Published in final edited form as:

Infect Dis (Lond). 2019 May ; 51(5): 380–383. doi:10.1080/23744235.2019.1568546.

A clinical pharmacist survey of prophylactic strategies used to prevent adverse events of lipid-associated formulations of amphotericin B

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Keywords

amphotericin B; infusion related adverse events; nephrotoxicity; antifungal agents

To the Editor,

Correspondence to: Daniel B. Chastain.

Conflicts of interest: CMB: Speaker's Bureau (Merck); Grant Funding: ALK Abello. All other authors have none to disclose.

Previous presentation: These data were presented at American Society of Health System Pharmacists (ASHP) 2017 Midyear Clinical Meeting in Orlando, Florida on December 4, 2017 (Abstract 2–090).

As illustrated by a recent report in this journal, lipid-associated formulations of amphotericin B (LFABs) have the potential to cause acute kidney injury and infusion-related adverse events [1]. Since LFABs affords an efficient therapy for invasive fungal infections, we undertook a study to identify prophylactic strategies aiming to prevent the adverse events at different institutions.

This study used a cross-sectional research design. The Institutional Review Board at the University of Georgia approved this study as exempt. An 18-item REDCap™ (Research Electronic Data Capture) survey was used to obtain responses from pharmacy professionals involved in LFAB administration and monitoring. Surveys were electronically distributed to pharmacy professionals who were members of the Infectious Diseases Practice and Research Network of the American College of Clinical Pharmacy and the Society of Infectious Diseases Pharmacists. Respondents were allowed a period of 4 weeks from the initial email to participate in the survey. Survey items assessed the following: demographic and practice characteristics (including level of experience, primary practice setting, and institution size), frequency of LFAB administration, dosing schemes, most frequent indication, and presence of an institutionally-adopted LFAB administration protocol. Respondents were asked to describe prophylactic strategies employed at their institution aimed at decreasing the risk of acute kidney injury and infusion-related adverse events, as well as estimate rates of discontinuation of LFABs due to renal dysfunction/acute kidney injury and infusion-related adverse events. Descriptive statistics were calculated to characterize participants' demographic and practice characteristics, and rates of prophylactic strategies administered. Bivariate and multivariate analyses were used to identify characteristics associated with acute kidney injury- or infusion-related adverse event-related discontinuations with significant associations determined at the apriori 0.05 level of significance. Statistical analyses were performed using STATA® version 15 (StataCorp. College Station, TX).

A total of 93 participants responded to the survey (table 1). Most participants were infectious diseases pharmacists (80.6%) with primary practice sites in academic/university medical centers (49.5%) or teaching community hospitals (28.0%). Liposomal amphotericin B was most commonly used (87.1%) at 5 mg/kg (63.4%) based on actual body weight (54.8%) for the treatment of cryptococcal meningitis (48.4%). At least monthly administration of LFABs was reported by 62.4% of respondents; however, most institutions lacked an established protocol for LFAB administration (61.3%).

Pharmacist experience did not significantly affect rates of discontinuation due to acute kidney injury ($p=0.216$) or infusion-related adverse events ($p=0.255$). The administrations of either amphotericin B lipid complex and liposomal amphotericin B were not associated with higher or lower rates of perceived discontinuation due to acute kidney injury ($p=0.943$) or infusion-related adverse events ($p=0.675$). An established protocol for LFAB administration, or lack thereof, did not impact discontinuation rate due to acute kidney injury ($p=0.715$) or infusion-related adverse events ($p=0.105$).

Routine administration of intravenous fluid boluses as a prophylactic strategy to prevent acute kidney injury was reported by 67.7% of respondents. LFABs were estimated to be discontinued due to AKI in 17.6% of cases (figure 1). Timing of intravenous fluid

administration was not associated with higher or lower rates of discontinuation due to acute kidney injury ($p=0.999$). The type of intravenous fluid used was not associated with higher or lower rates of discontinuation due to acute kidney injury ($p=0.309$). Pharmacists who reported using intravenous fluid boluses had significantly greater estimated rates of acute kidney injury-related discontinuations compared to those who did not ($p=0.003$).

Routine administration of pre-medications as a prophylactic strategy to prevent infusion-related adverse events was reported by 50% of respondents. Infusion-related adverse events were estimated to result in 4.8% of discontinuations (figure 1). There was not a significant increase or decrease in the rates of discontinuation due to infusion-related adverse events with or without the administration of pre-medications ($p=0.0613$). Estimated rate of infusion-related adverse event-related discontinuations was higher in participants reporting routine administration of pre-medications than those who did not, 6.1% vs 3.5% ($p=0.061$), respectively. Administration of acetaminophen ($p=0.063$) or corticosteroids ($p=0.525$) was not associated with significant increases or decreases in rates of discontinuation due to infusion-related adverse events. Bivariate analyses revealed that participants who used diphenhydramine to decrease the risk of infusion-related adverse events indicated a higher rate of discontinuation due to infusion-related adverse events in comparison to participants who did not indicate using diphenhydramine (6.4% vs. 3.4%, $p<0.05$).

Respondents reported limited use of prophylactic strategies to prevent acute kidney injury- and infusion-related adverse event-related discontinuations in patients receiving LFABs. The dissimilarities observed amongst prophylactic strategies are possibly linked to infrequent use of LFABs, as their primary role is in the management of life-threatening fungal infections, as well as a lack of conclusive evidence supporting these strategies. Additionally, controversy exists amongst data comparing rates of acute kidney injury and infusion-related adverse events with individual LFABs [2, 3]. This may be directly related to an incomplete understanding of the pathogenesis of amphotericin B-induced nephrotoxicity and infusion-related adverse events.

Afferent renal artery vasoconstriction, proximal tubular cell injury, and renal tubular acidosis have been proposed as mechanisms behind amphotericin B nephrotoxicity. Amphotericin B increases permeability of the macula densa cells leading to inappropriate activation of the tubuloglomerular feedback system inducing arteriolar vasoconstriction resulting in decreased glomerular filtration rate [4]. Volume expansion with saline is believed to decrease both the sensitivity of the tubuloglomerular feedback and release of atrial natriuretic peptide in order to preserve glomerular filtration rate [4]. While data supports the use of saline as a nephrotoxicity prevention strategy with AmB-d, the precise volume of saline necessary and whether this can be extrapolated to LFABs is less clear [4]. Routine administration of intravenous fluid boluses reported in our survey was lower than expected. This could be due the belief that slower release of amphotericin B by LFABs leads to less direct interaction with tubular cells which negates the need for volume expansion. Furthermore, this may also account for the discrepancy regarding intravenous fluid bolus type and volume. Results from our study revealed administration of intravenous fluid boluses were associated with a higher estimated rate of acute kidney injury-related LFAB

discontinuation; possibly lending support to the inconsistencies observed in respondent's practice patterns.

Although infusion-related adverse events typically subside over the course of initial infusions, infusion-related adverse events may lead to premature discontinuation of LFABs. The mechanism of amphotericin B-induced infusion-related adverse events is not completely understood. It has been proposed that AmB-d stimulates interleukin (IL)-1, IL-1 β , and tumor necrosis factor thereby increasing prostaglandin E2 release altering the hypothalamic set point. While most patients treated with AmB-d experienced an infusion-related adverse event, adjunctive pre-medication regimens vary in terms of composition and efficacy with some being no more effective than placebo [5]. Compared to AmB-d, overall rates of infusion-related adverse events are significantly decreased with LFABs [6]. However, in patients treated with LFABs who experience infusion-related adverse events, symptoms are notably different and include chest pain, flushing, and back pain, which is thought to be caused by the liposome rather than amphotericin B [7]. Limited data suggests benefit from prophylactic diphenhydramine, but also note a sporadic pattern of infusion-related adverse events year to year, despite using the same LFAB [6]. Approximately half of respondents reported routine use of pre-medications, of which almost all acknowledged use of both acetaminophen and diphenhydramine. The use of diphenhydramine was associated with a higher estimated rate of infusion-related adverse event-related discontinuation in our study but is comparable to previously published rates of infusion-related adverse event-related discontinuations [8].

Liposomal amphotericin B was the most common LFAB formulation used. Some data suggests it may be associated lower rates of nephrotoxicity when compared to other LFABs [9]. Additionally, most respondents reported dosing LFABs using actual body weight. While our survey did not assess specific patient demographics, literature suggests using lean body weight as low concentrations of amphotericin B are found in muscle or adipose tissue [10]. Dosing LFABs on actual body weight in obese patients may account for the higher estimated rates of acute kidney injury- and infusion-related adverse event-related discontinuations observed in our study.

Several limitations exist in our study that warrant discussion. The survey was sent to members of organizations that targeted pharmacists with interests in infectious diseases. This could introduce selection bias; however, this study sought to target professionals who are familiar and experienced in the dosing and administration of LFABs. The data collected in this study were self-reported which may be subject to recall bias, thus the rates of discontinuation are estimations. Therefore, in respondents who reported lower rates of discontinuation, it is unknown if more conservative approaches to therapies were made. These individuals may only administer LFABs to patients with low risk of developing adverse events, such as acute kidney injury or infusion-related adverse events. Lastly, clinical characteristics of patients were not collected included in the survey. This information is required when dosing and administering LFABs in practice. Future research should include patient specific data to identify any associations between patients' clinical status and history with rates of discontinuation.

Therapy discontinuations due to acute kidney injury and infusion-related adverse events are still reported in patients treated with LFABs. A variety of prophylactic strategies were reported to decrease rates of acute kidney injury- and infusion-related adverse event-related discontinuations. However, administration of intravenous fluid boluses or diphenhydramine was significantly associated with increased estimated rates of LFAB discontinuation due to acute kidney injury or infusion-related adverse events, respectively. Future studies should be conducted to identify a more efficacious prophylactic strategy to avoid these preventable adverse events to improve patient safety and tolerability during LFAB administration.

Acknowledgements:

We acknowledge the American College of Clinical Pharmacy Infectious Diseases Practice and Research Network (ACCP ID PRN) and the Society of Infectious Diseases Pharmacists (SIDP) for allowing survey distribution to its membership.

Funding: The use of REDCap™ was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002378. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Li SS, Tang XY, Zhang SG, et al. Voriconazole combined with low-dose amphotericin B liposome for treatment of cryptococcal meningitis. *Infect Dis (Lond)*. 2016;48:563–5. [PubMed: 27044559]
2. Mistro S, Maciel Ide M, de Menezes RG, et al. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. *Clin Infect Dis*. 2012;54:1774–7. [PubMed: 22491505]
3. Wingard JR, White MH, Anaissie E, et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis*. 2000;31:1155–63. [PubMed: 11073745]
4. Branch RA. Prevention of amphotericin B-induced renal impairment. A review on the use of sodium supplementation. *Arch Intern Med*. 1988;148:2389–94. [PubMed: 3056312]
5. Goodwin SD, Cleary JD, Walawander CA, et al. Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis*. 1995;20:755–61. [PubMed: 7795069]
6. Roden MM, Nelson LD, Knudsen TA, et al. Triad of acute infusion-related reactions associated with liposomal amphotericin B: analysis of clinical and epidemiological characteristics. *Clin Infect Dis*. 2003;36:1213–20. [PubMed: 12746764]
7. Szebeni J, Fontana JL, Wassef NM, et al. Hemodynamic changes induced by liposomes and liposome-encapsulated hemoglobin in pigs: a model for pseudoallergic cardiopulmonary reactions to liposomes. Role of complement and inhibition by soluble CR1 and anti-C5a antibody. *Circulation*. 1999;99:2302–9. [PubMed: 10226097]
8. Girois SB, Chapuis F, Decullier E, et al. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2006;25:138–49. [PubMed: 16622909]
9. Falci DR, da Rosa FB, Pasqualotto AC. Comparison of nephrotoxicity associated to different lipid formulations of amphotericin B: a real-life study. *Mycoses*. 2015;58:104–12. [PubMed: 25590436]
10. Christiansen KJ, Bernard EM, Gold JW, et al. Distribution and activity of amphotericin B in humans. *J Infect Dis*. 1985;152:1037–43. [PubMed: 4045244]

Figure 1.

Primary clinical factors reported with LFAB discontinuations due to AKI and IRAEs

IVF, intravenous fluid; LFAB, lipid-associated formulation of amphotericin B; AKI, acute kidney injury; IRAE, infusion related adverse event

Table 1.

Descriptive statistics of study variables (N=93)

Variable	n (%)
Level of experience	75 (80.6)
Infectious diseases pharmacist	
Practice site	46 (49.5)
Academic/university hospital	26 (28.0)
Teaching community hospital	
Administration frequency	21 (22.6)
Weekly	36 (38.7)
Monthly	36 (38.7)
Less than 6 times per year	
Formulation	81 (87.1)
Liposomal amphotericin B	12 (12.9)
Amphotericin B lipid complex	
Dose	19 (20.4)
3 mg/kg	12 (19.0)
4 mg/kg	59 (63.4)
5 mg/kg	3 (3.2)
6 mg/kg	
Dosing weight	7 (7.5)
Ideal body weight	51 (54.8)
Actual body weight	26 (27.9)
Adjusted body weight	
Indication	15 (16.1)
Empiric antifungal therapy	3 (3.2)
Coccidioidomycosis	45 (48.4)
Cryptococcal meningitis	15 (16.1)
Histoplasmosis	2 (2.2)
Candidiasis	
Protocol for LFAB administration	36 (38.7)
Routine use of intravenous fluid boluses	63 (67.7)
Timing of intravenous fluid boluses	25 (39.7)
Before only	38 (60.3)
Before and after	
Intravenous fluid bolus volume	44 (69.8)
500 mL	10 (15.9)
1000 mL	
Total volume of intravenous fluid boluses	20 (31.7)
500 mL	33 (52.8)
1000 mL	5 (7.9)
2000 mL	
Type of intravenous fluid	58 (92.1)
0.9% sodium chloride	3 (4.8)
Dextrose 5% in water	
Routine use of pre-medications	48 (51.6)
Acetaminophen	46 (95.8)
Diphenhydramine	45 (93.8)
Corticosteroids	8 (16.7)
Meperidine	1 (2.1)

LFAB, lipid-associated formulation of amphotericin B; IVF, intravenous fluids