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ORIGINAL RESEARCH

# Real-World Outcomes of Amphotericin B Colloidal Dispersion as Salvage Therapy for Invasive Fungal Disease

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**Purpose:** The incidence of invasive fungal disease (IFD) has significantly increased in recent years, partly driven by the expanding immunocompromised population, as well as severe influenza and COVID-19. Amphotericin B (AmB) is highly effective against a broad spectrum of fungal infections and has a low drug resistance rate, but its clinical use is limited by toxicity. Amphotericin B colloidal dispersion (ABCD), a lipid formulation of AmB, is preferred in China for its reduced toxicity. This study assesses real-world clinical outcomes of ABCD as salvage therapy in IFD patients who failed prior treatment with triazoles or echinocandins.

**Methods:** We conducted a single-center, retrospective study of IFD patients who received ABCD salvage therapy between September 2021 and February 2024. Clinical data were systematically reviewed to assess the clinical outcomes of ABCD.

**Results:** Among the 60 patients included, the clinical response rate to ABCD was 71.7% (43/60; 95% confidence interval [CI], 59.2–81.5%). Outcomes did not vary significantly with factors such as gender, underlying conditions, infection sites, or prior antifungal treatments. Incidence rates of hepatotoxicity, nephrotoxicity, and infusion-related reactions were 13.3%, 23.3%, and 1.7%, respectively. Five patients discontinued ABCD due to adverse events.

**Conclusion:** In this real-world setting, ABCD salvage therapy was associated with favorable clinical outcomes and an acceptable safety profile in IFD patients who failed prior azole or echinocandin therapy.

**Keywords:** amphotericin b colloidal dispersion, clinical response, invasive fungal infections, safety, salvage therapy

## Introduction

Invasive fungal disease (IFD) refers to the infiltration of fungi into human tissues and the bloodstream, leading to inflammation, tissue damage, and organ dysfunction. Recent studies estimate that approximately 6.5 million cases of IFD occur annually, resulting in 3.8 million deaths, with around 2.5 million directly attributable to the infection.[1] IFD primarily affects immunocompromised individuals, with an incidence of 2.0% among patients with hematologic malignancies undergoing chemotherapy and 6.3% in recipients of allogeneic hematopoietic stem cell transplants.[2] Furthermore, with the rapid development of cellular immunotherapies, the incidence of IFD in patients receiving chimeric antigen receptor T (CAR-T) cell therapy has emerged as a growing concern.[3] Regarding the spectrum of pathogens, *Candida* species remain the most prevalent cause of IFD globally, with candidemia being the most frequent clinical presentation associated with significant morbidity.[1,4] Among the causative pathogens, invasive aspergillosis (IA) and invasive mucormycosis (IM) are particularly lethal, with mortality rates ranging from 30% to 70% for IA and 35% to

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96% for IM.[5,6] Additionally, severe influenza and COVID-19 have significantly increased the incidence of invasive pulmonary aspergillosis,[7] while COVID-19 alone has markedly elevated the rates of *Candida* bloodstream infections and mucormycosis.[8]

The rising morbidity and mortality rates associated with IFD can be attributed to several factors, including diagnostic challenges, limited availability of effective antifungal therapies, the emergence of drug-resistant fungal strains, and the increasing size of the at-risk population, such as immunocompromised individuals. Current antifungal treatments are limited to three classes based on their molecular targets: ergosterol inhibitors (azoles and polyenes), 1,3-β-D-glucan synthase (GS) component FKS1 inhibitors (echinocandins and the newly approved ibrexafungerp), and flucytosine, which is typically used in combination with polyenes to disrupt RNA and DNA metabolism.[9] Amphotericin B (AmB) remains a cornerstone of antifungal therapy due to its broad-spectrum activity, low resistance rates, and strong clinical and pharmacological efficacy.[10]

The clinical use of amphotericin B deoxycholate (DAmB) is constrained by its infusion-related reactions (IRRs) and nephrotoxicity. To mitigate these adverse effects and enable higher dosing, various lipid formulations of amphotericin B have been developed. These include amphotericin B colloidal dispersion (ABCD, also known as amphotericin B cholesteryl sulfate complex, Amphocil™, or Amphotec™), amphotericin B lipid complex (Abelcet™), and liposomal amphotericin B (AmBisome™).[11] Currently, the availability of lipid formulations of amphotericin B in China is limited. However, since the approval of ABCD (manufactured by CSPC Zhongqi Pharmaceutical Technology Co., Ltd, Shijiazhuang, China) by the National Medical Products Administration on March 30, 2021, its use as an antifungal therapy has increased. This rise in utilization is attributed to its relatively lower nephrotoxicity compared to DAmB and its cost-effectiveness.[12]

To date, the efficacy profiles of ABCD have been largely derived from Western populations or strictly controlled clinical trials, which may not fully represent the genetic backgrounds or healthcare contexts of Asian patients.[13–17] Moreover, current real-world evidence remains fragmented and confined to highly specific cohorts, failing to capture the heterogeneity of patients encountered in routine practice.[12,18] This study addresses these gaps by presenting one of the first comprehensive evaluations of ABCD as salvage therapy within the Chinese population. By analyzing a broad spectrum of IFD patients who failed prior triazole or echinocandin therapy, we aim to clarify the clinical positioning of ABCD in resource-limited settings and establish its safety and efficacy profile in a diverse, real-world cohort.

# Materials and Methods

## Patients and Study Design

This single-center, retrospective, real-world study analyzed clinical data from patients with IFD who were treated with Amphotericin B Colloidal Dispersion (ABCD; The CSPC Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China) between September 2021 and February 2024.

Inclusion Criteria: Patients, encompassing both adult and pediatric age groups, who experienced treatment failure or drug intolerance with prior triazole or echinocandin antifungal therapy and were subsequently treated with ABCD were included in the study. This cohort comprised individuals with proven, probable, or possible IFD.

Exclusion Criteria: The following patients were excluded: 1) Patients with incomplete medical records or other factors that hindered the assessment of clinical efficacy; 2) Patients who received ABCD for less than three days; 3) Patients with undefined IFD; 4) Patients whose clinical response to prior antifungal treatments could not be assessed.

Ethical approval for this study was granted by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No.: TJ-IRB202509041). The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee waived the requirement for informed consent given the retrospective study design. All data were anonymized to maintain patient confidentiality.

## Evaluations and Definitions

Patient clinical data were meticulously extracted from the hospital's official Electronic Medical Records (EMR) system. The data collected included demographics (age, gender, weight), underlying conditions, clinical manifestations, infection

sites, imaging findings, laboratory results, prior antifungal treatments, duration of ABCD therapy, and other relevant factors.

According to the revised 2020 European Organization for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) criteria,[19] patients with IFD were classified into three categories: proven, probable, and possible. Proven IFD required histopathological or microbiological evidence from sterile site specimens. Probable IFD was defined by the presence of at least one host factor (eg, allogeneic hematopoietic stem cell transplantation), one clinical feature (eg, dense or well-circumscribed lesions on chest computed tomography), and mycological evidence (eg, mold culture from sputum). Possible IFD was diagnosed in cases meeting the host factor and clinical feature criteria but lacking mycological evidence. Of note, patients with mycological evidence who did not meet the host factor criteria were classified as Possible IFD to distinguish them from the classical host-factor-positive Probable cases. Additionally, metagenomic next-generation sequencing (mNGS) was utilized as a strong microbiological clue when conventional diagnostics were inconclusive. Although not yet incorporated into the 2020 EORTC/MSGERC criteria, mNGS is increasingly accepted as a diagnostic tool for IFD in China and was considered by the expert panel. Antifungal therapy was classified as targeted therapy for proven/probable IFD or diagnostic-driven therapy for possible IFD, corresponding to the EORTC diagnostic status shown in Figure 1.

Based on the efficacy criteria for IFD treatment,[20] the observation period was set at 6 weeks following the initiation of ABCD therapy. Specifically, efficacy was assessed within this period: for patients continuing ABCD up to 6 weeks, assessment was performed on day 42; for those who discontinued ABCD earlier, assessment was conducted at the end of ABCD therapy.

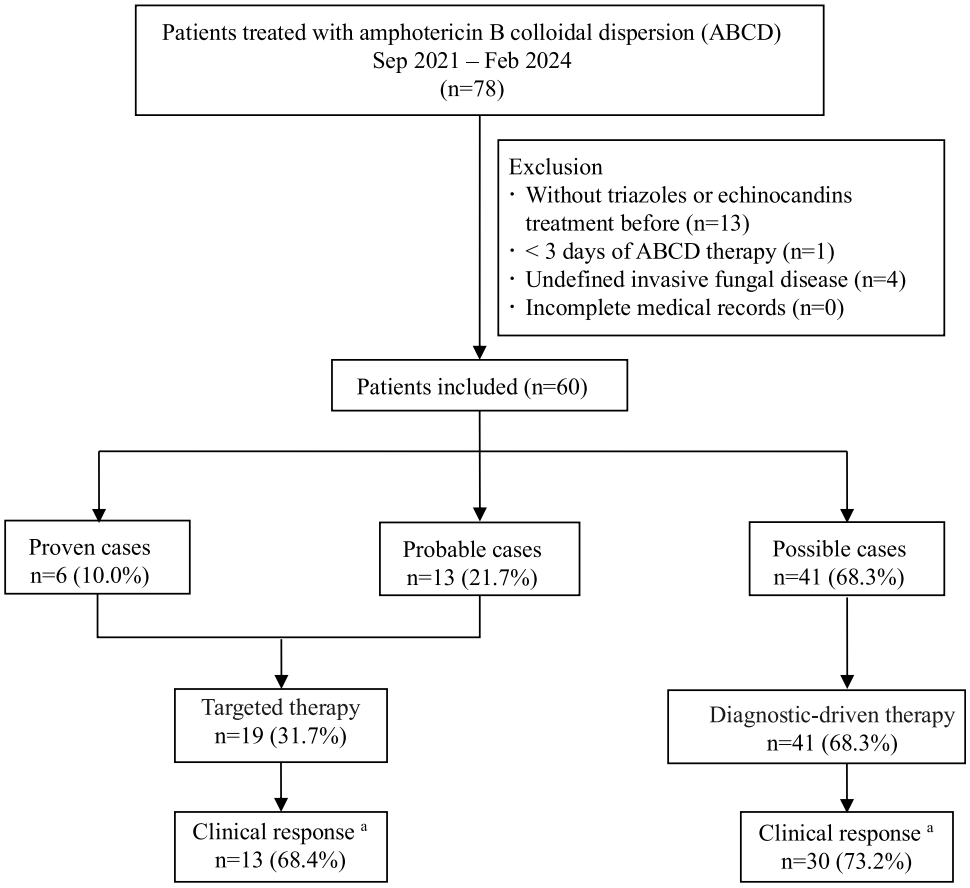


**Figure 1** Flowchart of patients included and excluded in this study. [a]Clinical response of ABCD therapy.
**Abbreviation**: ABCD, amphotericin B colloidal dispersion.


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The primary clinical outcome was defined as the clinical response, while the secondary outcomes included all-cause mortality at 30 days and 90 days (counted from the end of ABCD therapy). Based on clinical, radiological, and mycological criteria,[20] the clinical response to antifungal therapy was categorized as follows: 1) Complete remission (CR): Survival within the specified observation period, with complete resolution of IFD-related symptoms, signs, and radiological abnormalities, along with microbiological evidence of fungal clearance. 2) Partial remission (PR): Survival within the observation period, with improvement in IFD-related symptoms, signs, and radiological abnormalities, as well as quantitative laboratory markers indicating a reduced fungal burden or clearance. 3) Stable disease (SD): Survival within the observation period, with minimal or no improvement in IFD based on clinical, radiological, and mycological evaluations, but without evidence of disease progression. 4) Progressive disease (PD): Evidence of worsening fungal disease, determined through a combination of clinical, radiological, and microbiological evaluations. 5) Death: Death during the specified evaluation period, regardless of cause. CR and PR were defined as treatment success, while SD, PD, and death were considered treatment failure. The diagnostic criteria and clinical outcomes of all patients were reviewed by a data review panel composed of a respiratory specialist, an infectious disease specialist, a hematologist, and a radiologist.

Adverse events during ABCD treatment were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Versions 4.0 and 5.0. Hepatotoxicity was defined as an increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels to more than three times the upper limit of normal (ULN) for patients with normal baseline values, or 1.5 to 3.0 times the baseline value for those with abnormal baseline values. Nephrotoxicity was classified into four grades based on serum creatinine (SCr) levels: Grade 1, an increase in SCr of more than 26.52 μmol/L (0.3 mg/dL) or 1.5 to 2 times the baseline value; Grade 2, an increase of 2 to 3 times the baseline value; Grade 3, an increase of more than three times the baseline value or above 353.6 μmol/L (4.0 mg/dL); and Grade 4, life-threatening nephrotoxicity requiring dialysis.

## Statistical Analysis

Statistical analyses and data visualization were conducted using SPSS 25.0 and GraphPad Prism 9.5.0. Continuous variables were described as mean ± standard deviation or median [interquartile range (IQR, 25th–75th percentiles)], with differences analyzed using the Mann–Whitney *U*-test. Categorical variables were presented as counts and percentages, with differences evaluated by the chi-square test and Fisher's exact test. Clinical outcomes were assessed using 95% confidence intervals (95% CI), and a $p$-value $< 0.05$ was considered statistically significant.

# Results

## Patient Characteristics

A total of 78 IFD patients who were hospitalized at our center and received ABCD therapy between September 2021 and February 2024 were identified through the hospital's electronic database. Of these, 13 patients had not received prior treatment with triazoles or echinocandins, 1 patient received ABCD for less than 3 days, and 4 patients were not confirmed to have IFD. Consequently, 60 patients were included in the study. A flowchart of patient inclusion and exclusion is presented in Figure 1, and the demographic data for all included patients are shown in Table 1.

The median age of the patients was 50 years (IQR: 31–57), and the median weight was 60 kg (IQR: 51–66), with 33 patients (55.0%) being female. Underlying conditions included hematologic malignancies in 36 patients (60.0%), type 2 diabetes mellitus in 6 patients (10.0%), and kidney transplantation in 4 patients (6.7%), among others. Twenty patients (33.3%) presented with disseminated infection, and 40 (66.7%) with localized infection. Overall, the most common site of infection was the lung (47/60). The predominant pathogens were *Aspergillus* spp. (23/60), followed by *Candida* spp. (8/60), *Rhizopus* spp. (7/60), *Cunninghamella elegans* (3/60), *Mucor* spp. (1/60), and *Cryptococcus neoformans* (2/60).

Prior to ABCD treatment, 86.7% of patients (52/60) received monotherapy with either triazoles or echinocandins, with triazoles being the predominant choice (44/60, 73.3%) and echinocandins used in 8 patients (13.3%). In contrast, 13.3% of patients (8/60) underwent combination therapy, all of which involved voriconazole (VOR) in combination with another antifungal agent. Overall, VOR was the most frequently administered antifungal, used in 75.0% of patients (45/

**Table 1** Main Demographic and Clinical Characteristics of the Study Patients

| Variable | | Statistic |
|---|---|---|
| Age (year) | Median (IQR) | 50 (31 to 57) |
| Sex, n (%) | Male | 27 (45.0%) |
| | Female | 33 (55.0%) |
| Weight (kg) | Median (IQR) | 60 (51 to 66) |
| Underlying disease, n (%) | No | 3 (5.0%) |
| | Yes | 57 (95.0%) |
| | Hematologic malignancies [a] | 36 (60.0%) |
| | Type 2 diabetes mellitus | 6 (10.0%) |
| | Kidney transplantation | 4 (6.7%) |
| | Solid tumors [b] | 3 (5.0%) |
| | Others [c] | 8 (13.3%) |
| Site of infection [d], n (%) | Localized infection | 40 (66.7%) |
| | Pulmonary | 34 (56.7%) |
| | Sinuses | 2 (3.3%) |
| | Pulmonary/ Sinuses | 2 (3.3%) |
| | Brain | 2 (3.3%) |
| | Disseminated infection | 20 (33.3%) |
| | Pulmonary/ Blood | 8 (13.3%) |
| | Pulmonary/ Blood/ Urinary tract | 2 (3.3%) |
| | Pulmonary/ Peritoneum | 1 (1.7%) |
| | Kidney/ Blood | 1 (1.7%) |
| | Blood | 8 (13.3%) |
| Pathogen, n (%) | *Aspergillus* | 23 (38.3%) |
| | *Aspergillus fumigatus* | 18/23 |
| | *Aspergillus flavus* | 5/23 |
| | *Aspergillus oryzae* | 3/23 |
| | *Aspergillus terreus* | 1/23 |
| | *Aspergillus chevalieri* | 1/23 |
| | *Rhizopus* | 7 (11.7%) |
| | *Rhizopus microsporus* | 4/7 |
| | *Rhizopus oryzae* | 2/7 |
| | *Rhizopus delemar* | 1/7 |
| | *Mucor* | 1 (1.7%) |
| | *Candida* | 8 (13.3%) |
| | *Candida parapsilosis* | 4/8 |
| | *Candida albicans* | 5/8 |
| | *Cryptococcus* | 2 (3.3%) |
| | *Cryptococcus neoformans* | 2/2 |
| | Others | 5 (8.3%) |
| | *Cunninghamella elegans* | 3/5 |
| | *Pneumocystis jirovecii* | 1/5 |
| | *Aureobasidium pullulans* | 1/5 |
| | *Cladosporium* | 1/5 |
| | Unknown | 24 (40.0%) |
| Prior antifungal therapy, n (%) | Monotherapy | 52 (86.7%) |
| | Triazoles | 44 (73.3%) |
| | Voriconazole | 37 (61.7%) |
| | Posaconazole | 6 (10.0%) |
| | Fluconazole | 1 (1.7%) |
| | Echinocandins | 8 (13.3%) |
| | Micafungin | 7 (11.7%) |
| | Caspofungin | 1 (1.7%) |

(*Continued*)


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**Table 1** (Continued).

| Variable | | Statistic |
|---|---|---|
| | Combination therapy | 8 (13.3%) |
| | Voriconazole + Caspofungin | 4 (6.7%) |
| | Voriconazole + Micafungin | 3 (5.0%) |
| | Voriconazole + Flucytosine | 1 (1.7%) |

**Notes**: [a]Hematologic malignancies included: multiple myeloma, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, acute myeloid leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, follicular lymphoma, and natural/killer T-cell lymphoma. [b]Solid tumors included: ovarian cancer, lung cancer, and hepatocellular carcinoma. [c]Others included: aplastic anemia, stage 5 chronic kidney disease, depression, hemophagocytic syndrome, interstitial pneumonia, and primary biliary cirrhosis. [d]Infection was defined as disseminated when ≥ 2 non-contiguous sites or bloodstream were involved.
**Abbreviation**: IQR, interquartile range.

60), followed by micafungin in 16.7% of patients (10/60). In addition, the median duration of prior antifungal therapy was 10.5 days (IQR: 7–17).

Therapeutic drug monitoring (TDM) was routinely performed for patients on azole therapy, with trough concentrations confirmed to be within therapeutic limits. Prior treatment failure was primarily defined as clinical progression (lack of efficacy). While some patients experienced mild, tolerable adverse events (eg, mild liver function abnormalities in the context of polypharmacy, or transient visual disturbances/body pain with voriconazole), these events did not lead to treatment discontinuation. No prior antifungal treatment was stopped solely due to confirmed toxicity.

## ABCD Therapy

As detailed in Table 2, of the 60 patients included in the study, 65.0% (39 patients) received ABCD monotherapy, while 35.0% (21 patients) were treated with ABCD in combination with another antifungal agent. The most common combinations were with voriconazole (VOR) (8/21) or posaconazole (POS) (8/21). No patients received three or more antifungal agents simultaneously. Notably, all 8 patients who received a combination of ABCD and VOR had previously been treated with VOR. Of the 8 patients receiving ABCD and POS, 5 had a history of POS treatment, while 3 had previously used VOR.

The median duration of ABCD treatment was 9 days (IQR: 6–22). Among the 60 patients, 61.7% (37/60) were treated for 14 days or less. Only two patients, Case 8 and Case 38, received treatment for more than 42 days (see Table 3). Twelve patients (20.0%) received the fixed dose from the start without dose escalation, while the remaining 48 patients typically started with a dose of 50 mg, which was increased to 100–250 mg within 2–4 days. However, four patients within this group received lower initial doses, primarily driven by pediatric age and low body weight in most cases. Detailed patient characteristics for the three most representative cases are as follows: Case 31 (7 years old, 25 kg) and Case 42 (2 years, 10 months old, 16 kg) were started at 25 mg, and Case 41 (8 years old, 20 kg) was started at 18 mg. The remaining patient, who was older and received a 10 mg starting dose, was treated under specific, highly individualized clinical judgment and the dose was subsequently rapidly escalated.

Most patients (96.7%) received dexamethasone premedication 30 minutes prior to the ABCD infusion to reduce infusion-related reactions (IRRs). Only Cases 31 and 59 (see Table 3) did not receive premedication, but no significant IRRs were observed in these cases. The infusion duration of ABCD ranged from 4 to 12 hours, with a median infusion time of 8 hours. Reasons for discontinuing ABCD treatment included clinical or radiological improvement (31/60), transfer to another hospital for continued ABCD therapy (Cases 29, 36, 43, 44, 46, 56), lack of significant clinical improvement (Cases 1, 5, 18, 25, 45, 57), intolerable adverse events (Cases 3, 7, 38, 41, 53), patient discontinuation (Cases 12, 17, 52, 60), patient death (Cases 2, 11, 13), disease progression (Cases 15, 45, 59), and drug shortage (Cases 9 and 37).

**Table 2** Amphotericin B Colloidal Dispersion (ABCD) Treatment

| Variable | | Statistic |
|---|---|---|
| ABCD treatment, n (%) | Monotherapy | 39 (65.0%) |
| | Combination therapy | 21 (35.0%) |
| | Voriconazole | 8/21 |
| | Posaconazole | 8/21 |
| | Fluconazole | 1/21 |
| | Micafungin | 2/21 |
| | Flucytosine | 2/21 |
| ABCD therapy duration, d | Median (IQR) | 9 (6 to 22) |
| ABCD therapy duration, n (%) | 3 ~ 7 days | 23 (38.3%) |
| | 8 ~ 14 days | 14 (23.3%) |
| | 15 ~ 41 days | 21 (35.0%) |
| | ≥ 42 days | 2 (3.3%) |
| Ascending dose, n (%) | No | 12 (20.0%) |
| | Fixed dose 50mg | 1/12 |
| | Fixed dose 100mg | 5/12 |
| | Fixed dose 150mg | 6/12 |
| | Yes | 48 (80.0%) |
| | Initial dose 50mg | 44/48 |
| | Initial dose 25mg | 2/48 |
| | Initial dose 18mg | 1/48 |
| | Initial dose 10mg | 1/48 |
| Ascending time to maximum dose, d | Median (IQR) | 3 (2 to 3) |
| Maintenance of maximum dose, mg | Median (IQR) | 150 (100 to 150) |
| Duration of infusion, h | Median (IQR) | 8 (8 to 10) |
| Premedication, n (%) | No | 2 (3.3%) |
| | Yes | 58 (96.7%) |
| | Dexamethasone | 32/58 |
| | Dexamethasone + Promethazine | 26/58 |
| Reasons for termination of treatment, n (%) | Clinical or radiological improvement | 31 (51.7%) |
| | Transfer to another hospital | 6 (10.0%) |
| | Lack of clinical improvement | 6 (10.0%) |
| | Intolerable adverse events | 5 (8.3%) |
| | Patient discontinuation | 4 (6.7%) |
| | Patient death | 3 (5.0%) |
| | Disease progression | 3 (5.0%) |
| | Drug shortage | 2 (3.3%) |

**Abbreviations**: ABCD, amphotericin B colloidal dispersion; IQR, interquartile range.

## Efficacy Analysis

Overall, 71.7% of patients (43/60; 95% CI: 59.2% to 81.5%) achieved clinical remission. As detailed in Table 4, the clinical response rate was slightly lower in female patients compared to male patients (23/33 vs 20/27), though this difference was not statistically significant ($p$ = 0.708). Clinical response rates did not vary significantly based on diagnostic status, underlying diseases, or infection sites. Additionally, no significant differences were observed in response rates related to the method of ABCD administration, including treatment duration and dose escalation. Prior use of antifungal agents also did not affect the clinical response rate of ABCD salvage therapy. Additionally, all-cause 30-day and 90-day mortality were 26.7% (16/60) and 36.7% (22/60), respectively. Furthermore, Kaplan-Meier overall survival analysis demonstrated a statistically significant difference in survival probability between patients who achieved clinical remission and those who did not (Log-rank P = 0.005) (Figure 2).

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**Table 3** Characteristics of IFD Cases

| No. | Gender | Age | Underlying Disease | Treatment Duration/d | Combination | Outcome | Site of Infection | Key Evidence for IFD Diagnosis | Diagnosis | Prior Antifungal Therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 50 | Kidney transplantation | 9 | VOR | SD | Pulmonary | CT; *Aspergillus fumigatus* determined via sputum culture; *Pneumocystis jirovecii* determined via BALF mNGS | Probable | VOR |
| 2 | Male | 59 | Kidney transplantation | 4 | VOR | Death | Pulmonary/ Blood | CT; *Aspergillus fumigatus* determined via sputum culture; *Rhizopus microsporus* determined via blood mNGS | Probable | VOR |
| 3 | Male | 52 | Kidney transplantation | 8 | POS | PR | Sinuses | Fungal hyphae observed in the pathological sinus tissue; *Rhizopus oryzae* determined via sinus tissue culture | Proven | VOR |
| 4 | Female | 45 | Kidney transplantation | 21 | – [a] | PR | Kidney/ Blood | *Candida parapsilosis* determined via blood culture | Proven | Caspofungin + VOR |
| 5 | Male | 43 | DLBCL | 5 | – [a] | SD | Blood | *Aspergillus chevalieri* determined via blood mNGS | Possible | Micafungin |
| 6 | Male | 12 | AML | 17 | – [a] | PR | Pulmonary/ Blood | CT; *Aspergillus flavus* determined via blood mNGS | Probable | VOR |
| 7 | Male | 57 | HCC | 7 | – [a] | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via sputum culture | Probable | VOR + Micafungin |
| 8 | Female | 60 | AML | 82 | POS | PR | Pulmonary | CT | Possible | VOR |
| 9 | Female | 51 | Ovarian cancer | 7 | – [a] | PR | Pulmonary/ Urinary tract/ Blood | CT; *Candida parapsilosis* determined via urine mNGS, *Cryptococcus neoformans /Candida parapsilosis* determined via blood mNGS | Probable | VOR |
| 10 | Male | 21 | B-ALL | 23 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 11 | Male | 77 | Type 2 diabetes mellitus | 14 | – [a] | Death | Pulmonary | CT; *Candida parapsilosis* determined via BALF culture; *Candida albicans /Candida parapsilosis* determined via sputum culture | Possible | Micafungin |
| 12 | Female | 50 | MM | 19 | – [a] | PD | Pulmonary | CT | Possible | VOR |
| 13 | Female | 42 | None [b] | 16 | Micafungin | Death | Pulmonary/ Blood | *Candida albicans* determined via blood culture; *Rhizopus microspores /Aspergillus fumigatus* determined via blood mNGS | Proven | VOR |
| 14 | Female | 15 | AML | 9 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 15 | Male | 25 | AML | 14 | – [a] | PD | Pulmonary | CT | Possible | VOR |
| 16 | Male | 60 | CLL | 10 | – [a] | PR | Pulmonary | CT | Possible | VOR + Caspofungin |
| 17 | Female | 56 | AML | 4 | VOR | SD | Pulmonary/ Blood | CT; *Aspergillus fumigatus* determined via blood mNGS | Probable | VOR |
| 18 | Female | 55 | SAA | 22 | – [a] | SD | Pulmonary/ Sinuses | CT | Possible | VOR |
| 19 | Female | 54 | AML | 6 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 20 | Male | 26 | T-LBL | 15 | – [a] | PR | Pulmonary | CT | Possible | VOR |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Female | 57 | MM | 8 | – [a] | PR | Blood | *Aspergillus fumigatus* determined via blood mNGS | Possible | Micafungin |
| 22 | Male | 35 | AML | 5 | – [a] | PR | Blood | *Aspergillus fumigatus* determined via blood mNGS | Possible | Micafungin |
| 23 | Female | 57 | AML | 20 | – [a] | PR | Blood | *Rhizopus microsporus* determined via blood mNGS | Possible | VOR |
| 24 | Female | 54 | AML | 7 | POS | PR | Pulmonary | CT | Possible | POS |
| 25 | Female | 52 | AML | 12 | – [a] | SD | Pulmonary | CT | Possible | VOR |
| 26 | Female | 50 | AML | 35 | POS | PR | Pulmonary | CT | Possible | POS |
| 27 | Female | 34 | AML | 11 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 28 | Male | 24 | AML | 27 | POS | PR | Pulmonary | CT | Possible | POS |
| 29 | Male | 68 | AA | 11 | – [a] | PR | Pulmonary/ Blood | CT; *Aureobasidium pullulans /Cunninghamella elegans / Aspergillus fumigatus* determined via blood mNGS | Probable | POS |
| 30 | Female | 51 | ALL | 4 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 31 | Female | 7 | None [b] | 25 | Flucytosine | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via sputum culture | Possible | Micafungin |
| 32 | Female | 54 | AML | 6 | – [a] | SD | Blood | *Aspergillus oryzae /Aspergillus flavus* determined via blood mNGS | Possible | Caspofungin |
| 33 | Female | 56 | DLBCL | 30 | – [a] | PR | Pulmonary | CT | Possible | VOR + Caspofungin |
| 34 | Male | 68 | Interstitial pneumonia | 23 | – [a] | PR | Pulmonary/ Peritoneum | CT; *Candida parapsilosis* determined via perihepatic drainage fluid culture; *Aspergillus fumigatus /Aspergillus flavus* determined via BALF culture | Proven | Fluconazole |
| 35 | Male | 29 | FL | 9 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 36 | Female | 64 | ALL | 3 | POS | PR | Pulmonary | CT; *Cunninghamella elegans* determined via BALF mNGS | Probable | VOR |
| 37 | Male | 55 | PBC | 7 | Fluconazole | PR | Brain | *Candida albicans* determined via cerebrospinal fluid culture | Proven | Micafungin |
| 38 | Female | 11 | Type 2 diabetes mellitus | 62 | POS | PR | Blood/ Pulmonary/ Urinary tract | CT; *Candida albicans* determined via urine culture; *Rhizopus oryzae /Aspergillus fumigatus* determined via blood mNGS; *Aspergillus fumigatus /Aspergillus oryzae /Aspergillus flavus / Rhizopus oryzae* determined via BALF mNGS; *Rhizopus oryzae* determined via pleural effusion mNGS | Possible | POS |
| 39 | Female | 43 | CKD 5 | 35 | – [a] | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via BALF mNGS | Possible | VOR |
| 40 | Male | 37 | NKTL | 6 | VOR | PR | Blood | *Aspergillus terreus* determined via blood mNGS | Possible | VOR |
| 41 | Male | 8 | AML | 31 | – [a] | PR | Pulmonary/ Blood | CT; *Aspergillus oryzae /Aspergillus flavus* determined via blood mNGS | Probable | VOR |
| 42 | Male | 2 | ALL | 22 | – [a] | PR | Blood | *Aspergillus fumigatus* determined via blood mNGS | Possible | Micafungin |
| 43 | Female | 18 | Depression | 29 | Flucytosine | PR | Brain | *Cryptococcus neoformans* determined via cerebrospinal fluid culture | Proven | VOR |

(*Continued*)

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**Table 3** (Continued).

| No. | Gender | Age | Underlying Disease | Treatment Duration/d | Combination | Outcome | Site of Infection | Key Evidence for IFD Diagnosis | Diagnosis | Prior Antifungal Therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| 44 | Male | 37 | Type 2 diabetes mellitus | 34 | – [a] | PR | Sinuses/ Sphenoid sinus/ Ethmoid sinus | CT; *Candida albicans* determined via ocular secretions culture; *Candida albicans* /*Rhizopus delemar* determined via sinus tissue mNGS | Possible | VOR |
| 45 | Female | 18 | HPS | 7 | VOR | PD | Pulmonary | CT | Possible | VOR |
| 46 | Female | 62 | Type 2 diabetes mellitus | 7 | – [a] | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via BALF culture; *Aspergillus fumigatus* determined via sputum culture | Possible | Micafungin + VOR |
| 47 | Male | 23 | AML | 30 | – [a] | PR | Pulmonary/ Blood | CT; *Rhizopus microsporus* determined via blood mNGS | Probable | Micafungin + VOR |
| 48 | Male | 32 | Type 2 diabetes mellitus | 8 | Micafungin | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via BALF mNGS | Possible | VOR |
| 49 | Female | 38 | AML | 7 | – [a] | PR | Pulmonary | CT | Possible | Caspofungin + VOR |
| 50 | Female | 32 | AML | 3 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 51 | Male | 49 | AML | 17 | – [a] | PR | Blood | *Aspergillus fumigatus* determined via blood mNGS | Possible | VOR |
| 52 | Male | 66 | Lung cancer | 4 | VOR | SD | Pulmonary/ Blood | CT; *Cladosporium* determined via blood mNGS | Probable | VOR+ Flucytosine |
| 53 | Female | 55 | None [b] | 6 | VOR | SD | Pulmonary | CT; *Aspergillus fumigatus* determined via BALF culture | Possible | VOR |
| 54 | Female | 68 | Type 2 diabetes mellitus | 5 | VOR | PR | Pulmonary | CT; *Aspergillus fumigatus* determined via BALF mNGS | Possible | VOR |
| 55 | Female | 54 | AML | 7 | POS | PR | Pulmonary | CT | Possible | POS |
| 56 | Female | 64 | ALL | 3 | – [a] | PR | Pulmonary | CT; *Cunninghamella elegans* determined via BALF mNGS | Probable | VOR |
| 57 | Female | 55 | SAA | 22 | – [a] | SD | Pulmonary/ Sinuses | CT; *Mucor* determined via sputum culture | Probable | VOR |
| 58 | Male | 31 | AML | 8 | – [a] | PR | Pulmonary | CT | Possible | VOR |
| 59 | Female | 37 | AML | 13 | – [a] | PD | Pulmonary | CT | Possible | VOR |
| 60 | Male | 62 | AML | 3 | – [a] | SD | Pulmonary | CT | Possible | VOR |

**Notes**: [a] "-" denotes patients receiving ABCD monotherapy. [b] "None" indicates that the patient had no recorded underlying disease.

**Abbreviations**: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BALF, bronchoalveolar lavage fluid; B-ALL, B-cell acute lymphoblastic leukemia; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CR, complete remission; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCC, hepatocellular carcinoma; HPS, hemophagocytic syndrome; IFD, invasive fungal disease; mNGS, metagenomic next-generation sequencing; MM, multiple myeloma; NKTL, natural/killer T-cell lymphoma; PD, progression disease; PBC, primary biliary cholangitis; POS, posaconazole; PR, partial remission; SAA, severe aplastic anemia; SD, stable disease; T-LBL, T-cell lymphoblastic lymphoma; VOR, voriconazole.

**Table 4** Characteristics and Analysis of Patients Presenting Clinical Response

| Characteristics | Clinical Response Rate, % (n) | 95% CI | *p*-value |
|---|---|---|---|
| Sex | | | 0.708 |
| Female | 69.7 (23/33) | 52.7 to 82.6 | |
| Male | 74.1 (20/27) | 55.3 to 86.8 | |
| Diagnosis of IFD | | | 0.659 |
| Proven | 83.3 (5/6) | 43.6 to 99.1 | |
| Probable | 61.5 (8/13) | 35.5 to 82.3 | |
| Possible | 73.2 (30/41) | 58.1 to 84.3 | |
| Underlying diseases | | | 0.198 |
| Hematologic malignancies | 77.8 (28/36) | 61.9 to 88.3 | |
| Others | 62.5 (15/24) | 42.7 to 78.8 | |
| Site of infection | | | 0.839 |
| Localized infection | 72.5 (29/40) | 57.2 to 83.9 | |
| Disseminated infection | 70.0 (14/20) | 48.1 to 85.4 | |
| Pathogen | | | – [a] |
| IA | 69.6 (16/23) | 49.1 to 84.4 | |
| IC | 75.0 (6/8) | 40.9 to 95.6 | |
| IM [b] | 72.7 (8/11) | 43.4 to 90.2 | |
| Ascending dose | | | 0.943 |
| No | 66.7 (8/12) | 39.1 to 86.2 | |
| Yes | 72.9 (35/48) | 59.0 to 83.4 | |
| ABCD therapy duration | | | 0.239 |
| 3 ~ 7 days | 69.6 (16/23) | 49.1 to 84.4 | |
| 8 ~ 14 days | 57.1 (8/14) | 32.6 to 78.6 | |
| ≥15 days | 82.6 (19/23) | 62.9 to 93.0 | |
| Prior antifungal therapy | | | |
| Triazoles Monotherapy | 70.5 (31/44) | 55.8 to 81.8 | 0.529 |
| Echinocandins Monotherapy | 62.5 (5/8) | 30.6 to 86.3 | |
| Combination therapy | 87.5 (7/8) | 52.9 to 99.4 | |
| Voriconazole | 68.9 (31/45) | 54.3 to 80.5 | – [a] |
| Posaconazole | 100.0 (6/6) | 61.0 to 100.0 | |
| Micafungin | 80.0 (8/10) | 49.0 to 96.4 | |
| Caspofungin | 80.0 (4/5) | 37.6 to 99.0 | |
| ABCD combination therapy | | | 0.528 |
| No | 74.4 (29/39) | 58.9 to 85.4 | |
| Yes | 66.7 (14/21) | 45.4 to 82.8 | |
| ABCD + Voriconazole | 25.0 (2/8) | 4.4 to 59.0 | – [c] |
| ABCD + Posaconazole | 100.0 (8/8) | 67.6 to 100.0 | |

**Notes**: [a]The *p*-values were unavailable as the subgroups being compared were not mutually exclusive. [b]Invasive mucormycosis (IM) subgroup (n=11) includes all infections caused by the order Mucorales: *Rhizopus microsporus* (n=4), *Rhizopus oryzae* (n=2), *Rhizopus delemar* (n=1), *Mucor* species (n=1), and *Cunninghamella elegans* (n=3). [c]The *p*-value was not provided due to the small sample size and baseline imbalances.
**Abbreviations**: ABCD, amphotericin B colloidal dispersion; CI, confidence interval; IA, invasive aspergillosis; IC, invasive candidiasis; IFD, invasive fungal disease; IM, invasive mucormycosis.

As shown in Table 4, the clinical response rates for ABCD monotherapy and combination therapy were 74.4% (29/39) and 66.7% (14/21), respectively, with no statistically significant difference ($p = 0.528$). Of note, ABCD combined with VOR had a clinical response rate of only 25% (2/8), whereas ABCD combined with POS achieved a 100% response rate (8/8), as illustrated in Figure 3. However, the small sample size and baseline imbalances precluded further analysis.

## Adverse Events

According to the electronic medical records, only Case 24, who had received 5mg dexamethasone and 25mg promethazine as premedication 30 minutes prior to each ABCD infusion, experienced IRRs. On the second day of infusion, the


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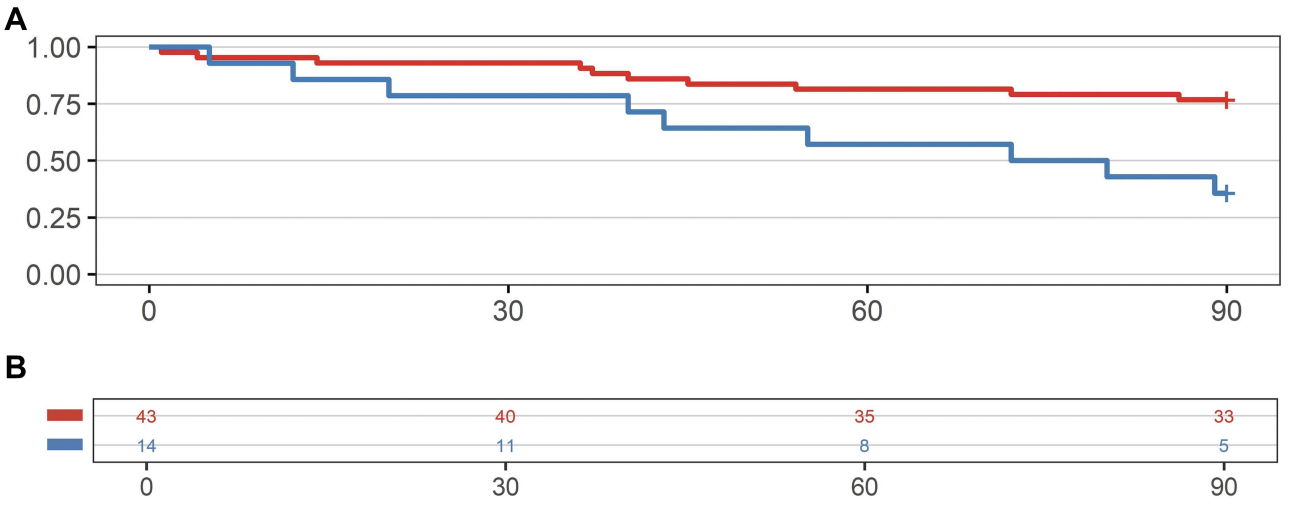


**Figure 2** Kaplan-Meier overall survival curves based on clinical response. (**A**) Overall survival by Outcome. The X-axis indicates Time (Days). The Y-axis indicates Survival Probability. The red line represents patients who achieved clinical remission. The blue line represents patients who did not achieve clinical remission (non-remission). The difference in overall survival between the two groups was statistically significant (Log rank test: P = 0.005). (**B**) Number at Risk. The X-axis indicates Time (Days). The Y-axis indicates Outcome. The top row of numbers corresponds to the remission group (red line), and the bottom row of numbers corresponds to the non-remission group (blue line).

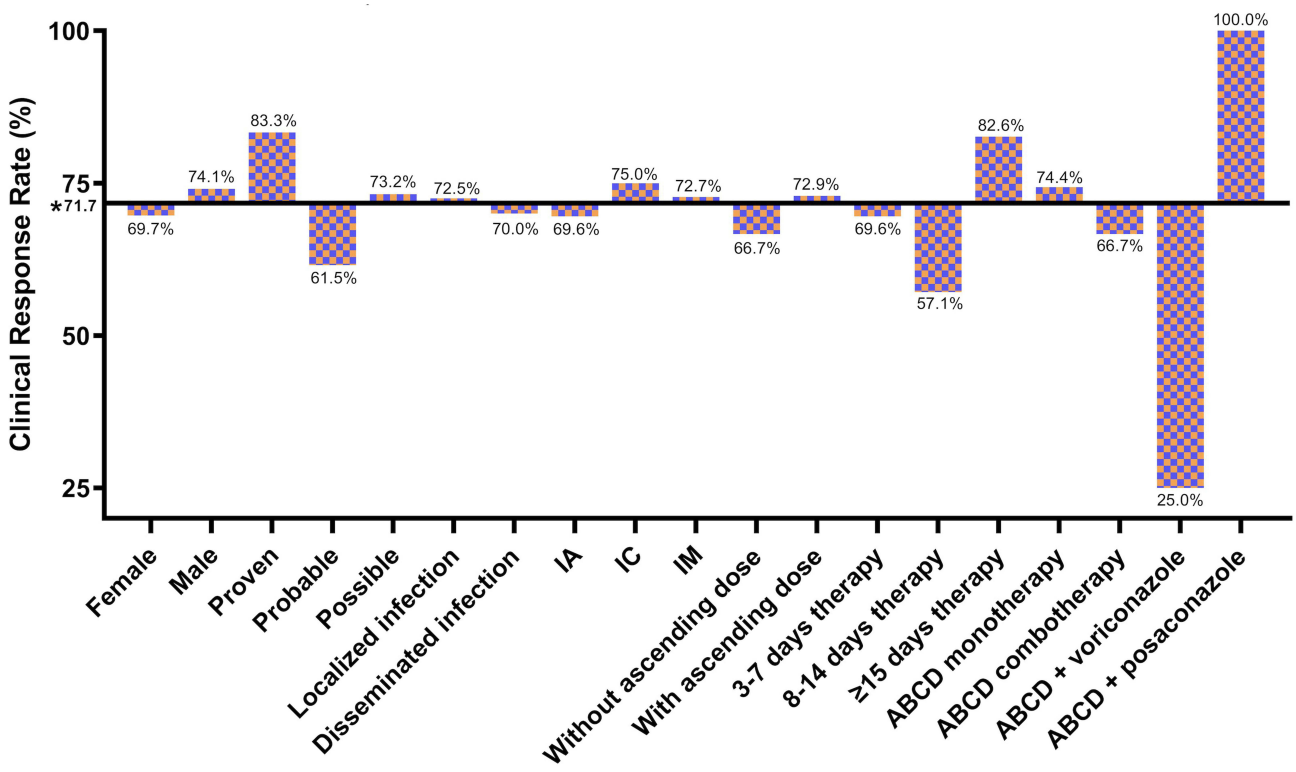


**Figure 3** Clinical response rates in different subgroups of cases. *Overall clinical response rate in all cases.
**Abbreviations**: ABCD, amphotericin B colloidal dispersion; IA, invasive aspergillosis; IC, invasive candidiasis; IM, invasive mucormycosis.

patient exhibited symptoms of palpitations and trembling, with the infusion rate set at 50 mL/h (100 mg of ABCD diluted in 500 mL of 5% dextrose solution). These symptoms alleviated after reducing the infusion rate. On the third day, the infusion continued at the same rate of 50 mL/h (150 mg of ABCD diluted in 500 mL of 5% dextrose solution), and no significant adverse reactions were observed.


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A total of 5 patients discontinued ABCD treatment due to adverse events: 1) Case 3 experienced an increase in SCr to 226 μmol/L and a significant drop in platelet count to 88 × $10^9$/L. Following discontinuation of ABCD, the patient's platelet count improved to 113 × $10^9$/L, but SCr levels showed no significant improvement. Although the combination of kidney injury and thrombocytopenia raised suspicion for microangiopathic hemolytic anemia (MAHA) or Hemolytic Uremic Syndrome (HUS), key markers for hemolysis, including Lactate Dehydrogenase (LDH) and indirect bilirubin, were within normal limits. The absence of hemolysis made the diagnosis of HUS/MAHA unlikely, and the event was classified as isolated drug toxicity. 2) Case 7 developed unexplained retinal bleeding and generalized myalgia, suspected to be related to ABCD. Symptoms improved after discontinuation of ABCD and administration of fresh frozen plasma. 3) Case 38 had an increase in SCr to 170 μmol/L, suspected to be caused by ABCD. Following discontinuation, SCr levels decreased to 123 μmol/L. 4) Case 41 experienced persistent hypokalemia, with the lowest potassium level recorded at 2.3 mmol/L. After stopping the drug and administering potassium supplements, potassium levels gradually returned to normal. 5) Case 53 presented with unexplained recurrent high fever (maximum 40.2°C) between the 4th and 6th day of ABCD treatment. Drug fever was suspected, leading to the discontinuation of ABCD. The fever decreased to 38.0°C after stopping the drug. Unfortunately, the patient died the following day due to congestive heart failure.

Overall, 13.3% of patients (8/60; 95% CI: 6.9% to 24.2%) experienced hepatotoxicity after ABCD treatment, all classified as mild hepatic function abnormalities. Regarding nephrotoxicity, 23.3% of patients (14/60; 95% CI: 14.4% to 35.4%) exhibited renal impairment. Among these, 8 patients had Grade 1 nephrotoxicity, and 5 patients had Grade 2 nephrotoxicity. Notably, Case 53 experienced a 6.3-fold increase in SCr from baseline, reaching 324 μmol/L.

## Sensitivity Analyses of Clinical Response and Mortality

In the sensitivity analyses limited to proven/probable IFD cases (n = 19), the clinical response rate was 68.4% (13/19), closely aligning with the overall cohort (71.7%, $p = 0.785$). All-cause 30-day mortality in this subgroup was 31.6% (6/19), slightly higher than in the full cohort (26.7%, 16/60, $p = 0.676$). Similarly, all-cause 90-day mortality was 42.1% (8/19) in the restricted subgroup versus 36.7% (22/60) in the full cohort ($p = 0.670$). None of these differences reached statistical significance, indicating consistent outcomes in patients with proven or probable IFD.

The observed discrepancy between the 90-day all-cause mortality and the clinical response rate was further clarified by sensitivity analysis. Among the 43 patients who achieved clinical remission, the 30-day all-cause mortality was 9.3% (4/43), compared to 70.6% (12/17) among those without ($p < 0.001$). Likewise, the 90-day all-cause mortality was 23.2% (10/43) in patients with clinical remission versus 70.6% (12/17) in those who did not ($p = 0.001$). These findings support the consistency between clinical efficacy and survival benefit.

# Discussion

Our study demonstrated a clinical response rate of 71.7% (95% CI: 59.2% to 81.5%) for ABCD salvage therapy in patients with IFD who had previously failed triazole or echinocandin treatments. This efficacy is comparable to or slightly higher than that reported in previous studies, which indicated an overall efficacy range of 34% to 70% for ABCD therapy.[13–18,21–23] Notably, initial ABCD treatment often exhibited higher clinical response rates compared to salvage therapy.[22] However, there is a lack of updated research comparing the efficacy of ABCD as a first-line versus salvage therapy. Early diagnosis and effective initial treatment have been emphasized as critical factors in improving outcomes, as salvage therapy often shows less favorable results.[24] Early and appropriate antifungal therapy is crucial for reducing IFD-related morbidity and mortality.[25] Therefore, Antifungal Stewardship (AF Stewardship) programs are considered essential for mitigating the challenges of increasing antifungal use, rising costs, and emerging resistance, with recognized benefits including decreasing inappropriate prescriptions.[26]

Gender did not significantly impact clinical response rates in our study, compared with findings from recent research that suggested a higher incidence of certain IFDs in men compared to women, particularly cryptococcosis and endemic fungal diseases.[27] However, the impact of gender on clinical response rates remains unclear, as previous studies have not extensively investigated this factor. Underlying diseases, which typically affect susceptibility to IFDs, did not show a significant impact on prognosis in our study. Retrospective analyses have identified various risk factors affecting

outcomes, such as older age and acute onset, but have not consistently linked underlying diseases to prognosis.[28] Variations in study methodologies and medical management further complicate the assessment of IFD prognosis.

Our study found that the clinical response rates for ABCD treatment were 75.0% for invasive candidiasis (IC), 69.6% for IA, and 72.7% for IM, a subgroup defined as 11 total cases of Mucorales infection, including *Rhizopus, Cunninghamella*, and *Mucor* species. Previous studies reported varying clinical response rates for IC (53% to 70%) and IA (34% to 52%).[13,17,21–23] IM, with its lower incidence, has limited data, but smaller studies suggest a response rate of approximately 60%.[14]

Regarding the type of ABCD therapy, our study found comparable clinical response rates for ABCD monotherapy (74.4%) and combination therapy (66.7%) ($p = 0.528$). Guidelines often recommend combination therapy due to the high mortality rates and increasing drug resistance.[29,30] Combining antifungal agents with different mechanisms of action was generally considered more effective, such as the use of echinocandins with VOR or AmB.[31–33] However, the combination of antifungal agents with different mechanisms of action, such as echinocandins with VOR or AmB, is debated. In vitro and animal studies have produced mixed results, showing both synergistic and antagonistic effects.[34–36] In clinical practice, the combination of AmB and azoles remains controversial, with some studies indicating concentration-dependent interactions and others finding no definitive evidence of antagonism.[35,36] Although our study showed an apparent difference in clinical response rates between ABCD combined with VOR (25%) and ABCD combined with POS (100%), the validity of this observation is limited by the small sample size and potential confounding factors.

Our study indicated that the incidence rates of nephrotoxicity and hepatotoxicity associated with ABCD were 23.3% and 13.3% respectively. The unique structure of ABCD results in pharmacokinetic characteristics distinct from those of DAmB, leading to lower renal distribution and reduced nephrotoxicity.[37] Several studies have demonstrated that ABCD did not cause renal dysfunction and could be safely used in patients with pre-existing renal impairment without increasing the risk of nephrotoxicity. And ABCD was not associated with dose-dependent nephrotoxicity.[14–16,38–40] By contrast, one meta-analysis indicated that the incidence of nephrotoxicity was the highest (29%) when using high doses of ABCD (6 mg/kg/day).[41] In terms of hepatotoxicity, multiple studies have shown that ABCD treatment had little or no impact on liver function.[15,21,39] Although these studies defined hepatotoxicity differently, they consistently indicated that the effects of ABCD on the liver were reversible.

Regarding IRRs, our study identified only one instance of IRRs to ABCD, which resolved after reducing the infusion rate. This low incidence of IRRs is noteworthy, especially given that IRRs associated with ABCD are typically dose-dependent. Previous Phase I and Phase II clinical trials have shown that patients receiving doses higher than 4 mg/kg/day experienced more IRRs compared to those receiving 4 mg/kg/day or less, with most reactions occurring during the initial doses.[38] Reports from earlier studies have documented a high incidence of IRRs with ABCD, ranging from 56% to 68%,[38,42] and some evidence suggested that ABCD could cause more IRRs compared to DAmB.[13,37,41] It's important to consider that many of these studies involved patients who either did not receive premedication or only received basic premedication such as acetaminophen or diphenhydramine, with shorter infusion durations typically around 4 hours. In contrast, a study utilizing the PRoACT registry system found that IRR incidence was significantly higher in patients who did not receive premedication compared to those who did (22.4% vs 10.8%, $p < 0.001$).[43] Corticosteroids, particularly dexamethasone, have been shown to be effective in reducing IRR incidence.[43] In the PRoACT registry study, premedication with corticosteroids was associated with a significantly lower incidence of IRRs compared to non-corticosteroid premedication (8.1% vs 19.9%, $p < 0.001$). Conversely, the use of antihistamines or acetaminophen as premedication was linked to a higher incidence of IRRs.[43]

In our study, the low incidence of IRRs may be attributed to most patients receiving premedication with dexamethasone and undergoing prolonged infusion durations, with a median infusion time of 8 hours. This suggests that appropriate premedication and extended infusion times may contribute to a reduced frequency of IRRs in patients receiving ABCD.

Hypokalemia associated with ABCD was reported in our study, with one patient requiring discontinuation due to persistent hypokalemia. Potassium monitoring and supplementation are standard practices in antifungal therapy.[41] Our study did not collect comprehensive potassium data, but monitoring and managing potassium levels remain important in clinical practice.

In addition, several limitations of the study must be considered: 1) The retrospective and single-center nature of this study inherently subjects the data to selection bias and may limit the generalizability of our findings.2) Due to the limited sample size, formal stratified analyses based on exposure-response modeling were not feasible, which should be taken into account when interpreting the results. 3) Short ABCD courses and non-uniform observation periods may introduce bias in efficacy assessment, although 30-day and 90-day all-cause mortality were included as secondary endpoints to mitigate this effect. 4) The high proportion of possible IFD cases and unknown pathogens may inflate clinical response estimates, although a sensitivity analysis showed similar results. 5) Data on specific molecular resistance mechanisms were unavailable, which limits our ability to definitively assess the role of fungal resistance in prior treatment failure.

## Conclusion

In this real-world setting, ABCD salvage therapy was associated with favorable clinical outcomes and an acceptable safety profile in IFD patients who failed prior azole or echinocandin therapy. To draw more definitive conclusions about the clinical utility of ABCD, further research is needed. Multi-center, prospective studies with larger sample sizes and control groups will be crucial in validating our findings and providing a more comprehensive evaluation of ABCD salvage therapy.

Specifically, future research should aim to address the following key questions: 1) Optimal Combination Therapy (POS vs VOR): Given the observed difference in our cohort, is the superior clinical efficacy of ABCD combined with POS sustained compared to ABCD combined with POS in larger-scale, prospective, and randomized controlled trials for IFD salvage therapy? 2) IRR Prevention Protocols: Are standardized premedication protocols and prolonged infusion durations effective strategies to significantly reduce the incidence of IRRs associated with ABCD, and thus negate the need for routine dose escalation? 3) Patient-Specific Prognosis: How do critical host factors, such as underlying diseases and gender, impact the prognosis and clinical response to ABCD salvage therapy across diverse patient populations?

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