MAJOR ARTICLE

Triad of Acute Infusion-Related Reactions Associated with Liposomal Amphotericin B: Analysis of Clinical and Epidemiological Characteristics

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We investigated the clinical characteristics and treatment of patients with a distinctive triad of acute infusion-related reactions (AIRRs) to liposomal amphotericin B (L-AMB) via single-center and multicenter analyses. AIRRs occurred alone or in combination within 1 of 3 symptom complexes: (1) chest pain, dyspnea, and hypoxia; (2) severe abdomen, flank, or leg pain; and (3) flushing and urticaria. The frequency of AIRRs in the single-center analysis increased over time. Most AIRRs (86%) occurred within the first 5 min of infusion. All patients experienced rapid resolution of symptoms after intravenous diphenhydramine was administered. The multicenter analysis demonstrated a mean overall frequency of 20% (range, 0%–100%) of AIRRs among 64 centers. A triad of severe AIRRs to L-AMB may occur in some centers; most of these reactions may be effectively managed by diphenhydramine administration and interruption of L-AMB infusion.

For many years, amphotericin B deoxycholate (D-AMB) was the only therapeutic option for the treatment of invasive mycoses. Its clinical utility, however, has been restricted by dose-limiting nephrotoxicity and infusion-related reactions (IRRs) [1, 2]. Intravenous infusions of D-AMB have been commonly associated with fever, chills, rigors, nausea, vomiting, and headaches [3, 4]. Although they are less common, more-severe reactions to D-AMB infusions, such as hypotension, anaphylaxis, and other cardiac events, also occur [5]. Consequently, many clinicians will administer premedication to patients with acetaminophen, diphenhydramine, or hydrocortisone before the infusion of the D-AMB in an effort to prevent or ameliorate these toxicities [6].

Liposomal amphotericin B (L-AMB; AmBisome, Fujisawa Healthcare) was approved for use in the United States in 1997. With this new formulation of amphotericin B came a significant decrease in both nephrotoxicity and the frequency of IRR [7]. In the absence of premedication, patients routinely tolerated the infusion of L-AMB well, with no associated infusion-related toxicity. Although there has been an overall decrease in the frequency of infusion-related toxicity with L-AMB compared with D-AMB, there still exists a less common but severe triad of reactions due to L-AMB [7–12]. This phenomenon is characterized by ≥ 1 of the following IRRs: chest pain, dyspnea, hypoxia, flank pain, abdominal pain, leg pain, flushing, and urticaria. We noted that these acute IRRs (AIRRs) have increased in frequency since the introduction of L-AMB. Although individual cases of AIRRs to L-AMB infusions have been previously described, the epidemiology and clinical manifestations of this unusual but severe re-

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action are poorly understood. Therefore, we investigated the clinical features and demographic characteristics of patients and the potential risk factors for and management of these reactions in patients who were observed prospectively during 6 years in 6 different clinical trials.

MATERIALS AND METHODS

Definitions of AIRRs. On the basis of our bedside observations, we classified a triad of 3 individual clusters of AIRRs, as follows: (1) chest pain, dyspnea, and hypoxia; (2) flank pain, abdominal pain, and leg pain; and (3) flushing and urticaria. An AIRR was defined as any one of these symptoms occurring alone or in combination during the course of the L-AMB infusion. The following signs and symptoms occurring during infusion of L-AMB were defined as follows for the purposes of this study: "chest pain," crushing substernal pressure; "dyspnea," subjective difficulty or distress in breathing (usually associated with chest pain); "hypoxia," decreased oxygen saturation (<90%) measured by pulse oximetry; "abdominal pain," sharp and severe discomfort in the abdomen and/or pelvis; "flank pain," sharp and severe discomfort in the lower back or lumbar region; "leg pain," sharp and severe discomfort in the lower extremities; "flushing," transient facial erythema; and "urticaria," an eruption of pruritic wheals (usually occurring on the face)

Single-center analysis. Six institutional review board–approved clinical trials of L-AMB were conducted at the National Cancer Institute of the Warren Grant Magnuson Clinical Center at the National Institutes of Health (NIH; Bethesda, MD) during 1994–1999. A total of 84 patients received L-AMB during 1 of these 6 clinical trials. All infusions of L-AMB were prospectively monitored for all IRRs through validated bedside monitoring sheets by the nurse administering the L-AMB infusion. Per protocol, the patients were not allowed to receive premedication before the first dose of L-AMB was administered. In 1999, as a result of an increased frequency of AIRRs, the last 5 patients in this cohort received premedication with diphenhydramine. Before 1999, if a patient developed an AIRR, the patient would be treated for the reaction and thereafter could receive premedication for subsequent doses. Thus, only the first infusion permitted a consistent assessment of IRRs uninfluenced by premedication. Consequently, the IRRs associated with only the first dose of L-AMB were analyzed. The case report forms, medical records, and bedside monitoring sheets for the first infusion were reviewed for all 84 patients who received L-AMB while enrolled in an institutional review board–approved clinical trial at the NIH Clinical Center during 1994–1999.

The study patient population consisted primarily of immunocompromised children and adults with cancer, aplastic anemia, HIV infection, or inherited immunodeficiencies, such as chronic granulomatous disease. Patients received L-AMB for either empirical antifungal therapy or for the treatment of proven or probable invasive mycoses. One immunocompetent patient was treated for leishmaniasis with L-AMB.

Statistical associations between possible risk factors and the development of AIRRs were evaluated. These potential risk factors included underlying disease, level of immunosuppression, L-AMB manufacturing lot, individual doses of L-AMB, rates of infusion, concentration of infusion, intravenous tubing, and type of central line through which the drug was infused. The administration and preparation procedures for the drug were reviewed in detail with the NIH Clinical Center's Department of Pharmacy.

Procedures for reconstitution by pharmacy. Each 50-mg vial is reconstituted with 12 mL of sterile water for injection to an initial concentration of 4 mg/mL, shaken vigorously for 30 s, and allowed to stand for 10 min to allow bubbles to dissipate. This initial suspension is referred to as the "reconstituted product concentrate." The reconstituted product concentrate may be stored at 2°C–8°C (36°F–46°F) for up to 24 h.

The volume of the reconstituted product concentrate required for the patient's daily dose is then filtered through a 5-μm filter and diluted with 5% dextrose in water to a final concentration of 2 mg/mL. The infusion of L-AMB should commence within 6 h of the final dilution with 5% dextrose.

There were slight differences among pharmacy units in the techniques used for shaking vials during reconstitution. For consistency across hospital pharmacy units, each vial of L-AMB was shaken by hand immediately after the diluent was added. Whether the vials were shaken immediately after rehydration or whether they were shaken by hand or by an automated device made no difference with regard to the occurrence of AIRRs.

Multicenter analysis. We then further sought to understand the extent of AIRR due to L-AMB in other institutions. All 422 patients from 64 centers who were randomized during the period of March 1998 through June 1999 to receive L-AMB in the randomized trial of voriconazole versus L-AMB for empirical antifungal therapy (National Institute of Allergy and Infectious Diseases Mycoses Study Group [NIAID MSG] Study 42) were also reviewed [13]. The frequency and characteristics of AIRRs were analyzed for each center and for the entire cohort of patients.

Statistical analysis. χ^2 Analysis and Fisher's exact test, when appropriate, were used to compare categorical variables, and Dunnett's correction was used for correction of multiple comparisons. Differences between categorical variables of potential risk factors also were assessed by 95% CIs and by relative risk ratios. The Wilcoxon rank sum test was used for determination of differences between continuous variables that were

nonparametrically distributed. $P \leq .05$ was considered to be statistically significant.

RESULTS

Single-Center Analysis

Demographic characteristics. Eighty-four patients received L-AMB at the NIH during 1994–1999. Patients were similarly distributed in AIRR and no-AIRR cohorts by age, sex, and type of immunosuppression. Patients were similar with regard to underlying disease, with exception of those with lymphoma and breast cancer. This was because of more-active enrollment into different antineoplastic protocols for lymphoma and breast cancer in 1994–1995 than in subsequent years (table 1). Those patients were not receiving chemotherapy or corticosteroids at the time that they experienced their IRRs.

Of the 84 patients treated, 29 (35%) exhibited symptoms of AIRRs with the first infusion of L-AMB. During 1994 and 1995, the overall frequency of AIRRs was 6% and 17% of infusions, respectively. Starting in 1996, the frequency of AIRRs abruptly increased to 50% of all infusions. The frequency of AIRR culminated in a peak of 65% of infusions in 1998. By 1999, patients received premedication with diphenhydramine before the L-AMB infusion in efforts to prevent AIRRs. The frequency of AIRRs, however, was still 40% with receipt of prophylactic diphenhydramine (figure 1).

Clinical characteristics. On the basis of this clinical experience, we categorized AIRRs into a triad of symptoms (figure 2). The first category of symptoms included chest pain, dyspnea, and hypoxia. The second category consisted of rapid onset of severe pain in the abdomen, flanks, or legs. The third category of symptoms was categorized by flushing and urticaria. Symptoms in the first 2 categories occurred usually within the first 5 min of infusion. By comparison, urticaria and flushing tended to occur toward the end of the infusion. Category 1 (chest pain, dyspnea, and hypoxia) was the most common cluster of adverse reactions, occurring in 17 patients, followed by categories 3 and 2. Overlap of these categories occurred for 7 patients.

These 3 individual symptom complexes that represent the triad were evaluated separately for risk factors. All 3 complexes increased in frequency over time. The demographic characteristics of patients with AIRRs were similar within each symptom complex. The underlying neoplasms were similar, with ~50%

Table 1. Demographic characteristics of patients receiving liposomal amphotericin B to treat acute infusion-related reactions (AIRRs), 1994–1999.

Characteristic	Patients with AIRRs	Patients without AIRRs	Total	*P*	95% CI
Age, mean years ± SEM	27.5 ± 14	39.3 ± 15	35.2 ± 15.4	.41	—
Sex					
Male	16	24	40	.44	0.75–2.45
Female	13	31	44	.44	0.41–1.34
Immunosuppression					
Neutropenia	25	47	72	.93	0.44–2.46
HIV infection	4	2	6	.18	1.08–3.99
Chronic granulomatous disease	2	0	2	.12	2.23–4.14
Graft-versus-host disease	0	1	1	1.0	—
None	1	0	1	.35	2.19–4.01
Underlying disease					
Leukemia	10	13	23	.42	0.77–2.54
Lymphoma	2	17	19	.01	0.07–0.97
Breast cancer	2	13	15	.07	0.09–1.28
Sarcoma	4	2	6	.18	1.08–4.00
HIV infection	4	2	6	.18	1.08–4.00
Aplastic anemia	2	2	4	.61	0.53–4.14
Myelodysplastic syndrome	1	3	4	1.00	0.13–4.00
Multiple myeloma	0	3	3	.55	—
Chronic granulomatous disease	2	0	2	.12	2.23–4.14
Paroxysmal nocturnal hemoglobinuria	1	0	1	.35	2.19–4.01
Leishmaniasis	1	0	1	.35	2.19–4.01

NOTE. Data are no. of patients, unless otherwise indicated.

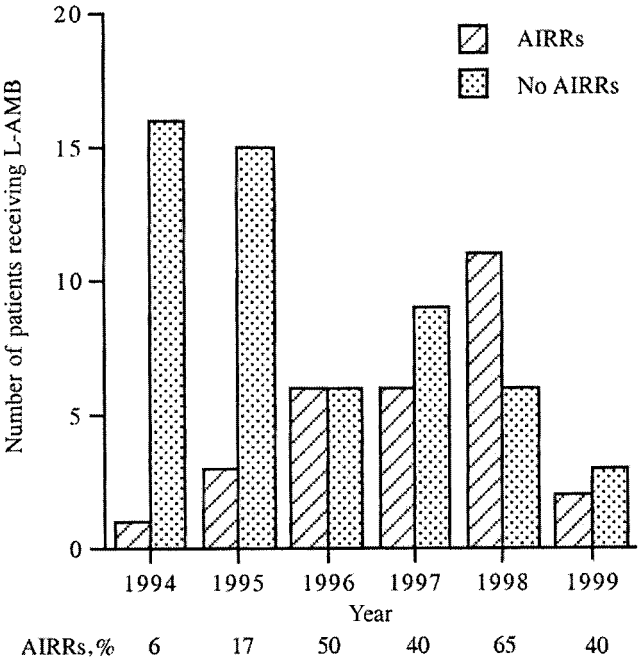

Figure 1. Frequency of acute infusion-related reactions (AIRRs), 1994–1999. L-AMB, liposomal amphotericin B.

of patients within each symptom complex having hematological malignancies.

The majority (86%) of the AIRRs occurred within the first 5 min of study drug administration. There were 2 patients (6.9%) with chest pain, which occurred 20 min into the infusion. There also were 2 patients (6.9%) with urticarial responses that developed toward the end of the infusion. All other episodes occurred within the first 5 min of infusion.

Management. All of the patients who experienced AIRRs had rapid relief of symptoms when treated with diphenhydramine (1 mg/kg) and with interruption of L-AMB infusion. Of the patients who developed respiratory symptoms, 21% received oxygen by mask or nasal cannula. Of those patients who developed AIRRs, 93% were rechallenged; these patients tolerated the remainder of that infusion well and were able to tolerate subsequent infusions with receipt of diphenhydramine premedication. It is of interest that 2 patients were rechallenged without diphenhydramine and were able to tolerate the infusion without reactivation of symptoms, which suggests acclimation through the depletion of mediators (table 2).

Because of the increased frequency of these events, in 1999, premedication with diphenhydramine was routinely administered. Patients intravenously received 1 mg/kg of diphenhydramine 30 min before their first infusion of L-AMB. Of the 5 patients who were treated with L-AMB in 1999, 2 continued to have breakthrough AIRRs, despite receipt of 1 mg/kg of diphenhydramine premedication. Both patients exhibited chest pain with some associated respiratory distress.

Potential risk factors. We examined potential risk factors for the development of AIRRs. Among the different lots, only the lot of 1994, which was associated with the lowest frequency of AIRRs, was significantly different from the overall events, when adjusted for multiple comparisons ($P = .04$). There was no correlation between the development of AIRRs and other specific lot numbers; dosage, duration, and concentration of L-AMB therapy; vehicles used to administer the drug; type of vascular catheter; or tubing type (table 3). Nor was there any correlation between AIRRs and demographic characteristics. The frequency of AIRRs associated with lot 0422012E in 1994 was only 6%, suggesting that some modification in the manufacturing or preparation may have occurred during 1995 and thereafter.

The procedures for pharmacy preparation and administration were reviewed in detail with the pharmacy staff and the manufacturer. All doses of L-AMB used in this study were from the investigational drug supply and were prepared according to the manufacturer's procedures (Fujisawa USA).

Multicenter Analysis

To determine whether AIRRs were a problem observed in other institutions, we reviewed the IRRs for all patients randomized

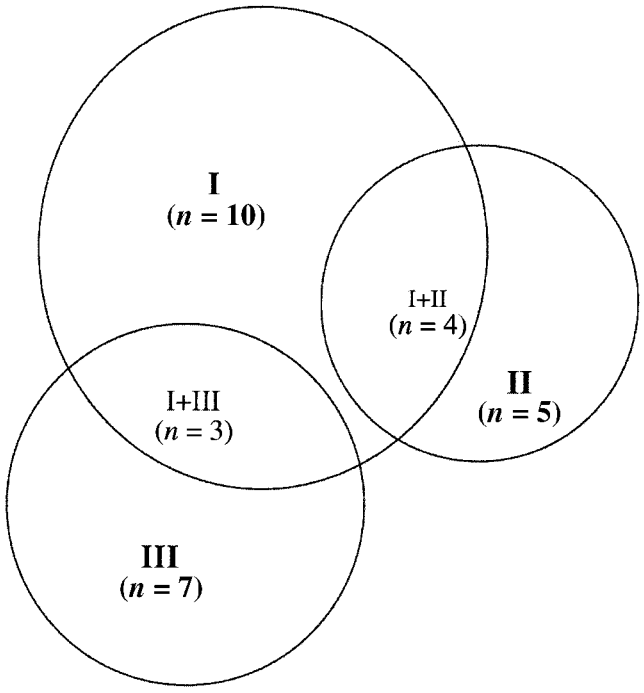

Figure 2. Triad of acute infusion-related reactions occurring alone or in combination. Triad of symptoms and signs consists of 3 clusters of adverse reactions: cluster I, chest pain, dyspnea, and hypoxia; cluster II, flank abdominal and leg pain; and cluster III, flushing and urticaria.

Table 2. Clinical characteristics of 29 patients who exhibited symptoms of acute infusion-related reactions (AIRRs) and management of AIRRs.

Clinical characteristic or management	No. (%) of patients
Clinical characteristic	
Chest pain	13 (45)
Dyspnea	10 (34)
Hypoxia	2 (7)
Abdominal pain	1 (3)
Flank pain	7 (24)
Leg pain	1 (3)
Flushing	7 (24)
Urticaria	4 (14)
Management	
Diphenhydramine administration	27 (93)
Infusion interruption and resumption after diphenhydramine administration	27 (93)
Oxygen administration	6 (21)
Infusion permanently discontinued	4 (14)
Successful continuation of liposomal amphotericin B therapy upon rechallenge ($n = 25$)	25 (100)

NOTE. Some patients had >1 symptom or sign of an AIRR.

to receive L-AMB in the clinical trial of voriconazole versus L-AMB for empirical antifungal therapy in persistently febrile, neutropenic patients (NIAID MSG Study 42). All infusions were prospectively monitored in this trial by the nurse who administered the infusion at the bedside. IRRs were recorded on validated bedside monitoring sheets that were part of the source documents for this clinical trial and were monitored for 100% source verification. This analysis demonstrated that other centers also experienced relatively high frequencies of AIRRs. The mean frequency of patients experiencing AIRRs due to L-AMB was 20% (range, 0%–100%) and led to 65% of all premature discontinuations of L-AMB in this trial. Although some centers had very few, if any, patients with AIRRs, other centers had frequencies of 50%–100%. Intersite variation in the frequency of AIRRs is detailed in figure 3.

The distribution of lots used in the multicenter study was analyzed as a variable. However, there continued to be variation in the frequency of AIRRs among those centers that received the same lot. For example, the NIH received 1 lot throughout the clinical trial, and the frequency of AIRRs associated with that lot was 57% (12 of 21 recipients). The same lot was distributed to another site, and the frequency of AIRRs at that site with the same lot was 7% (1 of 14 recipients).

DISCUSSION

Dose-limiting, infusion-related toxicity associated with D-AMB is well described. The introduction of the lipid formulations of amphotericin has made a substantial contribution to diminishing the frequency of these events. The double-blind, randomized trial that compared D-AMB with L-AMB for empirical antifungal therapy demonstrated significant reductions in both nephrotoxicity and infusion-related toxicity for L-AMB [7]. Consistent with this observation, another double-blind, randomized trial that compared L-AMB with amphotericin B lipid complex also demonstrated that there was significantly less overall infusion-related toxicity associated with the L-AMB preparation of amphotericin than with amphotericin B lipid complex [14].

The symptoms that occur in response to L-AMB infusion differ substantially from those associated with D-AMB administration. Infusion-related toxicity with the latter is typically associated with fever, chills, rigors, nausea, vomiting, and headache. Onset of these toxicities usually began within 1–3 h after initiation of the infusion and could be ameliorated by slowing the rate of infusion [15, 16]. Conversely, the onset of AIRRs associated with L-AMB usually occurs within the first 5 min of infusion. Slowing of the L-AMB infusion appeared to have no effect. Once the patients received diphenhydramine (1 mg/kg), symptoms quickly abated, and patients were able to tolerate the remainder of the first infusion and subsequent infusions without incident. It was not necessary in any of these cases to slow the rate of infusion. Within our institution, there was no evidence of any potentially contributing variables to have caused these reactions. We attempted to change the intravenous tubing in which the drug was infused and the bottle or bag in which the drug was prepared. We also attempted to decrease the concentration of the infusion and lengthened the duration of the infusion. Unfortunately, none of these interventions resulted in the prevention of AIRRs associated with the first infusion.

That AIRRs were not unique to one institution was demonstrated in the multicenter trial of NIAID MSG Study 42. This subset of patients who developed AIRRs to L-AMB appears to be clustered within specific institutions, and, overall, the frequency of events has increased over time. The frequency of patients with AIRRs reported in 1995–1996 during the empirical trial of L-AMB and D-AMB (MSG 32) was <5% [7]. The overall frequency of patients with AIRRs reported in 1998–1999 during the empirical trial comparing voriconazole with L-AMB (MSG 42) was 20% [13].

To further understand these IRRs, we also queried the US Food and Drug Administration MedWatch database for 1998–2002. There were 33 cases of AIRRs reported from other institutions. All were very similar in presentation to what we described. Of the 33 reported patients, 26 had symptoms from complex 1, 7 had symptoms from complex 2, and 5 had symptoms from complex 3. Of those patients with documented onset of symptoms, onset occurred within the first 5 min of infusion

Table 3. Potential risk factors for acute infusion-related reactions (AIRRs) in patients receiving liposomal amphotericin B (L-AMB).

Potential risk factor	No. of patients			RR (95% CI)	*P*
	With AIRRs	Without AIRRs	Overall		
Catheter type					
Hickman[a]	27	50	77	1.23 (0.37–4.12)	.73
Intrajugular line	0	3	3	0 (—)	.55
Percutaneously inserted central line	0	1	1	0 (—)	1.00
Port-a-Cath[a]	1	0	1	2.96 (2.19–4.01)	.35
Groshong[a]	0	1	1	0 (—)	1.00
Femoral	0	1	1	0 (—)	1.00
Peripheral	1	0	1	2.96 (2.19–4.01)	.35
Year and tubing type					
1994–1999, Alaris or Codan	22	41	63	1.49 (0.80–2.77)	.27
1995–1998, Abbott provider	7	14	21	0.95 (0.48–1.91)	.90
L-AMB dose, mg/kg					
1.0	0	3	3	0 (—)	.55
2.5	1	4	5	0.56 (0.10–3.34)	.66
3	15	21	36	1.43 (0.79–2.57)	.34
4	1	0	1	2.96 (2.19–4.01)	.35
5	—	13	18	0.76 (0.34–1.72)	.69
7.5	4	7	11	1.06 (0.46–2.47)	1.00
10	3	6	9	0.96 (0.36–2.55)	1.00
12.5	0	1	1	0 (—)	1.00
Infusion rate, mg/mL					
0.5	1	0	1	2.96 (2.19–4.01)	.35
1	3	11	14	0.58 (0.20–1.65)	.36
2	23	40	63	1.28 (0.60–2.71)	.69
200	2	4	6	0.96 (0.3–3.11)	1.00

NOTE. RR, risk ratio.

[a] Manufactured by Bard.

for 73%, which was also consistent with what we reported. That symptoms of complex 1 were more frequent than were those of complex 2 or complex 3 is also consistent with our single-center data (figure 2). Because MedWatch data are collected through voluntary reporting, an accurate estimate of incidence of AIRR cannot be ascertained.

The liposome rather than the amphotericin B component of L-AMB appears to be the key factor inducing AIRRs. A similar triad of symptoms occurs with the administration of liposomal doxorubicin. The triad that has been reported typically consists of chest pain, flushing, and back pain [17, 18]. As with our patients, the symptoms usually occurred within the first 5 minutes of the infusion and resolved when the infusion was discontinued. These patients were also able to tolerate subsequent doses of lipid-associated doxorubicin without incident. Because the pattern of toxicity for L-AMB and L-doxorubicin is different than that for D-AMB, it is likely that the patients are reacting to the liposome vehicle as opposed to the active drugs.

Complement activation may contribute to the pathogenesis of this syndrome. Clinical studies of some lipid-associated drugs demonstrate a 7%–9% frequency of IRRs, similar to the frequencies seen for L-AMB [17, 18]. The symptoms are described as rash, flushing, urticaria, and mild-to-severe respiratory and cardiovascular symptoms occurring immediately or shortly after the initiation of the infusion. The reaction has been referred to as "pseudoallergic," because there is no classic IgE-mediated, type 1 mechanism associated with the reactions [19]. Laboratory investigations conducted by Szebeni et al. [19] demonstrated that minute doses of liposomes administered to pigs led to pulmonary vasoconstriction, tachycardia, and changes in systemic arterial pressure. The effects were transient and reproducible in the same animal without tachyphylaxis. The effect was mediated by a heat-sensitive plasma factor, indicating the

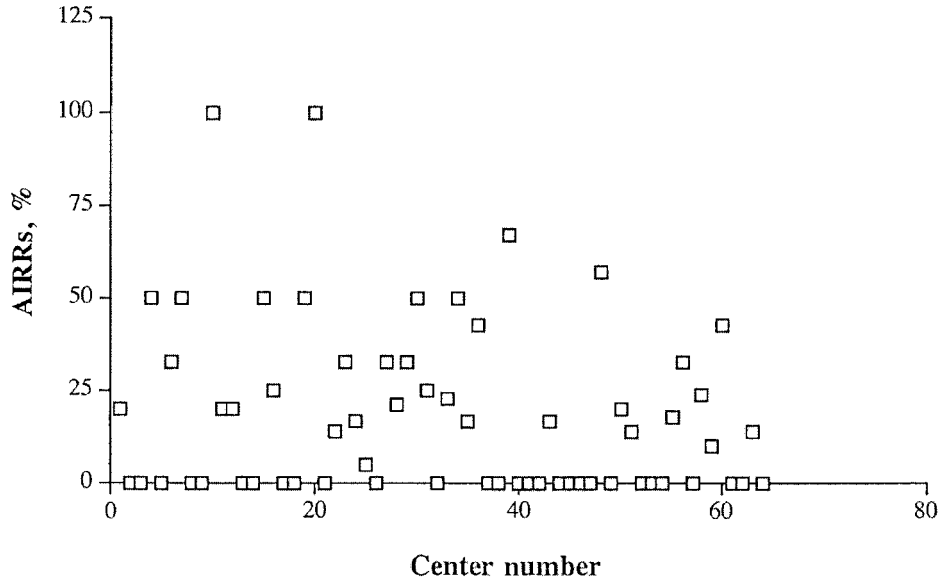

Figure 3. Frequency of acute infusion-related reactions (AIRRs) in 64 health care centers during 1998–1999 from National Institute of Allergy and Infectious Diseases Mycoses Study Group Study 42 [13]. There was marked intercenter variation in the frequency of AIRRs.

role of complement. The liposome also induced pulmonary changes that were significantly reduced with GS1, an anti-C5a monoclonal antibody, and were completely suppressed by soluble complement receptor type 1 (sCR1), a recombinant, truncated form of the erythrocyte membrane protein CRI. The pulmonary and hemodynamic physiological changes observed in this experimental model are similar to those observed in a patient who received a multilamellar lipid formulation of amphotericin B [9].

A change in manufacturing methods in 1995 may be one variable contributing to the change in frequency of AIRRs over time. Furthermore, in 1994 and 1995, the frequencies of AIRRs at our institution were 6% and 17%, respectively. During the years 1996, 1997, 1998, and 1999, the frequency changed to 50%, 40%, 65%, and 40%, respectively. This change in frequency is also supported by the large randomized trials of L-AMB that were conducted during 1994–1999. This change, however, does not explain the interinstitutional variation in AIRR.

Approximately 30% of the institutions in the multicenter study reported a $\geqslant$25% frequency of AIRRs. A subtle change in manufacturing coupled with some idiosyncrasy at individual centers may be the only variables that can be related to the increased frequency of these events. We have reviewed the preparation and administration procedures with several staff members of our center's pharmacy. The manufacturer also verified appropriate preparation of the compound by our pharmacy in a visit to our site that we requested. It was verified that all procedures were followed in accordance with the package insert and that no unique variable in preparation could be isolated.

For one patient who experienced an AIRR, a sample of the reconstituted L-AMB and unused vials from the same lot were sent to the industrial sponsor for analytical testing. It was revealed that the reconstituted drug met all product release specifications, including K50 values. Short-term stability studies of the unopened vials concluded that there was no significant change in quality since the time of manufacture in 1997. It was concluded that the drug lot shipped and stored at the NIH remained within the standards set at the time of manufacture of the drug and thus most likely was not the underlying cause of the reactions.

L-AMB remains an important compound for the prevention and management of invasive mycoses in immunocompromised patients. Within our institution, we continue to use the compound with close observation of patients during the first infusion and provide prophylaxis for toxicity with diphenhydramine.

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References

1. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis **1990**; 12:308–29.
2. Johnson MD, Drew RH, Perfect JR. Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. Pharmacotherapy **1998**; 18:1053–61.

3. Groll AH, Piscitelli SC, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. Adv Pharmacol **1998**; 44:343–500.
4. Utz JP, Bennett JE, Brandiss WT, et al. Amphotericin B toxicity. Ann Intern Med **1964**; 61:334–54.
5. Sawaya BP, Briggs JP, Schnermann J. Amphotericin B nephrotoxicity: the adverse consequences of altered membrane properties. J Am Soc Nephrol **1995**; 6:154–64.
6. 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.
7. Walsh TJ, Finberg R, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med **1999**; 340:764–71.
8. Arning M, Heer-Sonderhoff AH, Wehmeier A, et al. Pulmonary toxicity during infusion of liposomal amphotericin B in two patients with acute leukemia. Eur J Clin Microbiol Infect Dis **1995**; 14:41–3.
9. Levine SJ, Walsh TJ, Martinez A, et al. Cardiopulmonary toxicity after liposomal amphotericin B infusion. Ann Intern Med **1991**; 114:664–6.
10. Cesaro S, Calore E, Messina C, Zanesco L. Allergic reaction to the liposomal component of liposomal amphotericin B. Support Care Cancer **1999**; 7:284–6.
11. Ringden O, Andstrom E, Remberger M, et al. Safety of liposomal amphotericin B (AmBisome) in 187 transplant recipients treated with cyclosporin. Bone Marrow Transplant **1994**; 14(Suppl 5):S10–4.
12. Bishara J, Weinberger M, Lin AY, et al. Amphotericin B—not so terrible. Ann Pharmacother **2001**; 35:308–10.
13. Walsh TJ, Pappas P, Winston BJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med **2002**; 346:225–34.
14. 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.
15. Ellis ME, al-Hokail AA, Clink HM, et al. Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. Antimicrob Agents Chemother **1992**; 36:172–9.
16. Oldfield EC III, Garst PD, Hostettler C, et al. Randomized, double-blind trial of 1- versus 4-hour amphotericin B infusion durations. Antimicrob Agents Chemother **1990**; 34:1402–6.
17. Gabizon A, Isacson R, Libson E, et al. Clinical studies of liposome-encapsulated doxorubicin. Acta Oncol **1994**; 33:779–86.
18. Olson F, Mayhew E, Maslow D, et al. Characterization, toxicity and therapeutic efficacy of adriamycin encapsulated in liposomes. Eur J Cancer Clin Oncol **1982**; 18:167–76.
19. 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.