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ORIGINAL RESEARCH

Efficacy and Safety of Amphotericin B Colloidal Dispersion for Patients with Invasive Fungal Disease and Febrile Neutropenia: A Registry-Based, Multicenter, Retrospective, Real-World Study

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Purpose: This study aimed to explore the efficacy and safety of amphotericin B colloidal dispersion (ABCD) in treating patients with invasive fungal disease (IFD) or febrile neutropenia.

Patients and Methods: This study retrospectively included patients diagnosed with IFD or febrile neutropenia who received ABCD treatment from 22 hospitals. The efficacy and safety were evaluated at the end of ABCD treatment. The characteristics of patients diagnosed with possible, probable and proven IFD according to the revised EORTC-MSG criteria were then further analyzed to conduct sensitivity analysis.

Results: A total of 503 patients were enrolled in this study. Of these patients, 391 received ABCD treatment for a minimum of seven days, and the overall efficacy of ABCD was determined to be 71.87% (281/391). 183 patients were diagnosed with possible, probable and proven IFD, the ABCD efficacy of whom was 67.76% (124/183). The efficacy of ABCD in patients with hematologic malignancies, AIDS and diabetes was 70.10% (211/301), 88.24% (30/34), and 83.33% (10/12), respectively. In terms of various fungal species, the efficacy of ABCD in patients with *Aspergillus, Mucorales* and *Candida* infections was 62.96% (34/54), 80.49% (33/41) and 66.67% (22/33), respectively. For patients in the targeted therapy, diagnostic-driven therapy, and empirical therapy groups, the efficacy of ABCD was 76.92% (60/78), 70.17% (207/295), and 77.78% (14/18), respectively. The most common adverse events (AEs) were infusion reactions (30.22%, 152/503) and hypokalemia (38.97%, 196/503), with the majority of these AEs classified as grade 1–2. This study was registered with ClinicalTrials.gov, NCT05116059.

Conclusion: ABCD has demonstrated satisfactory therapeutic efficacy and safety in the treatment of IFD or febrile neutropenia.

Keywords: amphotericin B colloidal dispersion, invasive fungal disease, antifungal therapy, febrile neutropenia

Introduction

Invasive fungal diseases (IFD) are infectious conditions caused by opportunistic fungal pathogens that invade deep-seated organs or the bloodstream, exhibiting a diverse range of clinical manifestations. The significant rise in the occurrence of IFD primarily stems from a surge in immunocompromised individuals, such as AIDS patients, cancer patients, and organ transplant recipients.[1,2] Moreover, febrile neutropenia, one of the most serious complications that occur following chemotherapy for haematological malignancies, is often complicated with fungal infection.[3] Among patients with IFD or febrile neutropenia,

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Aspergillus and *Candida* are the most common pathogens, with associated morbidity and mortality rates ranging from 30% to 85%.[4–6] However, their early diagnosis is difficult and it is increasingly important to select the effective and safe antifungal agent for applications such as empirical therapy and diagnostic-driven therapy.

Currently, epidemiological data indicate an escalating trend of fungal pathogens developing resistance to triazoles and echinocandins, potentially contributing to the rising mortality rates of IFD.[7] Furthermore, in comparison to triazoles and echinocandins, polyene antibiotics have broad-spectrum activity that effectively covers common clinical pathogens, recommended by international and domestic guidelines as a treatment choice for IFD[8] Amphotericin B (AmB) has historically been regarded as the most prevalent antifungal pharmaceutical agent. Amphotericin B deoxycholate (AmB-D) has demonstrated efficacy in the treatment of IFD; however, its clinical application is constrained by its nephrotoxicity.[9] Among IFD patients treated with AmB-d, more than 50% developed nephrotoxicity.[10] To alleviate adverse reactions, AmB lipid formulations that are lower in toxicity and more tolerable have gradually entered clinical practice and have become a more preferred choice.[11] AmB lipid formulations have been demonstrated to possess clinical efficacy comparable to that of AmB-D, while concurrently exhibiting reduced nephrotoxicity.[12]

As a kind of lipid formulation of AmB, Amphotericin B colloidal dispersion (ABCD) is a discoidal complex of AmB and sodium cholesterol sulfate in a molar ratio of 1:1. The presence of sodium cholesterol sulfate reduces the binding rate to cholesterol on the renal tubular cell membrane, mitigates renal tubular damage and consequently ameliorate the nephrotoxicity of AmB.[13] Evidence suggests that for patients with a history of renal insufficiency or nephrotoxicity owing to prior AmB treatment and intolerant or unresponsive to AmB, ABCD is effective and safe.[14] Nevertheless, with large molecular weight of ABCD, infusion-related adverse events (AEs) are inevitable and need special attention in clinical practice. In addition to ABCD, the lipid formulation of AmB also includes liposomal amphotericin B (L-AmB) and aerosolized amphotericin B lipid complex (ABLC). However, L-AmB produced in China is different from L-AmB produced in other countries; compared with AmB-d, there is no significant improvement in nephrotoxicity.[12] Moreover, the considerable expense of original L-AmB and ABLC renders them unaffordable for most patients, consequently leading to limited availability in most hospitals in China and a paucity of relevant data. As a result, it becomes imperative to carry out a study with a substantial sample regarding the efficacy and safety of ABCD in the treatment of various kinds of patients with IFD or febrile neutropenia in real-world settings.

This multicenter, observational study aimed to describe the baseline characteristics of Chinese patients with IFD and febrile neutropenia in real-world settings and to evaluate the efficacy and safety of ABCD in treating patients with IFD and febrile neutropenia on large sample, offering evidence-based support for the clinical application of ABCD.

Materials and Methods

Study Design

Patients diagnosed with IFD[15] or febrile neutropenia, with onset at 18 years or older and who received ABCD treatment from 22 hospitals in China between September 2021 and December 2022, were collected retrospectively. Demographic, clinical, laboratory and treatment data were evaluated. The treatment data, in particular, encompasses antifungal therapy, including pretreatment measures, route of ABCD administration, dosage and duration of ABCD administration, efficacy, and AEs. A standardized electronic data capture system was utilized to collect clinical data of patients during their hospitalization from multiple centers. This study was approved by the Institutional Review Boards of Peking Union Medical College Hospital (PUMCH) (JS-3048B). Informed consent was waived owing to the retrospective nature of the study. This study was registered with ClinicalTrials.gov, NCT05116059 in 2021/10/12.

Eligibility for Patients

The inclusion criteria for this study are as follows: (1) Age ≥ 18 years old. (2) Patients with febrile neutropenia, defined as persistent agranulocytosis (neutrophil < 0.5×10^9/L) and fever, with an ineffective treatment after 4–7 days broad-spectrum antifungal drugs. (3) Patients with IFD according to the Chinese guidelines for the diagnosis and treatment of IFD.[15] The diagnosis of IFD was divided into four categories, including undetermined IFD, possible IFD, clinically diagnosed IFD, and confirmed IFD (Table S1).[15] The definitions of the latter three categories were consistent with the EORTC/MSG criteria.[16] Differently, undefined IFD covers patients with clinical imaging abnormalities or positive serum

GM/G test.[15] (4) Patients receiving treatment with ABCD alone or in combination with other antifungal therapy. The exclusion criteria are as follows: (1) Patients judged by clinicians to be unsuitable for this study. (2) Patients with incomplete data or other factors that affect efficacy and safety assessment.

ABCD Treatment

Patients with febrile neutropenia received empirical therapy, while diagnostic-driven therapy was adopted by patients with undefined IFD and possible IFD. In addition, patients with probable IFD and proven IFD were treated with targeted therapy. The dosage and duration of ABCD treatment were determined by the clinician. Specifically, ABCD was frequently administered intravenously. The initial dosage of ABCD was 0.5 to 1.0 mg/kg/day, and the dosage was increased on a daily basis depending on the patient's condition, increasing to a therapeutic dose of 3.0 to 4.0 mg/kg/day on the third day.

Efficacy Assessment

Given that a period of time was necessary for drugs to take effect, the efficacy assessment was conducted among patients who had been treated with ABCD for at least 7 days at the end of ABCD treatment. Based on a composite of clinical, radiological, and mycological criteria, the responses to antifungal therapy were classified as effective treatment and ineffective treatment.[15] For patients treated with targeted therapy, complete response (CR) and partial response (PR) were defined as effective treatment (Table S2).[15] For patients treated with empirical therapy and diagnostic-driven therapy, effective treatment was estimated by the expert group.[15]

Safety Assessment

Safety was assessed by discontinuations and AEs. AEs related to ABCD were recorded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0)[8] and defined as events that changed from normal to abnormal or aggravated compared with the baseline occurred during treatment with the drug.

Statistical Analysis

The treatment efficacy rate in this study is estimated to be 60% based on the preceding ABCD efficacy rate of 52%.[18] With two-sided test, set $\alpha = 0.05$ and 90% test power, the required sample size was 404 according to the sample size calculation formula. In addition, considering a dropout rate of 20%, a total of 505 patients would be required.

Data analysis was carried out using SPSS version 25.0 (SPSS Inc. IBM Corp). For continuous data, normality was assessed using the Shapiro–Wilk method. When data met the normality assumption, they were presented as mean ± standard deviation. Those not conforming to a normal distribution were expressed as median (IQR). Categorical data were presented as percentages (%) and frequencies and compared using the chi-squared test or fisher exact test. The Bonferroni correction was applied for multiple testing. Unless stated otherwise, missing values were not considered in percentage calculations. All statistical tests were bilateral tests and a P-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Totally, 503 patients were included in this study. Among the enrolled patients, the median (range) age was 51 (18, 82) years old, of which 65.81% (331/503) were males. The proportions of patients with hematologic malignancies, AIDS and diabetes were 77.73% (391/503), 13.32% (42/503) and 2.98% (15/503), respectively. Moreover, the proportions of patients with IFD diagnosed with "proven", "probable" and "possible" were 17.10% (86/503), 8.55% (43/503), and 17.10% (86/503), respectively. Among the patients with identified microbiologic evidence, 38.73% (67/173) were infected by *Aspergillus*, followed by *Mucorales* (30.06%, 52/173), *Candida* (24.86%, 43/173), *Talaromyces marneffei* (15.61%, 27/173), and *Cryptococcus* (8.09%, 14/173). Lung (93.91%, 432/460) accounted for the largest proportion of the confirmed infection sites. 73.16% (368/503) patients had received antifungal therapy in the past. The most frequently used antifungal drug was voriconazole (72.28%, 266/368). Detailed information was shown in Table 1.

Table 1 Baseline Demographic and Clinical Characteristics of Patients

Characteristics	Total (n = 503)
Age, (years), Median (Range)	51 (18–82)
Gender, n (%)	
Male	331 (65.81)
Main primary disease, n (%)	
Hematologic malignancy (Chemotherapy)	324 (64.41)
Hematologic malignancy (allo-HSCT)	67 (13.32)
AIDS[a]	42 (8.35)
Diabetes	15 (2.98)
Chronic respiratory disease	6 (1.19)
Fungus species, n (%)	
Unknown	330 (65.61)
Identified	173 (34.39)
Aspergillus[b]	67 (38.73)
Mucor	52 (30.06)
Candida[c]	43 (24.86)
Talaromyces marneffei	27 (15.61)
Cryptococcus[d]	14 (8.09)
Infection site, n (%)	
Unknown	43 (8.55)
Confirmed	460 (91.45)
Lung	432 (93.91)
Blood	44 (9.57)
Central nervous system	19 (4.13)
Upper respiratory tract	7 (1.52)
Trachea and bronchi	5 (1.09)
Gastrointestinal tract	3 (0.65)
Ocular region	2 (0.43)
Urinary system	1 (0.22)
Previous antifungal agents, n (%)	
No	135 (26.84)
Yes	368 (73.16)
Voriconazole	266 (72.28)
Caspofungin	110 (29.89)
AmB	83 (22.55)
Posaconazole	74 (20.11)
Micafungin	49 (13.32)
Diagnosis, n (%)	
Febrile neutropenia	25 (4.97)
Undefined IFD	295 (58.65)
Possible IFD	86 (17.10)
Probable IFD	43 (8.55)
Proven IFD	54 (10.74)

Notes: [a]42 IFD patients complicated with HIV/AIDS, identified fungus species were: *Aspergillus* (14, 33.33%), *Mucor* (0, 0), *Candida* (8, 19.05%), *Talaromyces marneffei* (25, 59.52%), and *Cryptococcus* (10, 23.81%), respectively. [b]Among 67 patients with *Aspergillus*, 45 patients failed in previous treatment, and 9 patients were intolerant of previous treatment drugs. [c]Among 43 patients with *Candida*, 23 patients failed in previous treatment, and 7 patients were intolerant in previous treatment drugs. [d]There were 4 patients of pneumonia with *Cryptococcus* and 10 patients of cryptococcal meningitis complicated with other infectious sites.

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; AIDS, acquired immune deficiency syndrome; AmB, amphotericin B; ABCD, amphotericin B colloidal dispersion; IFD, invasive fungal disease.

ABCD Treatment

As shown in Table 2, 68.39% (344/503) of the 503 patients included in the study switched to ABCD treatment after previous antifungal therapy was ineffective.

The proportions of patients in the empirical therapy, diagnostic-driven therapy and targeted therapy as previously defined in the Patients and Methods sections were 4.97% (25/503), 75.75% (381/503) and 19.28% (97/503), respectively. ABCD was used as salvage treatment in 73.16% (368/503) patients. In terms of antifungal treatment regimens, 47.91% (241/503) of patients received monotherapy with ABCD, while 52.09% (262/503) received combination therapy including ABCD. The median treatment duration of the 503 patients treated with ABCD was 10 (7, 17) days. The median mean dose was 2.03 (1.48, 2.49) mg/kg/d and the median cumulative dose was 1200.00 (750.00, 2250.00) mg. Besides, the reasons for patients discontinuing ABCD treatment were complex. As a result of the efficacy of ABCD treatment, 157 patients (31.21%) switched to de-escalation therapy, and 124 patients (24.65%) completed the antifungal treatment regimen. Additionally, 16.90% (85/503) of patients discontinued treatment due to factors such as disease progression, financial constraints, and loss of follow-up. Furthermore, 10.93% (55/503) of patients ceased ABCD therapy due to intolerance.

Table 2 The Administration of ABCD for Patients with IFD and Febrile Neutropenia

Characteristics	Total (n = 503)
Main reasons for switching to ABCD, n (%)	
Ineffective treatment[a]	344 (68.39)
Intolerance[b]	29 (5.77)
Identified the fungus species	4 (0.80)
ABCD therapy strategy, n (%)	
Empirical therapy	25 (4.97)
Diagnostic-driven therapy	381 (75.75)
Targeted therapy	97 (19.28)
ABCD therapy phase, n (%)	
First-line therapy	135 (26.84)
Salvage therapy	368 (73.16)
Antifungal treatment regimen, n (%)	
Monotherapy	241 (47.91)
Combination therapy	262 (52.09)
Administration dosages, Median (IQR)	
Treatment duration, (days)	10 (7, 17)
Mean dose, (mg/kg/d)	2.03 (1.48, 2.49)
Cumulative dose, (mg)	1200.00 (750.00, 2250.00)
Reasons for discontinuation of treatment, n (%)	
Effective treatment. Switch to de-escalation therapy	157 (31.21)
Effective treatment. End of the course	124 (24.65)
Treatment abandonment[c]	85 (16.90)
Ineffective treatment	56 (11.13)
Intolerance	55 (10.93)
Death	22 (4.37)
Unknown	3 (0.60)

Notes: [a]Among the 344 patients, 64 patients failed in previous treatment with AmB. [b]Among the 29 patients, 21 patients were intolerant to AmB. [c]The reasons for treatment abandonment included primary disease progression, financial constraints, and loss of follow-up. Among these patients, 5 cases discontinued due to financial constraints.

Abbreviations: ABCD, amphotericin B colloidal dispersion; IFD, invasive fungal disease.

Efficacy Analysis

As shown in Table 3, 391 patients were treated with ABCD for at least 7 days, and the overall efficacy of ABCD was 71.87% (281/391). The efficacy of ABCD in patients with hematologic malignancies, AIDS and diabetes were 70.10% (211/301), 88.24% (30/34) and 83.33% (10/12), respectively. The efficacy of ABCD in patients with AIDS was significantly higher than the efficacy of patients without AIDS (88.24% vs 70.31%, $P = 0.026$). In terms of different infection sites, the efficacy of ABCD in patients with lung, blood, and central nervous system infections was 70.54%

Table 3 The Efficacy of ABCD Treatment for Patients with IFD and Febrile Neutropenia

ABCD Efficacy,% (n[a]/n)	Patients (n = 391)	P[b] value
Overall ABCD efficacy		< 0.001
Effective	71.87 (281/391)	
Ineffective	28.13 (110/391)	
Hematologic malignancy		0.155
No	77.78 (70/90)	
Yes	70.10 (211/301)	
Chemotherapy	69.80 (178/255)	0.792
allo-HSCT	71.74 (33/46)	
Diabetes	83.33 (10/12)	
AIDS		0.026
Yes	88.24 (30/34)	
No	70.31 (251/357)	
Infection site		0.514
Lung	70.54 (237/336)	0.148
Blood	67.74 (21/31)	0.595
Central nervous system	85.71 (12/14)	0.241
Upper respiratory tract	100.00 (5/5)	0.328
Trachea and bronchi	100.00 (4/4)	0.580
Gastrointestinal tract	66.67 (2/3)	>0.999
Ocular region	50.00 (1/2)	0.484
Bone marrow	100 (1/1)	>0.999
Fungus species		0.039
Aspergillus	62.96 (34/54)	0.120
Mucor	80.49 (33/41)	0.164
Candida	66.67 (22/33)	0.512
Talaromyces marneffei	95.24 (20/21)	0.012
Cryptococcus	76.92 (10/13)	0.656
Previous preventive therapy	72.22 (13/18)	0.943
Previous therapy with AmB	67.47 (56/83)	0.244
ABCD antifungal therapy[c]		0.424
Empirical therapy	77.78 (14/18)	0.568
Diagnostic-driven therapy	70.17 (207/295)	0.191
Targeted therapy	76.92 (60/78)	0.267
ABCD therapy phase		0.035
First-line therapy	79.63 (86/108)	
Salvage therapy	68.90 (195/283)	

Notes: [a]Effective ABCD treatment. P^b value referred to the comparison between 2 or 3 groups in different subgroups in 391 patients who received ABCD treatment for at least 7 days. [c]Patients with febrile neutropenia received empirical therapy, while diagnostic-driven therapy was adopted by patients with undefined IFD and possible IFD; In addition, patients with probable IFD and proven IFD were treated with targeted therapy.

Abbreviations: ABCD, amphotericin B colloidal dispersion; IFD, invasive fungal disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation; AIDS, acquired immune deficiency syndrome.

(237/336), 67.75% (21/31), and 85.71% (12/14), respectively. Of note, there was greater variation in the efficacy of ABCD among patients with confirmed infection at upper respiratory tract, trachea and bronchi, bone marrow, and ocular region, possibly accounting for the smaller populations.

With regard to various fungal species, the efficacy of ABCD in treating patients with *Aspergillus* and *Candida* infection was 62.96% (34/54) and 66.67% (22/33), while the efficacy in patients with *Talaromyces marneffei, Mucorales* and *Cryptococcus* infections was 95.24% (20/21), 80.49% (33/41) and 76.92% (10/13), respectively. In the context of targeted therapy, the efficacy of ABCD was 76.92% (60/78). For patients undergoing empirical and diagnostic-driven therapy, the efficacy of ABCD were 77.78% (14/18) and 70.17% (207/295), respectively. Additionally, the efficacy of ABCD among patients in the first-line therapy was significantly higher than that in the salvage therapy (79.63% vs 68.90%, $P = 0.035$). The detailed efficacy of ABCD was shown in Table 3.

Safety Analysis

Main AEs related to ABCD treatment were shown in Table 4, most of which were grade 1–2. Symptoms of infusion reactions (30.22%, 152/503) mostly included fever (26.44%, 133/503) and chills (11.53%, 58/503) within 24 hours of infusion. Among grade 3–4 AEs, hypokalemia (17.89%, 90/503) accounted for the largest proportion, followed by decreased platelet count (9.94%, 50/503). The main manifestations of hepatotoxicity were liver damage (8.15%, 41/503), increased alanine aminotransferase (3.18%, 16/503), and increased alkaline phosphatase (2.19%, 11/503), which were mainly grade 1–2. The incidence of nephrotoxicity was 5.57% (28/503), which was characterized by the increased serum creatinine.

Sensitivity Analysis

Totally, 183 patients were diagnosed with possible (n = 86, 46.99%), probable (n = 43, 23.50%) and proven (n = 54, 29.51%) IFD according to the EORTC-MSG criteria. Nearly 70% of patients were men. The ABCD efficacy of 183 patients with possible, probable, and proven IFD was 67.76% (124/183), of which 4.84% (6/124) of patients achieved CR and 95.16% (118/124) achieved PR. In patients with hematological malignancies, the efficacy of ABCD treatment was 65.57% (80/122), of which 2.50% (2/80) of patients achieved CR and 97.50% (78/80) achieved PR. In patients with diabetes, the efficacy of ABCD treatment was 72.73% (8/11), of which 12.50% (1/8) of patients achieved CR and 87.50% (7/8) achieved PR. In patients with AIDS, the efficacy of ABCD treatment was 88.46% (23/26), of which 13.04% (3/23) of patients achieved CR and 86.96% (20/23) achieved PR. In terms of various fungus species, the efficacy of ABCD in treating patients with *Aspergillus, Mucorales*, and *Candida* infection was 71.43% (30/42), 71.05% (27/38) and 66.67% (18/27), respectively. Among patients with *Aspergillus, Mucorales*, and *Candida* infections who were treated effectively with ABCD, the proportion of patients achieving

Table 4 Main AEs Related to ABCD Treatment for Patients with IFD and Febrile Neutropenia

Main AEs[a], n (%)	Total (n = 503)	Grade 1–2	Grade 3–4
Hypokalemia	196 (38.97)	106 (21.07)	90 (17.89)
Fever	133 (26.44)	131 (26.04)	2 (0.40)
Chills	58 (11.53)	57 (11.33)	1 (0.20)
Decreased blood platelet count	69 (13.72)	19 (3.78)	50 (9.94)
Hypocalcemia	54 (10.74)	53 (10.54)	1 (0.20)
Liver damage	41 (8.15)	37 (7.36)	4 (0.80)
Anemia	28 (5.57)	10 (1.99)	18 (3.58)
Increased serum creatinine	28 (5.57)	27 (5.37)	1 (0.20)
Decreased white blood cell count	25 (4.97)	9 (1.79)	16 (3.18)
Decreased neutrophil count	18 (3.58)	7 (1.39)	11 (2.19)
Increased alanine aminotransferase	16 (3.18)	13 (2.58)	3 (0.60)
Increased alkaline phosphatase	11 (2.19)	10 (1.99)	1 (0.20)

Notes: [a]This table presented AEs related to ABCD treatment with an overall incidence of more than 2%.
Abbreviations: AEs, adverse events; ABCD, amphotericin B colloidal dispersion.

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CR was 3.33% (1/30), 0.00% (0/27), and 5.56% (1/18), respectively, the proportion of patients achieving PR was 96.67% (29/30), 100.00% (27/27), and 94.44% (17/18), respectively. In addition, AEs of special interest (AESI) such as hypokalemia, fever, decreased blood platelet count; liver damage and increased serum creatinine were presented in Table 5.

Table 5 Demographic Characteristics, Clinical Efficacy and AESI of Patients with Possible, Probable and Proven IFD

Characteristics	Patients (n = 183)
Baseline characteristics	
Age, (years), Median (Range)	50 (18–82)
Male, n (%)	128 (69.95)
Diagnosis, n (%)	
Possible IFD	86 (46.99)
Probable IFD	43 (23.50)
Proven IFD	54 (29.51)
ABCD efficacy, n[a]/n (%)	124/183 (67.76)
Complete response	6/124 (4.84)
Partial response	118/124 (95.16)
Hematologic malignancy, n[a]/n (%)	80/122 (65.57)
Complete response	2/80 (2.50)
Partial response	78/80 (97.50)
Diabetes, n[a]/n (%)	8/11 (72.73)
Complete response	1/8 (12.50)
Partial response	7/8 (87.50)
AIDS, n[a]/n (%)	23/26 (88.46)
Complete response	3/23 (13.04)
Partial response	20/23 (86.96)
Fungus species, n[a]/n (%)	
Aspergillus	30/42 (71.43)
Complete response	1/30 (3.33)
Partial response	29/30 (96.67)
Mucorales	27/38 (71.05)
Complete response	0/27 (0.00)
Partial response	27/27 (100.00)
Candida	18/27 (66.67)
Complete response	1/18 (5.56)
Partial response	17/18 (94.44)
Talaromyces marneffei	15/17 (88.24)
Complete response	4/15 (26.67)
Partial response	11/15 (73.33)
Cryptococcus	9/11 (81.82)
Complete response	0/9 (0.00)
Partial response	9/9 (100.00)
AESI, n (%)	
Hypokalemia	70 (38.25)
Grade 1–2	42 (22.95)
Grade 3–4	28 (15.30)
Fever	46 (25.14)
Grade 1–2	45 (24.59)
Grade 3–4	1 (0.55)

(*Continued*)

Table 5 (Continued).

Characteristics	Patients (n = 183)
Decreased blood platelet count	40 (21.86)
Grade 1–2	12 (6.56)
Grade 3–4	28 (15.30)
Liver damage	23 (12.57)
Grade 1–2	21 (11.48)
Grade 3–4	2 (1.09)
Increased serum creatinine	13 (7.10)
Grade 1–2	13 (7.10)
Grade 3–4	0 (0)

Note: [a]Effective ABCD treatment.
Abbreviations: ABCD, amphotericin B colloidal dispersion; IFD, invasive fungal disease; AESI, adverse events of special interest.

Discussion

To the best of our knowledge, this study firstly represented the inaugural investigation into the application of ABCD for the treatment of IFD and febrile neutropenia in a decade. Historical data stemming from 2 open-label multicenter studies had suggested an efficacy with 49% (48/97) and 67.2% (39/58) in the treatment of fungal infections with ABCD.[19,20] Remarkably, in this study, ABCD has showcased an overarching treatment efficacy of 71.87% (281/391) for patients with IFD or febrile neutropenia. Notably, for patients diagnosed with possible, probable and proven IFD, the efficacy was 67.76% (124/183). Moreover, this research showed that ABCD had a commendable therapeutic performance for patients with IFD who suffered from divergent underlying diseases, were at different stages of treatment and infected with different fungus species, especially in China, where it carried the potential for substantial clinical utility.

In the complex clinical background, the treatment of IFD remains challenging. Most of the people included in this study had received antifungal therapy and were in the rescue treatment stage (73.16%, 368/503). The main reason for using ABCD was the failure of antifungal therapy (68.39%, 344/503). A real-world prospective observational study indicated that among 399 patients, L-AmB were nearly the same efficacy with nearly 50% whether it was used as the first-line, second-line, or subsequent choice of drug.[21] A large multicenter observational study demonstrated that the favourable rate of different AmB formulations for treating IFD was 62%. Among these formulations, the favourable response rates of AmB-d, L-AmB, and ABLC in the treatment of IFD were 61.6%, 53.9%, and 61.1%, respectively.[22] Delightedly, in the present study, ABCD achieved an efficacy of 68.90% in these patients. Although this rate was lower than that observed in the first-line therapy stage (79.63% vs 68.90%, $P = 0.035$) (possibly due to the more severe condition of patients in salvage therapy stages), it still represented a satisfactory treatment outcome. In view of the antifungal treatment strategy for IFD, Yang et al analyzed the efficacy of low-dose AmB in 97 patients under different treatment strategies, with efficacy of 75%, 63.6%, and 72.7% for empirical, diagnostic-driven, and targeted therapies, respectively.[23] In this study, the efficacy of ABCD under different treatment strategies were 77.78%, 70.17%, and 76.92%, respectively, which was equivalent to the aforementioned research findings, suggesting that ABCD was a reliable treatment option for patients with IFD under different treatment strategies. Moreover, in this study, there were 83 patients who had previously used AmB, 64 patients failed and 21 patients were intolerant of AmB and switched to ABCD. ABCD still achieved a response rate of 67.47% (56/83) after 7 days of treatment, indicating that ABCD could still achieve satisfactory therapeutic effect even in patients who failed or were intolerant of AmB, which was consistent with a previous small-sample study.[13] An open, multicenter clinical trial demonstrated that in patients with invasive aspergillosis who are intolerant to amphotericin B or triazole drugs, the favorable response to caspofungin treatment was 45% (37/83), which is numerically lower than the results of our study.[24] Besides, multiple studies have ascertained that IFD occurs more frequently in immunocompromised patients.[25] In this study, the efficacy of ABCD in patients with hematologic malignancies, AIDS and diabetes were as high as 70.10%-88.24%, indicating the satisfactory efficacy of ABCD even in patients with IFD with poor basic conditions. Particularly, we found that ABCD showed a significant

efficacy in patients with IFD with AIDS (88.24% vs 70.31%, $P = 0.026$), which may be due to the fact that most AIDS patients suffered from *talaromycosis marneffei*.[26]

Previous studies have indicated that *Aspergillus* is the most common pathogen of IFD in hematological patients, with the lungs being the most frequent site of infection.[27] Similarly, in this study, patients with *Aspergillus* were in the largest portion, accounting for 38.73%, followed by patients with *Mucorales* and *Candida*, accounting for 30.06% and 24.86%, respectively. For invasive aspergillosis, voriconazole is the recommended first-line antifungal drug, with Amphotericin B as an alternative for patients with contraindications to azole agents. A study reported an efficacy of 52.8% for voriconazole in treating invasive aspergillosis,[28] but its propensity for resistance made the antifungal treatment often unsustainable.[29] A review investigated the trends in the global prevalence of AmB-Resistance (AmBR) from 2010 to 2020, and found higher prevalence of AmBR among *Aspergillus* species in Asian than American and European.[30] Encouragingly, in this study, the efficacy of ABCD in the treatment of aspergillosis patients was as high as 62.96%, on par with voriconazole. Similarly, a recent open-label prospective multicenter study demonstrated that L-AmB exhibited overall efficacy (46.6%, 186/399) and survival rates for ≥7 days after the completion of therapy (83.7%, 334/399) in the IFD treatment,[21] reinforcing confidence in the clinical application of ABCD for a broad population of aspergillosis patients. For invasive candidiasis patients, echinocandins are the preferred treatment,[31] and AmB can be used for patients who cannot tolerate or obtain these antifungal drugs or for those with drug resistance.[32] Furthermore, a previous study has indicated that L-AmB is the preferred treatment for central nervous system candidiasis.[33] Caspofungin was as effective as AmB in 244 patients who had candidemia, with a favorable response in 71.7% and 62.8% of patients, respectively.[34] Besides, Oppenheim et al reported that ABCD exhibited efficacy of 58% for candidiasis patients.[19] In this study, ABCD achieved an efficacy of 66.67% for candidiasis, comparable to caspofungin, suggesting that ABCD was a promising alternative for candidiasis patients. Guidelines recommend initial treatment with conventional AmB for mucormycosis, talaromycosis and cryptococcal meningitis (CM), but substantial side effects needed more attention.[35] Previous studies reported that ABCD exhibited efficacy of 77.8–100% for mucormycosis.[13,19] An open-label trial reported that, among 217 hIV-infected adults who had talaromycosis, treatment with AmB was associated with faster clinical resolution and fungal clearance.[36] In this study, ABCD treatment showed respectable efficacy of 80.49% (33/41) for mucormycosis, 95.24% (20/21) for talaromycosis, and 76.92% (10/13) for candidiasis most of whom were CM, suggesting that the efficacy of ABCD was not inferior to other dosage forms. Overall, this study revealed the potential advantages of ABCD in the treatment of various fungal infections when other treatments have proven ineffective or intolerable.

Similar to previous studies,[13] infusion reactions were concerning AEs (30.22%, 152/503) related to ABCD, primarily presenting as fever (26.44%, 133/503) and chills (11.53%, 58/503), most commonly during the initial infusion. A randomized, double-blind, multicenter trial reported that the incidence of infusion-related fever in L-AmB group (343 cases) and AMB group (344 cases) was 17% and 44%, respectively, and infusion-related chills of 18% and 54%, respectively.[37] These data suggested that the incidence of infusion reactions of ABCD is significantly lower than that of AmB, which is equivalent to that of L-AmB. However, these AEs were mostly grade 1 or grade 2, and symptoms typically, rapidly subsided after the administration of steroids. Besides, in this study, over 30% of patients experienced hypokalemia, but improved after symptomatic treatment. Although lower than traditional AmB formulations, it was still recommended to closely monitor and provide routine oral potassium supplementation during ABCD treatment.[9] Encouragingly, in this study, ABCD exhibited remarkable safety in terms of hepatotoxicity and nephrotoxicity, with a particularly low incidence of renal impairment, with an increased serum creatinine rate of only 5.57%. An early study indicated a significant reduction in nephrotoxicity with ABCD compared to AmB (8.2% vs 43.1%, $P < 0.001$).[38] An open-label prospective multi-center study reported that the kidney function deteriorated from early after the start of L-AmB treatment in 17.5% (74/424) of the patients,[21] which seemed higher than ABCD in this study. In this study, the median treatment duration with ABCD was 10 (7, 17) days, with a median average dose of 2.03 (1.48, 2.49) mg and a median cumulative dose of 1200.00 (750.00, 2250.00) mg. Patients with IFD had sound tolerance to ABCD. Even patients with IFD complicated with renal injury caused by AmB could still use ABCD as an alternative or salvage therapy.[21] Among the enrolled patients, 10.93% (55/503) discontinued ABCD because of intolerance. Besides, we observed that 0.99% (5/503) of patients discontinued ABCD early due to economic reasons, which was significantly decreased compared with previous study (22.22%, 2/7).[13] In summary, ABCD presented satisfactory safety during the treatment of IFD, and the occurrence of AEs were generally manageable.

This study has several limitations. Firstly, the retrospective design of this study has inherent recall or selection bias. Secondly, in some subgroups, the sample size was small, which might lead to potential biases in the reported efficacy of ABCD treatment. Thirdly, in a real-world setting, this study faced complex clinical situations and lacked corresponding drug control groups. A larger-scale, multicenter, prospective, randomized controlled trial is necessary to evaluate the causal effects of ABCD treatment on patient outcomes. In addition, the efficacy of ABCD in patients with febrile neutropenia might be affected by the recovery of neutrophils after the treatment of the underlying disease. Finally, the number of proven IFD patients in this study is relatively small, and further studies with larger cohorts of proven IFD cases are warranted to provide a more comprehensive exploration of treatment options for IFD. Moreover, given the global rise in fungal infections and the challenges posed by antifungal resistance, it is essential to validate the findings of this study in various geographic and healthcare settings to understand the universal applicability and effectiveness of ABCD.

Conclusion

IFD and febrile neutropenia mostly occurred in immunocompromised individuals suffering from complex primary diseases. *Aspergillus, Mucorales*, and *Candida* were the most prevalent pathogens. In the real-world clinical practice, ABCD has demonstrated satisfactory efficacy and safety, showing vast potential in antifungal therapy.

Data Sharing Statement

All data generated or analyzed were included in this published article.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Boards of Peking Union Medical College Hospital (PUMCH) (JS-3048B). Informed consent was waived owing to the retrospective nature of the study. This study was registered with ClinicalTrials.gov, NCT05116059 in 2021/10/12.

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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.

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