SUPPLEMENT ARTICLE

Amphotericin B Lipid Complex in the Management of Invasive Aspergillosis in Immunocompromised Patients

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The efficacy and renal safety of amphotericin B lipid complex (ABLC) were assessed in 398 patients with invasive aspergillosis. The most common underlying conditions were hematopoietic stem-cell transplantation (101/398 [25%]), hematologic malignancy (101/398 [25%]), and solid-organ transplantation (109/398 [27%]). The most common reason for administration of ABLC was lack of response to prior antifungal therapy. Overall, 65% of patients had a favorable clinical response: 44% were cured or improved, and 21% were stabilized. Clinical responses were similar for patients who received ABLC as either first-line or second-line therapy. One hundred forty-four patients whose results could be evaluated received ABLC concurrently with or after therapy with itraconazole. No antagonism was observed when therapy with ABLC followed therapy with itraconazole. Patients infected with *Aspergillus terreus,* an innately polyene-resistant species, experienced a 37% response rate. Changes in serum creatinine levels were not clinically significant in most patients; however, dialysis was initiated in 7 patients, of whom 6 had prior antifungal therapy or preexisting renal disease. Analysis of this large database demonstrated the efficacy and safety of ABLC in the treatment of invasive aspergillosis.

Invasive fungal infections are a serious concern in immunocompromised patients, and the types of pathogens seen in patients have shifted over time. Groll et al. [1] documented the changing patterns in pathogens responsible for invasive fungal infections from the late 1970s to the early 1990s at a German university hospital. The overall prevalence of invasive fungal infections identified at autopsy increased from 2% during 1978–1982 to 7% in 1992 [1]. During 1978–1982, *Candida* species were the most commonly isolated fungal pathogens at autopsy, but, during 1988–1992, *Aspergillus* species were detected most frequently, suggesting that mortality due to aspergillosis was increasing.

A similar shift in epidemiology has been noted in the United States. An analysis of the National Center for Health Statistics multiple-cause-of-death record tapes revealed that mortality associated with candidiasis had decreased by 50% during 1989–1997, whereas mortality associated with aspergillosis had increased by 357% during 1980–1997 [2]. Other studies have also documented the emergence of *Aspergillus* species in the United States, with *Aspergillus fumigatus* as the most frequently encountered *Aspergillus* species. Compared with 1994 figures, *Aspergillus* isolates recovered from specimens submitted to a Detroit microbiology laboratory increased by 2.5–4.5-fold each year from January 1996 to December 1999 [3]. The incidence of invasive aspergillosis among both allograft and autograft recipients at a large transplantation center more than tripled between 1985 and 1999 [4].

High mortality occurs among patients with invasive aspergillosis, despite therapy. Only about one-third of patients infected with invasive aspergillosis and treated with conventional amphotericin B (AmB) survive [5]. A recent comprehensive review of available data suggests that outcomes may be improved when such patients receive lipid formulations of AmB [6]; however, no controlled data evaluating the various lipid forms

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Table 1. Baseline characteristics of 398 patients with proven invasive aspergillosis.

Characteristic	Value
Age, median (range), years	48 (0–89)
Sex	
Female	152 (38)
Male	244 (61)
Unknown	2 (1)
Race	
White	302 (76)
Black	45 (11)
Hispanic	28 (7)
Other	14 (4)
Unknown	9 (2)
Primary underlying medical condition	
HSCT[a]	101 (25)
Hematologic malignancy	101 (25)
SOT	109 (27)
Solid tumor	21 (5)
AIDS	11 (3)
Other[b]	55 (14)
ANC, cells/mm^3	
<500	88 (22)
500–1000	58 (15)
>1000	244 (61)
Unknown	8 (2)

NOTE. Data are no. (%) of patients, except where noted. ANC, absolute neutrophil count; HSCT, hematopoietic stem-cell transplantation; SOT, solid-organ transplantation.

[a] Includes both allogeneic and autologous HSCT.

[b] Includes diabetes, hematologic malignancy plus SOT, cardiovascular pulmonary disease, prematurity, gastrointestinal disease or surgery, infections other than AIDS, renal disease, steroid use, and others.

of AmB in the treatment of invasive aspergillosis are available.

The Collaborative Exchange of Antifungal Research (CLEAR) program represents the largest known database of patients treated for proven aspergillosis by means of an antifungal agent. Created from information supplied by treating clinicians, it contains demographic characteristics, laboratory data, treatment information, and clinical outcomes for 398 patients with invasive aspergillosis caused by a single documented pathogen and treated with amphotericin B lipid complex (ABLC) injection (Enzon Pharmaceuticals). This analysis of data originating from CLEAR evaluates the epidemiology of invasive aspergillosis and assesses the efficacy and renal safety of ABLC in the treatment of this infection.

METHODS

The complete methods used in the CLEAR project for data collection and analysis are explained in the introduction to this supplement [7], including the definitions for patient status prior to ABLC therapy and those for clinical outcomes of cured, improved, stable, deteriorated, and indeterminate. In addition to the standard methodology, further analyses of treatment outcome by underlying condition, site of infection, *Aspergillus* species, neutrophil counts, and prior or concomitant use of itraconazole therapy were performed. Patients were grouped according to underlying condition in the hierarchical order of hematopoietic stem-cell transplantation (HSCT), hematologic malignancy, solid-organ transplantation, solid tumor, or other conditions. Other underlying conditions included AIDS, diabetes, hematologic malignancy plus solid-organ transplantation, cardiovascular or pulmonary disease, prematurity, infections other than AIDS, renal disease, steroid use, and other. Sites of infection were defined as single site or multiple site/disseminated. Patients included in this CLEAR analysis were classified by the participating clinicians as having proven invasive aspergillosis caused by a single, documented *Aspergillus* species. Patients infected with multiple pathogens and those infected with multiple non-*Aspergillus* species were excluded to avoid confounding factors that assessment of multiple pathogens might cause.

RESULTS

Baseline patient characteristics. Of 3514 patients described in the CLEAR database, 398 patients with proven invasive as-

Table 2. Characteristics of 398 cases of *Aspergillus* infection.

Characteristic	No. (%) of infections
Aspergillus species	
A. fumigatus	147 (37)
A. flavus	45 (11)
A. terreus	19 (5)
A. niger	13 (3)
A. versicolor	3 (1)
A . glaucus	2 (1)
Other	169 (42)
Infection site for single-site disease	
Lungs	284 (71)
Sinus	31 (8)
CNS	7 (2)
Cutaneous	17 (4)
Other	11 (3)
Total	350 (88)
Infection site for multiple-site disease	
Lungs + sinus	10 (3)
Lungs + CNS	19 (5)
Lungs + other	8 (2)
CNS + sinus	5 (1)
CNS + other	2 (1)
Sinus + other	3 (1)
Other	1 (<1)
Total	48 (12)

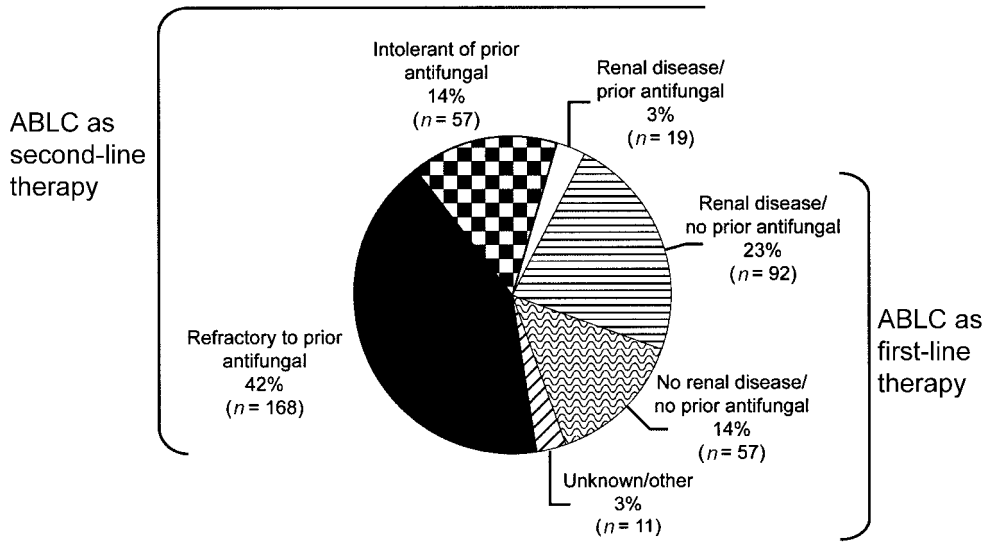

Figure 1. Status of patients ($n = 398$) at baseline. ABLC, amphotericin B lipid complex.

pergillosis who fulfilled inclusion criteria were identified (table 1). The median age was 48 years (range, 0–89 years), and most patients were male (244/398 [61%]). The vast majority of patients had 1 of 3 primary underlying conditions: 25% had undergone HSCT, 25% had a hematologic malignancy, and 27% had undergone solid-organ transplantation.

Most patients (61%) had an absolute neutrophil count (ANC) of >1000 cells/mm^3 at the time of diagnosis. Neutropenia (ANC, <500 cells/mm^3) was seen in 22% of patients.

Infection characteristics. The most commonly isolated *Aspergillus* species were *A. fumigatus* ($n = 147$), *A. flavus* ($n = 45$), and *A. terreus* ($n = 19$) (table 2). The species of *Aspergillus* was not specified in 42% of patients. Most patients (350/398) had single-site infections, the majority of which involved the lungs (71%) or sinuses (8%). Of those with >1 infected site, the lungs were the most common site, with the sinuses or CNS as additional sites.

Treatment with ABLC. The most common reason for the administration of ABLC was a lack of response to prior antifungal therapy (figure 1). This was generally true regardless of the *Aspergillus* species. For example, 39% of patients (57/147) with an infection caused by *A. fumigatus* received ABLC because the infection was refractory to previous antifungal therapy.

The median daily dose of ABLC was 4.8 mg/kg/day (range, 0.2–10 mg/kg/day), and the median cumulative dose was 4125 mg (range, 18.9–74,000 mg). ABLC was administered for a median of 15 days (range, 1–274 days). Ninety-four patients received concomitant itraconazole, and 56 received itraconazole prior to treatment with ABLC.

Outcomes. Of the 398 patients with invasive aspergillosis, 368 were evaluated for response. Overall, 65% of patients had a favorable clinical response to ABLC; 44% (162/368) were cured or improved, and 21% (78/368) had stabilization of infection at the end of therapy. Clinical response rate (cured and

Table 3. Clinical response in 368 patients with proven invasive aspergillosis treated with amphotericin B lipid complex (ABLC), by prior status.

		Second-line therapy with ABLC			First-line therapy with ABLC			
Clinical response	Unknown ($n = 11$)	Refractory to prior antifungal therapy ($n = 157$)	Underlying renal disease/prior antifungal therapy ($n = 9$)	Intolerant of prior antifungal therapy ($n = 50$)	Underlying renal disease no prior antifungal therapy ($n = 88$)	No prior antifungal therapy/no renal disease ($n = 51$)	Other ($n = 2$)	Total ($n = 368$)
Cured	…	15 (10)	…	4 (8)	16 (18)	6 (12)	1 (50)	42 (11)
Improved	2 (18)	45 (29)	7 (78)	23 (46)	30 (34)	13 (26)	…	120 (33)
Stable	2 (18)	33 (21)	1 (11)	12 (24)	20 (23)	10 (20)	…	78 (21)
Deteriorated	7 (64)	64 (41)	1 (11)	11 (22)	22 (25)	22 (43)	1 (50)	128 (35)

NOTE. Data are no. (%) of patients.

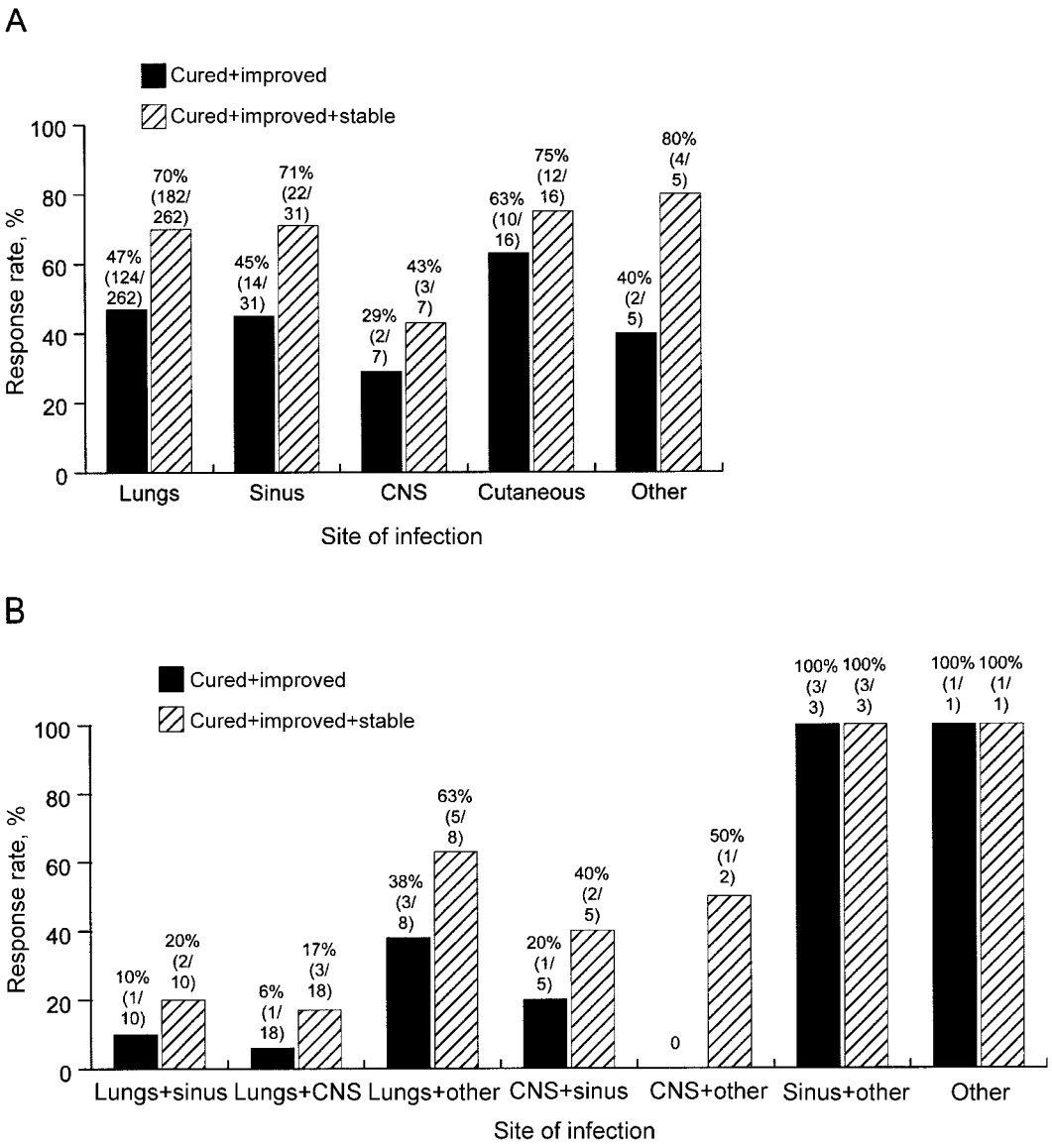

Figure 2. Clinical response, by site of infection. *A,* Single-site infections. *B,* Multiple-site infections.

improved) was significantly higher among patients who had undergone solid-organ transplantation (52%) than among those who had undergone HSCT (34%; $P = .014$).

Forty-seven percent of patients (65/139) who received ABLC as first-line therapy were cured or improved, compared with 44% of patients (94/216) who received ABLC as second-line therapy. Clinical response rates by prior status were as follows: 38% (60/157) among patients whose infections were refractory to prior antifungal therapy, 52% (46/88) among patients with underlying renal disease who had received no prior antifungal therapy, 54% (27/50) among patients who were intolerant of prior antifungal therapy, and 78% (7/9) among patients with underlying renal disease who had received prior antifungal therapy (table 3). A 47% response rate among patients who received ABLC as first-line therapy versus a 38% response rate among patients whose infections were refractory to prior antifungal therapy is noteworthy.

The response rates among patients with single-site infections were generally higher than those among patients with multiple-site infections (figure 2). When patients with single-site aspergillosis were sorted by underlying medical condition, those who had undergone solid-organ transplantation or who had solid tumors had the highest response rates for the specified conditions, whereas HSCT recipients had the lowest response rates (figure 3).

Response rates to therapy with ABLC were substantially higher among nonneutropenic patients. Forty-nine percent of patients with normal neutrophil counts (ANC, ⩾500 cells/

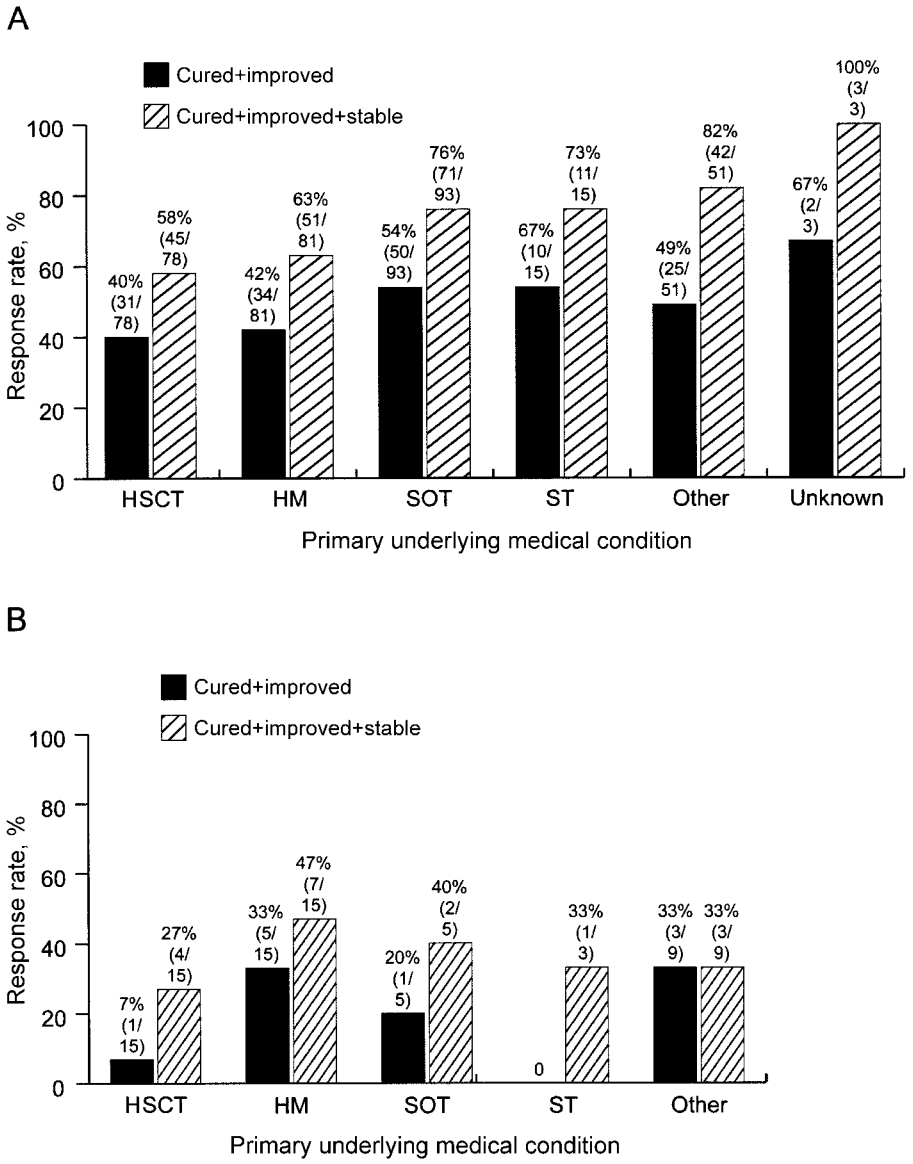

Figure 3. Clinical response, by primary underlying medical condition. *A,* Single-site infections. "Other" includes the following conditions: AIDS, diabetes, hematologic malignancy (HM) plus solid-organ transplantation (SOT), cardiovascular pulmonary disease, prematurity, infections other than AIDS, renal disease, steroid use, and other. *B,* Multiple-site infections. "Other" includes gastrointestinal disease or surgery, AIDS, renal disease, steroid use, and other. HSCT, hematopoietic stem-cell transplantation; ST, solid tumor.

mm^3) at both the start and end of therapy were cured or improved. Fifty-five percent of patients (23/42) with neutropenia (ANC, <500 cells/mm^3) at the start of therapy but normal neutrophil counts at the end were cured or improved. However, only 10% of patients (4/42) who were neutropenic at both the start and end of therapy were cured or improved. Two (29%) of 7 patients who had normal neutrophil counts at the start of therapy but who became neutropenic at the end of therapy were cured or improved.

Depending on the infecting *Aspergillus* species, the response rate for patients receiving therapy with ABLC was 33%–50% (figure 4). Response rates for patients infected with *A. fumigatus* and *A. flavus* were 42% and 34%, respectively. Notably, a 37% response rate was seen among patients infected with *A. terreus* (7/19).

One hundred forty-four patients whose results could be evaluated received ABLC concurrently with or after itraconazole therapy. Of 54 patients who received ABLC after therapy with itraconazole, 27 (50%) were cured or improved, and 9 (17%) were stabilized. Of 33 patients who continued prior therapy with itraconazole after starting therapy with ABLC, 9 (27%) were cured or improved. Another 12 (36%) of these 33 patients

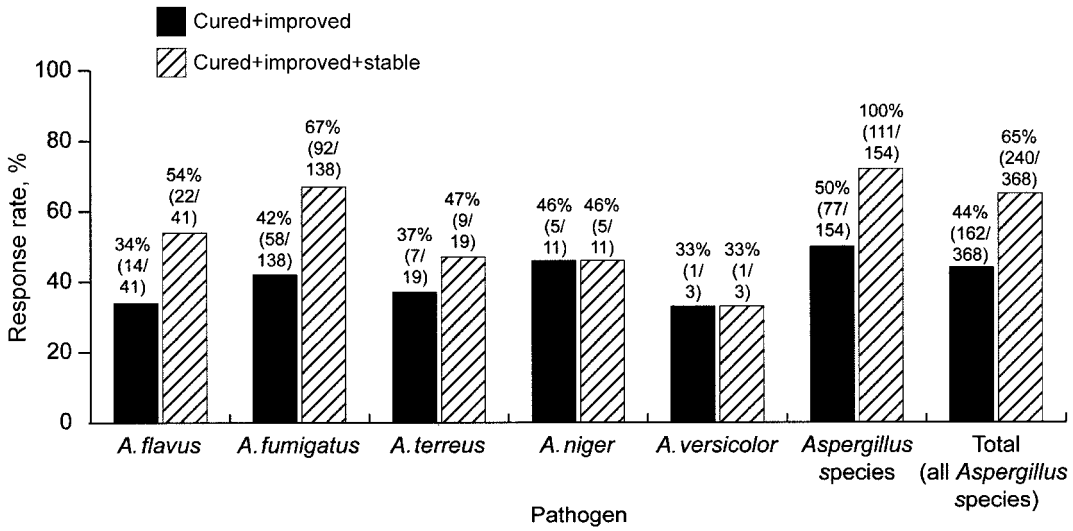

Figure 4. Clinical response, by infecting *Aspergillus* pathogen

were stabilized. Of 57 patients who started itraconazole concomitantly with ABLC, 21 (37%) were cured or improved, and 10 additional patients (18%) were stabilized (table 4).

Renal safety. All 398 patients with aspergillosis were evaluated for renal safety. The median serum creatinine levels at baseline and at the end of therapy for all patients were 1.40 and 1.60 mg/dL, respectively. Most changes noted were not clinically significant. Doubling of serum creatinine level from baseline occurred in 14% of patients (57/398). Serum creatinine level increased from <2.5 mg/dL at baseline to ⩾2.5 mg/dL in 12% of all patients (46/398).

In patients who either had been exposed to another antifungal or had preexisting renal disease, serum creatinine doubled in 14% of patients (44/327) and increased from <2.5 mg/dL at baseline to ⩾2.5 mg/dL in 8% of patients (26/327). Among patients who were naive to antifungal therapy and had normal renal function, serum creatinine doubled in 18% of patients (10/57) and increased from <2.5 mg/dL at baseline to ⩾2.5 mg/dL in 11% of patients (6/57). Dialysis was initiated in 7 patients (table 5). Of these 7 patients, 1 had no underlying renal disease or prior exposure to other antifungal drugs. Dialysis was initiated in 3% of patients receiving ABLC as first-line therapy (4/149) and in 1% of patients receiving ABLC as second-line therapy (3/235).

Overall, patients with underlying renal disease and prior antifungal therapy at baseline had the greatest increase in serum creatinine (0.43 mg/dL) over the duration of the study. Doubling of serum creatinine level from baseline was noted in 14% of patients receiving ABLC as either first-line or second-line therapy.

DISCUSSION

Available therapies for invasive aspergillosis include voriconazole, conventional AmB, lipid formulations of amphotericin B (e.g., ABLC, amphotericin B liposome, and amphotericin B cholesteryl sulfate complex), itraconazole, and caspofungin (an echinocandin). Data with echinocandins are limited; efficacy data on caspofungin as salvage therapy in patients with refractory infection were reported recently [8]. Newer agents, such as other echinocandins, other triazoles, and investigational agents, may be useful, although data are limited. The CLEAR data demonstrate that ABLC is effective for the treatment of invasive aspergillosis when used as first-line or second-line therapy. Although response rates were slightly higher among patients treated with ABLC as first-line, rather than second-line, therapy, this difference was not statistically significant, possibly as a result of selection bias.

Table 4. Clinical response to therapy with amphotericin B lipid complex (ABLC), by sequential, combination, or continued use of itraconazole.

Clinical response	Sequential itraconazole[a]	Combination itraconazole[b]	Continued itraconazole[c]
Cured/improved	27/54 (50)	21/57 (37)	9/33 (27)
Cured/improved/stable	36/54 (67)	31/57 (54)	21/33 (64)

NOTE. Data are no. of patients with clinical response/no. of patients evaluated (%).

[a] Defined as prior therapy with itraconazole that was stopped prior to start of therapy with ABLC.

[b] Defined as no prior therapy with itraconazole but started concomitantly with therapy with ABLC.

[c] Defined as prior therapy with itraconazole and continued after start of therapy with ABLC.

Table 5. Renal function of 398 patients with proven invasive aspergillosis treated with amphotericin B lipid complex, by prior status.

	Prior status							
Renal parameter	Refractory to prior antifungal therapy (n = 168)	Underlying renal disease/prior antifungal (n = 10)	Underlying renal disease no prior antifungal (n = 92)	Intolerant of prior antifungal therapy (n = 57)	No prior antifungal therapy/no underlying renal disease (n = 57)	Other (n = 3)	Unknown (n = 11)	Total (n = 398)
Baseline S-Cr level, median mg/dL (no. of patients)	1.10 (164)	2.00 (10)	1.60 (90)	1.60 (55)	1.10 (56)	1.50 (3)	2.00 (9)	1.40 (387)
End of therapy S-Cr level, median mg/dL (no. of patients)	1.50 (160)	2.10 (9)	1.90 (89)	1.55 (54)	1.45 (56)	1.70 (3)	2.05 (10)	1.60 (381)
Change from baseline S-Cr level, median mg/dL (no. of patients)	0.20 (159)	0.43 (9)	0.00 (88)	0.10 (54)	0.30 (55)	0.00 (3)	−0.10 (9)	0.20 (377)
Doubling of baseline S-Cr level, no. (%) of patients	30 (18)	1 (10)	11 (12)	2 (4)	10 (18)	…	3 (27)	57 (14)
S-Cr level ⩾2.5 mg/dL at baseline and end of therapy, no. (%) of patients	9 (5)	1 (10)	12 (13)	3 (5)	4 (7)	1 (33)	1 (9)	31 (8)
S-Cr level <2.5 mg/dL at baseline and ⩾2.5 mg/dL at end of therapy, no. (%) patients	21 (13)	…	11 (12)	5 (9)	6 (11)	…	3 (27)	46 (12)
New dialysis, no. (%) of patients	3 (2)	…	3 (3)	…	1 (2)	…	…	7 (2)

NOTE. S-Cr, serum creatinine.

As expected, patients with adequate neutrophil counts had better outcomes than those without, and patients with solid tumors or who had undergone solid-organ transplantation had better outcomes than patients with other underlying conditions. The response rate of 40% among the HSCT recipients with aspergillosis, typically considered to have the poorest prognosis, compares favorably with the findings of Herbrecht et al. [9], who documented a 32% response rate among allogeneic HSCT recipients treated with voriconazole. Another noteworthy comparison to Herbrecht's report is the overall percentage of patients who achieved a stable outcome. The stable response rate in CLEAR was 21%, compared with 6% in Herbrecht's analysis. However, the proportion of patient types is different in the 2 studies. For instance, in Herbrecht's analysis, although the proportion of allogeneic HSCT recipients was similar across study groups, the number of patients with acute leukemia was significantly higher, and the number of patients who had undergone solid-organ transplantation was significantly lower.

Certain *Aspergillus* species have innate resistance to AmB in vitro and, thus, may be difficult to treat successfully. *A. terreus* is an important emerging pathogen that is innately resistant to AmB [10–13] but susceptible to voriconazole in vitro. Given the relationship between resistance and outcomes [12], concerns about poor outcomes in patients infected with *A. terreus* are well grounded. The clinical relevance of resistance to AmB among isolates of *A. terreus* was illustrated by Iwen et al. [14] in a 12-year retrospective analysis, which revealed that invasive pulmonary aspergillosis caused by *A. terreus* progressed rapidly in immunocompromised patients treated with AmB, resulting in a 9% survival rate. In the CLEAR database, patients infected with *A. terreus,* who might be expected to respond poorly due to documented resistance issues, achieved a 37% response rate. Hachem et al. [15] recently presented findings on 70 cases of *A. terreus,* reporting a 28% response rate to conventional or lipid forms of AmB, itraconazole, or posaconazole. In a retrospective cohort study of infections caused by *A. terreus* from 1997 to 2002, Steinbach et al. [16] reported a response rate of 22% and mortality rate of 73% among patients treated with antifungal therapies other than voriconazole. Results from CLEAR in the "real world" setting indicate the possible utility of ABLC in treating aspergillosis caused by *A. terreus.*

In severely immunocompromised patients with aspergillosis, combination therapy with polyenes and azoles is increasingly utilized. However, in some cases, combination regimens may be associated with antagonism. Prior in vitro and in vivo (animal model) data suggest antagonism in both sequential (azole to polyene) and combination regimens (azole plus polyene) [17–21]. A possible explanation for this phenomenon is that azoles inhibit the synthesis of ergosterol in the fungal cell membrane, the target of polyene antifungal agents [22]. Interestingly, in the CLEAR analysis, no antagonism was observed when ABLC treatment followed itraconazole therapy. Thus, in sequential use of azole followed by polyene, concerns of antagonism may not be warranted. However, lower response rates occurred when ABLC was used concurrently with itraconazole, especially when ABLC was added to continuing itraconazole therapy. Because these patients received combination therapy, it is fair to assume that clinicians may have deemed them to be sicker patients who would have benefited from 2 drugs. Of particular note, the cured and improved response rate was 27% among patients continuing itraconazole therapy with the addition of ABLC but increased to 64% when stable patients were considered as responders. In light of the high mortality rate associated with this difficult-to-treat infection, a stable outcome is encouraging. These results may be due to selection bias. Given the increasing use of azole therapy, including prophylactic or first-line use of voriconazole or itraconazole, this clinical observation warrants further study.

In the analysis of renal safety in 398 patients with aspergillosis, the renal tolerability of ABLC therapy is confirmed, even in severely immunocompromised patients. Our analysis of the CLEAR data adds to the available evidence supporting the efficacy and safety of ABLC therapy for the treatment of invasive aspergillosis.

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