatment for COVID-19-associated pulmonary aspergillosis/aspergillus tracheobronchitis. *Crit Care*. 2021;25(1):298. doi:10.1186/s13054-021-03728-w
41. Rutsaert L, Steinfort N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care*. 2020;10(1):71. doi:10.1186/s13613-020-00686-4
42. Soriano MC, Narváez-Chávez G, López-Olivencia M, et al. Inhaled amphotericin B lipid complex for prophylaxis against COVID-19-associated invasive pulmonary aspergillosis. *Intensive Care Med*. 2022;48(3):360–361. doi:10.1007/s00134-021-06603-y
43. Lee JSF, Cohen RM, Khan RA, et al. Paving the way for affordable and equitable liposomal amphotericin B access worldwide. *Lancet Glob Health*. 2024;12(9):e1552–e1559. doi:10.1016/S2214-109X(24)00225-0
44. Venanzi E, Martín-Dávila P, López J, et al. Aerosolized lipid amphotericin B for complementary therapy and/or secondary prophylaxis in patients with invasive pulmonary aspergillosis: a single-center experience. *Mycopathologia*. 2019;184(2):239–250. doi:10.1007/s11046-019-00331-0
45. Noel GJ. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *J Pediatr*. 1999;135(3):399.
46. Allende MC, Lee JW, Francis P, et al. Dose-dependent antifungal activity and nephrotoxicity of amphotericin B colloidal dispersion in experimental pulmonary aspergillosis. *Antimicrob Agents Chemother*. 1994;38(3):518–522. doi:10.1128/AAC.38.3.518
47. Alexander BD, Dodds Ashley ES, Addison RM, et al. Non-comparative evaluation of the safety of aerosolized amphotericin B lipid complex in patients undergoing allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2006;8(1):13–20. doi:10.1111/j.1399-3062.2006.00125.x
48. Monforte V, Ussetti P, Gavaldà J, et al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for Aspergillus infection prevention in lung transplantation. *J Heart Lung Transplant*. 2010;29(5):523–530. doi:10.1016/j.healun.2009.11.603