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PHARMACOLOGY

Evaluation of Amphotericin B Lipid Formulations for Treatment of Severe Coccidioidomycosis

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ABSTRACT Patients with severe coccidioidomycosis infections are often treated with either amphotericin B lipid complex (ABLC) or liposomal amphotericin B (L-AmB). Outcome data with these agents in severe coccidioidomycosis cases are currently lacking. The purpose of this study is to evaluate the efficacy and toxicity of ABLC and L-AmB in treating severe coccidioidomycosis. A retrospective pre-post study design was employed. Chart reviews were completed from 1 January 2005 to 31 December 2014 for all patients who received lipid-based amphotericin B. Inclusion criteria included having a follow-up complement fixation (CF) titer or a treatment emergent adverse event (TEAE) prior to follow-up. Patients with meningeal involvement and pregnant patients were excluded. Treatment outcomes were assessed based on documented completion of therapy as well on symptoms, complement fixation titer, and changes to laboratory monitoring parameters. A total of 108 patients were identified, 69 of whom met the inclusion criteria. There were no statistical differences in demographics or disease burden in those that received ABLC and those that received L-AmB, except that those who received L-AmB were more likely to have previously diagnosed chronic kidney disease ($n_{\text{L-AmB}} = 4$, 12.5% vs $n_{\text{ABLC}} = 0$, 0.0%; $P = 0.042$) and to have a lower creatinine clearance at the start of therapy (L-AmB = 79.6 mg/dl versus ABLC = 100.4 mg/dl; $P = 0.008$). Successful treatment was achieved in 27 (73.0%) of ABLC patients and 22 (68.8%) of L-AmB patients ($P = 0.700$). Amphotericin B was discontinued due to documented completion of therapy for 17 (45.9%) ABLC patients and 18 (56.3%) L-AmB patients ($P = 0.553$). Acute kidney injury (AKI) was the documented reason of treatment cessation for 10 (27.0%) ABLC and 1 (3.1%) L-AmB patient ($P = 0.007$). ABLC and L-AmB both appear to be equally efficacious in the treatment of severe coccidioidomycosis. L-AmB may have less renal toxicity than ABLC and may be the preferred agent in baseline renal impairment.

KEYWORDS coccidioidomycosis, amphotericin B, AmBisome, Abelcet, treatment

Coccidioidomycosis is a reemerging infectious disease that is predominantly caused by *Coccidioides immitis* in California and by *Coccidioides posadasii* in Arizona (1). The disease is contracted through inhalation of *Coccidioides* spp. spores, which germinate in the lungs, forming mature spherules that can avoid phagocytosis due to their size (2–4). Of those infected, 60% will be asymptomatic, 40% will develop mild-to-moderate influenza-like illness, and less than 1% will develop extrapulmonary disease (5–7). Within California, coccidioidomycosis is most prevalent in the San Joaquin Valley, and the disease is endemic to the southwestern United States, Mexico, and Central and South America (3). Hospitalization rates due to coccidioidomycosis in California have increased from 2.3 initial hospitalizations per 100,000 person-years in 2000 to 5.0 initial hospitalizations per 100,000 person-years in 2011. The 2011 infection rate is consider-

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ably higher in regions of California where coccidioidomycosis is more endemic, such as Kern County (61.9 initial hospitalizations/100,000 person-years) and Kings County (63.5 initial hospitalizations/100,000 person-years) (3, 8, 9).

Treatment of coccidioidomycosis typically involves oral triazole derivatives in less severe cases and intravenous amphotericin B in severe cases. Meningeal coccidioidomycosis may require intrathecal amphotericin B (1, 10, 11). Assessment of treatment progress is often difficult to quantify, due to the varied course of the disease. A composite scoring system based on symptoms, physical examination, complement fixation (CF) titers, and culture results, known as the Mycosis Study Group (MSG) score is the recommended modality for assessing therapeutic response, with success being defined as a 50% or greater reduction in MSG score from baseline at eight or fewer months (1, 12). Even though amphotericin B is reputed to be the gold standard in acute, severe coccidioidomycosis, studies investigating the better-tolerated lipid formulations of amphotericin B in the disease are not adequate and are limited to murine and rabbit models and a few case studies (13–18).

Lipid-based amphotericin B is commonly available as two formulations in the United States, amphotericin B lipid complex (ABLC) (Abelcet) and liposomal amphotericin B (L-AmB) (AmBisome). There have been few prospective randomized controlled trials that directly compared ABLC with L-AmB (19). These lipid formulations, along with the conventional deoxycholate form, are generally considered to be equally efficacious, as supported by comparative studies on the empirical treatment of neutropenic fever patients and on the treatment of invasive fungal infections in immunocompromised patients (20, 21). There is some disagreement in the literature regarding the toxicities of the three amphotericin B agents. Conventional amphotericin B is associated with the greatest amount of nephrotoxicity and poorest tolerability of all amphotericin B formulations (21). Wingard et al. were the first to show that L-AmB causes less nephrotoxicity than ABLC, but a subsequent meta-analysis suggested that the rates of nephrotoxicity are generally similar between the two agents (20–24). In addition to nephrotoxicity, amphotericin B has been associated with hepatotoxicity, which occasionally results in discontinuation of therapy (25).

The purpose of this study is to describe the efficacy and toxicity of lipid-based amphotericin B in the treatment of severe coccidioidomycosis, as well as to investigate differences between the two lipid-based formulations.

RESULTS

A total of 108 patients were identified as having received lipid-based amphotericin B on an outpatient basis for the treatment of coccidioidomycosis. Ten patients were excluded due to the lack of baseline records, 13 were lost prior to follow-up assessment, and 16 patients were pregnant. Sixty-nine patients met inclusion/exclusion criteria and were included in the primary analysis.

Patient demographics are described in Table 1 and show no significant differences between the ABLC and L-AmB groups. The study population was predominantly male ($n = 53$, 76.8%; $n_{ABLC} = 30$, 81.1% versus $n_{L\text{-}AmB} = 23$, 71.9%; $P = 0.817$). The median age was 37 years old (ABLC = 41 years versus L-AmB = 34.5 years; $P = 0.753$). Nearly half ($n = 34$, 49.3%) of the study population were identified as nonwhite Hispanic and almost a third ($n = 21$, 30.4%) were black or African-American; there was no statistically significant difference in terms of ethnicity between the ABLC and L-AmB groups ($P = 0.766$). The population was otherwise relatively healthy, with only 26 total patients (37.7%) having any comorbid condition ($n_{ABLC} = 13$, 35.1% versus $n_{L\text{-}AmB} = 13$, 40.6%; $P = 0.639$). There was one statistically significant difference between the lipid-based amphotericin B groups, as those who were diagnosed with baseline chronic kidney disease ($n = 4$) exclusively received L-AmB ($P = 0.042$).

Table 2 and Table 3 summarize severity of coccidioidomycosis disease at the initiation and cessation of therapy, respectively. Patients had active disease in multiple organ systems ($n = 38$, 55.1%; $n_{ABLC} = 20$, 54.1% versus $n_{L\text{-}AmB} = 18$, 56.3%; $P = 0.513$). Dissemination of coccidioidomycosis to the skeletal system was also present in over

TABLE 1 Demographics

Variable[a]	Treatment			*P* value
	Combined	Amphotericin B lipid complex	Liposomal amphotericin B	
No. of subjects	69	37	32	0.547
Age in yrs (median [IQR])	37 (28–45)	41 (28–44)	34.5 (27.75–45.25)	0.753
No. of males (%)	53 (76.8)	30 (81.1)	23 (71.9)	0.817
Ethnicity (*n* [%])				
White	8 (11.6)	3 (8.1)	5 (15.6)	0.766
Hispanic nonwhite	34 (49.3)	20 (54.1)	14 (43.8)	
Black	21 (30.4)	10 (27.0)	11 (34.4)	
Asian	3 (4.3)	2 (5.4)	1 (3.1)	
Other	3 (4.3)	2 (5.4)	1 (3.1)	
Preexisting conditions (*n* [%])				
Any	26 (37.7)	13 (35.1)	13 (40.6)	0.639
DM	20 (29.0)	13 (35.1)	7 (21.9)	0.226
CKD	4 (5.8)	0 (0.0)	4 (12.5)	0.042
Malignancy	2 (2.9)	2 (5.4)	0 (0.0)	0.495
Corticosteroid	1 (1.4)	1 (2.7)	0 (0.0)	1.000
HIV/AIDS	6 (8.7)	3 (8.1)	3 (9.4)	1.000
Pulmonary TB	1 (1.4)	1 (2.7)	0 (0.0)	1.000
Anemia	2 (2.9)	0 (0.0)	2 (6.3)	0.211
COPD/asthma	6 (8.7)	3 (8.1)	3 (9.4)	1.000
Hepatitis	4 (5.8)	2 (5.4)	2 (6.3)	1.000
CAD/CHF	8 (11.6)	3 (8.1)	5 (15.6)	0.457

[a]IQR, interquartile range; CKD, chronic kidney disease; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; CAD/CHF, coronary artery disease/congestive heart failure.

half of the study population ($n = 39$, 56.5%; $n_{ABLC} = 19$, 51.4% versus $n_{L\text{-}AmB} = 20$, 62.5%; $P = 0.352$). Sputum or tissue cultures were positive for *Coccidioides immitis* in 30 (43.5%) patients ($n_{ABLC} = 16$, 43.2% versus $n_{L\text{-}AmB} = 14$, 43.8%; $P = 0.966$). Complement fixation antibody titer was greater than or equal to 1:64 (the maximum serial-dilution category in the MSG score) in 49 (71.0%) patients ($n_{ABLC} = 26$, 70.3% versus $n_{L\text{-}AmB} = 23$, 71.9%; $P = 0.348$). There were no statistically significant differences in symptoms (e.g., cough, fever, myalgia, etc.) at presentation (data not shown) or in number of symptoms at presentation ($\text{median}_{ABLC} = 4$ versus $\text{median}_{L\text{-}AmB} = 5$; $P = 0.219$).

Modified MSG (mMSG) scores showed significant improvement from beginning of therapy to end ($mMSG_{StartAll} = 7$, $mMSG_{EndAll} = 3$, $P < 0.001$; $mMSG_{StartABLC} = 7$, $mMSG_{EndABLC} = 3$, $P < 0.001$; $mMSG_{StartL\text{-}AmB} = 7$, $mMSG_{EndL\text{-}AmB} = 3$, $P < 0.001$). Although starting mMSG scores were numerically larger in the group that received liposomal amphotericin B (median, 7; interquartile range [IQR], 5 to 9.25) compared to those in the group that received amphotericin-B lipid complex (median, 7; IQR, 4 to 8), there were no statistically significant differences between the two groups at start ($P = 0.119$) or end ($P = 0.549$) of therapy. Predefined success of therapy was met in 49 (71.0%) patients, and there was no statistically significant difference between groups ($n_{ABLC} = 27$, 73.0% versus $n_{L\text{-}AmB} = 22$, 68.8%; $P = 0.700$).

Routinely monitored laboratory tests are shown in Table 4 with starting and ending laboratory values, as well as a follow-up creatinine clearance. Statistical tests were completed both between and within groups at start and end of therapy. There were no statistically significant changes in common liver/biliary function tests, such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AlkPhos), and total bilirubin (Tbili) between the two amphotericin B products or from start to end of therapy, with the exception that the L-AmB group showed a significant improvement in AST from start of therapy to end (52.2 units/liter versus 19.2 units/liter, respectively; $P < 0.001$). Both ABLC and L-AmB patients showed a decrease in platelets from start of therapy to end, but no thrombocytopenia (defined as a platelet count of less than $150 \times 10^3/\mu l$) was observed. Males and females within the ABLC group had a modest

TABLE 2 Disease burden at start of therapy

Variable	Treatment			*P* value
	Combined	Amphotericin B lipid complex	Liposomal amphotericin B	
Active disease sites (*n* [%])	69	37	32	
Pulmonary	54 (78.2)	30 (81.1)	24 (75.0)	0.541
Cutaneous	9 (13.0)	3 (8.1)	6 (18.8)	0.285
Soft tissue	19 (27.5)	11 (29.7)	8 (25.0)	0.661
Lymph	4 (5.8)	2 (5.4)	2 (6.3)	1.000
Osseous	39 (56.5)	19 (51.4)	20 (62.5)	0.352
No. of active disease sites (*n* [%])				
1	31 (44.9)	17 (45.9)	14 (43.8)	0.513
2	15 (21.7)	7 (18.9)	8 (25.0)	
3	13 (18.8)	9 (24.3)	4 (12.5)	
4	10 (14.5)	4 (10.8)	6 (18.8)	
Symptoms[a]				
Total at presentation (median [IQR])	5 (2–6)	4 (2–6)	5 (3–7)	0.219
Positive *C. immitis* culture (*n* [%])	30 (43.5)	16 (43.2)	14 (43.8)	0.966
CF antibody titer				
MSG CF antibody titer score (median [IQR])	3 (2–3)	3 (2–3)	3 (2–3)	0.803
MSG CF antibody titers (*n* [%])				
≤1:2	6 (8.7)	5 (13.5)	1 (3.1)	0.348
1:4 or 1:8	4 (5.8)	1 (2.7)	3 (9.4)	
1:16 or 1:32	10 (14.5)	5 (13.5)	5 (15.6)	
≥1:64	49 (71.0)	26 (70.3)	23 (71.9)	
Starting mMSG Score (median [IQR])	7 (5–9)	7 (4–8)	7 (5–9.25)	0.119

[a]There were no significant differences between specific symptoms at presentation.

decrease in hemoglobin. At baseline, the ABLC group had a lower serum creatinine (0.88 mg/dl versus 1.11 mg/dl, respectively, $P = 0.028$) and corresponding higher creatinine clearance than the L-AmB group (100.4 ml/min versus 79.6 ml/min, respectively; $P = 0.008$), but this difference was not seen at the end of therapy ($P = 0.902$ and $P = 0.498$, respectively). Both groups had a statistically significant increase in serum creatinine (SCR) (starting $SCR_{ABLC} = 0.88$ mg/dl, ending $SCR_{ABLC} = 1.49$, $P < 0.001$; starting $SCR_{L\text{-}AmB} = 1.11$, ending $SCR_{L\text{-}AmB} = 1.51$, $P < 0.05$) and decrease in creatinine clearance (CrCl) (starting $CrCl_{ABLC} = 100.4$ ml/min, ending $CrCl_{ABLC} = 63.3$ ml/min, $P < 0.001$; starting $CrCl_{L\text{-}AmB} = 79.6$ ml/min, ending $CrCl_{L\text{-}AmB} = 58.7$ ml/min, $P < 0.001$) from start to end of therapy.

Follow-up of study subjects' renal function is shown in Table 5. Patients who received ABLC displayed a small, but statistically significant, change in renal function from baseline to follow-up (Start $SCR_{ABLC} = 0.86$, end $SCR_{ABLC} = 1.01$, $P = 0.009$; start $CrCl_{ABLC} = 102.4$ ml/min, end $CrCl_{ABLC} = 86.3$ ml/min, $P = 0.001$). This change in renal function was not seen in L-AmB patients (start $SCR_{L\text{-}AmB} = 1.20$, end $SCR_{L\text{-}AmB} = 1.25$, $P = 0.760$; start $CrCl_{L\text{-}AmB} = 77.3$ ml/min, end $CrCl_{L\text{-}AmB} = 77.1$ ml/min, $P = 0.969$). Reason for drug discontinuation (Table 6) was analyzed for the 69 patients, 5 of whom switched amphotericin formulations during treatment. Therapy was stopped early in a total of 33 (47.8%) patients (ABLC = 19, 51.4%; L-AmB = 14, 43.8%), but only 5 (7.2%) patients were deemed to have failed therapy ($n_{ABLC} = 1$, $n_{L\text{-}AmB} = 4$; $P = 0.117$), including 2 deaths (both treated with L-AmB). Only 4 (5.8%) patients were unable to tolerate lipid-based amphotericin B therapy ($n_{ABLC} = 3$, $n_{L\text{-}AmB} = 1$; $P = 0.377$). Acute kidney injury was documented in 10 (27%) ABLC patients compared to 1 (3.1%) L-AmB patient ($P = 0.007$).

DISCUSSION

This is the first study that has investigated lipid-based amphotericin B use in severe coccidioidomycosis, and it is also the first study to compare the two lipid-based

TABLE 3 Disease burden at end of therapy

Variable	Treatment			*P* value
	Combined	Amphotericin B lipid complex	Liposomal amphotericin B	
Treatment duration in weeks (median [IQR])	7 (16–24)	16 (6–23)	16.5 (10–24.25)	0.337
Symptoms[a]				
Total at end of therapy (median [IQR])	0 (0–1)	0.5 (0–1)	0 (0–2)	0.889
CF antibody titer				
MSG CF antibody titer score (median [IQR])	3 (2–3)	2 (2–3)	3 (2–3)	0.246
MSG CF antibody titers (*n* [%])				
≤1:2	3 (4.3)	2 (5.4)	1 (3.1)	0.630
1:4 or 1:8	4 (5.8)	1 (2.7)	3 (9.4)	
1:16 or 1:32	13 (18.8)	8 (21.6)	5 (15.6)	
≥1:64	49 (71.0)	26 (70.3)	23 (71.9)	
Ending mMSG score	2.9	2.7	3.2	0.212
Ending mMSG score (median [IQR])	3 (2–4)	3 (2–4)	3 (2–4)	0.549
mMSG Decrease of ≥50%	49 (71.0)	27 (73.0)	22 (68.8)	0.700

[a]There were no significant differences between specific symptoms at presentation.

formulations in these patients. Despite our inability to use the Mycosis Study Group score in this retrospective study, the combination of the modified score and physician assessment allow for an accurate assessment of therapy. Overall, 35 (50.7%) patients were determined to have successfully completed the amphotericin B therapy, and 49 of the 69 patients (71.0%) achieved a 50% or greater decrease in our cumulative score of symptoms and CF titer. The efficacy data combined with the few treatment failures ($n = 5$; 7.2%) suggest that lipid-based amphotericin B is highly effective for the treatment of severe coccidioidomycosis. Although the starting and ending mMSG scores were numerically larger in the liposomal amphotericin B group, both groups had similar rates of documented completion. Both amphotericin B lipid complex and liposomal amphotericin B appear to be equally efficacious in the treatment of coccidioidomycosis as has been suggested in other disease states (20, 22, 24).

Both lipid formulations have been documented as causing infusion reactions (chills, fever, nausea, vomiting, etc.) in upwards of 80% of patients, with the liposomal formulation causing significantly fewer reactions compared to the lipid complex formulation (20, 22). Our study found lipid-based amphotericin B to be well tolerated, as only 4 (5.8%) patients stopped therapy due to intolerance; however, data regarding the frequency of minor infusion reactions, such as fever and chills was not available and all patients received prophylaxis as part of a standardized order set. These data suggest that infusion reactions are not a major cause of discontinuation. Treatment burden, in the form of thrice-weekly, half-day visits to the infusion clinic, appears to be the greatest contributor to early cessation of therapy as 3 (4.3%) patients explicitly stated so to their prescribing physician and 10 (14.5%) patients were noncompliant with regularly thrice-weekly treatment. Quality of life outcomes would be useful in helping to evaluate the differences between ABLC and L-AmB treatment.

The L-AmB group had greater renal insufficiency ($P = 0.008$) and higher rates of documented chronic kidney disease ($P = 0.042$) compared to those of the ABLC group at baseline, but acute kidney injury occurred less often in the L-AmB group compared to the ABLC group ($P = 0.007$). Because of the incidence of AKI, ABLC therapy was either stopped or suspended more often. This difference in nephrotoxicity was comparable to the study by Wingard et al. that was not observed in the most recent meta-analyses (22, 25). While the effect of amphotericin B on kidney function is believed to be reversible, we found that a small change in serum creatinine ($P = 0.009$) and creatinine clearance

TABLE 4 Metabolic Laboratory Data

Assay[a]	Treatment			*P* value
	Combined	Amphotericin B lipid complex	Liposomal amphotericin B	
ALT (U/liter)				
Starting	45.8	36.3	56.8	0.151
Ending	37.5	40.4	34.1	0.432
AlkPhos (U/liter)				
Starting	134.4	128.7	141.0	0.617
Ending	143.6	136.8	151.6	0.500
AST (U/liter)				
Starting	38.7	27.0	52.2[b]	0.092
Ending	21.7	23.9	19.2[b]	0.206
Serum creatinine (mg/dl)				
Starting	0.99	0.88[c]	1.11[b]	0.028
Ending	1.50	1.49[c]	1.51[b]	0.902
CrlCl (ml/min)				
Starting	91.2	100.4[c]	79.6[c]	0.008
Ending	61.2	63.3[c]	58.7[c]	0.498
HgB (g/dl)				
Starting HgB_{males}	11.3	11.6[b]	11.1	0.437
Ending HgB_{males}	10.8	10.7[b]	10.8	0.920
Starting $HgB_{females}$	11.2	11.8[b]	10.6	0.157
Ending $HgB_{females}$	10.1	9.8[b]	10.4	0.408
Mg (mg/dl)				
Starting	1.8	1.8	1.8	0.927
Ending	1.8	1.9	1.8	0.111
Plt ($1 \times 10^3/\mu l$)				
Starting	372.0	357.8[c]	388.5[c]	0.338
Ending	292.2	289.3[c]	295.5[c]	0.811
K (mEq/liter)				
Starting	3.9	3.9	3.8	0.552
Ending	3.9	4.0	3.8	0.058
TBili (mg/dl)				
Starting	0.4	0.4	0.4	0.430
Ending	0.4	0.4	0.4	0.366

[a]ALT, alanine transaminase; AlkPhos, alkaline phosphatase; AST, aspartate transaminase; CL_{CR}, creatinine clearance; HgB, hemoglobin; Plt, platelets; TBili, total bilirubin.
[b]*P* value < 0.05.
[c]*P* value < 0.001.

(0.001) did persist in the ABLC group after treatment cessation but did not persist not in the L-AmB group (SCR $P = 0.760$, CrCl $P = 0.969$). More studies and longer follow-up is needed to determine if these differences are clinically significant.

There was also a minor, but statistically significant, decrease in hemoglobin seen in both male and female ABLC patients, but not in L-AmB patients. Although there is a lack of data within the literature concerning lipid-based amphotericin B formulations and their effects on hemoglobin, amphotericin B deoxycholate has been shown to directly suppress erythropoietin production, resulting in decreased hemoglobin levels (26, 27). Neither iron studies nor other potential explanations for decreased hemoglobin levels were investigated further. The decrease in hemoglobin and impaired renal function after discontinuation in the ABLC group may suggest ABLC-related vasoconstriction and renal tubular cell toxicity, which may be irreversible (28, 29). There were no other significant changes in routinely monitored laboratory values, such as bilirubin, which had previously been reported in the literature (20–22, 24, 25).

TABLE 5 Follow-up renal function

Assay	Time		*P* value
	Start of treatment	End of treatment	
Serum creatinine (mg/dl)			
Amphotericin B lipid complex	0.86	1.01	0.009
Liposomal amphotericin B	1.20	1.25	0.760
Creatinine clearance (units/liter)			
Amphotericin B lipid complex	102.4	86.3	0.001
Liposomal amphotericin B	77.3	77.1	0.969

Limitations. This study was a retrospective chart review and is subject to the inherent limitations of such a study design. The lack of blinding and the role of selection bias may be considered a weakness of the study, as those with chronic kidney disease, and perhaps those with more severe baseline disease, appear to have preferentially been given L-AmB. Patients were identified through outpatient registries, and those with acute disease were therefore not included in the study. Most of the patients in our study had pulmonary coccidioidomycosis, but due to the retrospective nature of our study, we were unable to consistently categorize lung involvements, such as severe primary pulmonary, mild pulmonary incidental to more serious disseminated infection, diffuse reticulonodular pulmonary indicative of fungemia, or chronic fibrocavitary infections. We were also therefore not able to clarify response rates between these subcategories. Lastly, we were unable to completely evaluate patients using the Mycosis Study Group scoring system, as follow-up radiology evidence was neither consistently available nor quantified according to the MSG scoring system, and repeat cultures were not collected due to the invasive nature of specimen collection.

Conclusion. This was the first descriptive study of lipid-based amphotericin B therapy in severe coccidioidomycosis patients. All previous studies involving amphotericin B and coccidioidomycosis have been limited to either the conventional deoxycholate formulation or were conducted in nonhuman animal models. Both amphotericin B lipid complex and liposomal amphotericin B were effective and well tolerated in severe coccidioidomycosis patients. A gap in the medical literature remains for treating severe coccidioidomycosis patients, and comparative studies of lipid-based amphotericin B, intravenous triazole therapy, and oral triazole therapy in these patients is needed. Questions about the effects of ABLC and L-AmB on kidney function persist. Clinicians treating those with baseline kidney dysfunction may prefer to use liposomal amphotericin B instead of amphotericin B lipid complex. Prospective studies need to be conducted to evaluate the differences between the lipid-based amphotericin B formulations.

MATERIALS AND METHODS

Eligibility. This study was a retrospective chart review on patients identified through our outpatient infusion center records between January 2005 and December 2014. Inclusion criteria consisted of

TABLE 6 Reasons for switch of formulation or cessation

Documented reason for cessation	Treatment			*P* value
	Combined	Amphotericin B lipid complex	Liposomal amphotericin B	
Total no. of subjects (*n* [%])	69 (100.0)	37 (56.6)	32 (43.4)	
Completion of therapy (*n* [%])	35 (50.7)	17 (45.9)	18 (56.3)	0.553
Early discontinuation of therapy (*n* [%])	33 (47.8)	19 (51.4)	14 (43.8)	
Failure or death	5 (7.2)	1 (2.7)	4 (12.5)	0.117
Acute kidney injury	11 (15.9)	10 (27.0)	1 (3.1)	0.007
Not tolerated	4 (5.8)	3 (8.1)	1 (3.1)	0.377
Noncompliance	10 (14.5)	4 (10.8)	6 (18.9)	0.350
Treatment burden	3 (4.3)	1 (2.7)	2 (6.3)	0.471
Current (*n* [%])	1 (1.4)	1 (2.7)	0 (0.0)	

receiving lipid-based amphotericin B therapy as either amphotericin B lipid complex (ABLC) (Abelcet) or liposomal amphotericin B (L-AmB) (AmBisome) at Kern Medical (KM) outpatient infusion center for the treatment of coccidioidomycosis, having baseline medical records and laboratory assessment prior to initiation of therapy and either one outpatient follow-up for assessment of disease progression (in the form of an infectious disease clinic visit with CF antibody titer and laboratory blood work) or an adverse effect requiring drug discontinuation prior to such a follow-up assessment. All patients received lipid-based amphotericin at the standard dose of 5 mg/kg. Exclusion criteria consisted of age less than 18 years old, meningeal involvement, pregnancy, and patients lost to follow-up after initial assessment.

Assessment. A monitoring form was completed for each patient who met inclusion criteria. The form included demographics, comorbidities, site(s) of coccidioidomycosis infection, radiologic information, culture results, symptoms before and after treatment, type of lipid-based amphotericin B product received, number of weeks of treatment, baseline and end-of-treatment laboratory values, and physician-documented reason for discontinuation of lipid-based amphotericin B. Repeat serum creatinine (SCR) was also recorded after discontinuation for at least a period of 1 month and up to 1 year. All serum creatinine measurements were also analyzed using creatinine clearance (CrCl), as determined by the Cockcroft-Gault equation. Follow-up CrCl was assessed at 1 month post amphotericin cessation or at the first available follow-up within 1 year. Pretreatment regimens for lipid-based amphotericin B included normal saline with or without potassium and/or magnesium, acetaminophen, diphenhydramine, and metoclopramide as needed, but premedications were not included in the analysis.

In lieu of MSG scoring, which was not possible in this retrospective study because of incomplete studies at the conclusion of treatment, we compared the numbers of symptoms and the difference in the coccidioidal CF titers before and at the conclusion of treatment to evaluate the success of response. Symptoms and CF titers were scored as per conventional MSG scoring and were combined into a cumulative score, which we titled the modified MSG score (mMSG).

Statistical analysis. The primary outcome was treatment success; secondary outcomes included physician-documented reason for amphotericin discontinuation and changes in laboratory organ function tests. All changes in lipid-based amphotericin B therapy were recorded and analyzed in terms of reasons requiring treatment discontinuation. Change of formulation was considered treatment failure. For comparisons between the two lipid-based amphotericin B groups, Pearson's chi-square tests or Fisher's exact chi-square tests were used for categorical variables when appropriate, and Mann-Whitney U tests were used for both continuous and discrete ordinal variables. Comparisons within variables from start to end of therapy with the two lipid-based amphotericin B groups were analyzed using Wilcoxon signed-rank tests. All analyses were conducted using STATA version 12.0 (StataCorp LP, College Station, TX).

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