

BRIEF REPORT

Experience with Community-Based Amphotericin B Infusion Therapy

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Study Objectives. To identify the types and frequencies of adverse events associated with community-based amphotericin B infusion therapy. A second objective was to validate the effectiveness of a monitoring system, based on guidelines from the Infectious Diseases Society of America (IDSA).

Design. Retrospective medical record review.

Setting. Outpatient clinic at a tertiary care center.

Patients. One hundred five patients who received amphotericin B therapy from a home care provider between January 1997 and July 2002.

Measurements and Main Results A total of 113 courses of amphotericin B formulations were administered: liposomal amphotericin B, 41 courses (36%), amphotericin B deoxycholate, 31 courses (27%), amphotericin B lipid complex, 31 courses (27%), and amphotericin B colloidal dispersion, 3 courses (3%); an additional 7 courses consisted of sequential therapy with two different formulations. Nephrotoxicity was associated with 46 (41%) courses, electrolyte abnormalities with 40 (35%) courses, venous access device complications with 12 (11%) courses, and infusion reactions with 13 (12%) courses. Nephrotoxicity occurred most frequently in adults aged 60 years or older, solid organ transplant recipients, and those receiving concomitant cyclosporine. Only two (12%) of 17 courses in children younger than 13 years were associated with nephrotoxicity. Thirteen of all 113 courses resulted in patients requiring hospital admission due to their adverse events. Monitoring of electrolyte, serum creatinine, and blood urea nitrogen levels 2 or 3 times/week was adequate for identifying these events.

Conclusion. Significant rates of adverse events occurred in patients who received community-based amphotericin B infusion therapy. A monitoring system based on IDSA guidelines was effective in facilitating the detection and management of these adverse events.

Key Words: amphotericin B, community-based therapy, adverse effects, nephrotoxicity, monitoring.
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Community-based antiinfective therapy has enjoyed increasing popularity during the past 2 decades. Today, with sufficient support and education, antimicrobials can be administered safely and cost-effectively in the home setting.¹⁻⁶ However, adverse events related to outpatient

antimicrobial infusion can have a significant impact on patient health.^{2, 7, 8} Bone marrow suppression, diarrhea, rash, nephrotoxicity, and catheter-related complications were among the adverse events identified during a 2-year period in 261 patients receiving community-based

antiinfective therapy.⁷ Of 10 patients who received amphotericin B (AmB), seven developed renal failure. A retrospective study of thrombotic complications with peripherally inserted central catheters identified AmB therapy as a significant independent risk factor for development of this complication.⁸

Adverse events related to inpatient use of AmB are well established and include infusion-related toxicities, renal failure, and electrolyte abnormalities.⁹⁻¹¹ Today, an increasing number of patients are receiving extended courses of antifungal therapy, including AmB. Previous studies have not specifically addressed the safety of infusing AmB in the outpatient setting. We sought to identify the types and frequencies of adverse events associated with this form of therapy and the appropriateness of our monitoring system, based on guidelines from the Infectious Diseases Society of America.⁶

Methods

Setting and Patients

The University of Michigan Health System (UMHS) is an 850-bed tertiary care center. Our study population included all adult and pediatric outpatients who received any formulation of AmB between January 1997 and July 2002 through HomeMed, a UMHS Joint Commission on Accreditation of Healthcare Organizations–accredited home care provider. Working in conjunction with the referring physician, HomeMed clinical pharmacists and nursing staff start infusion therapy, order relevant laboratory tests, and fill prescriptions for infusion products and home care supplies. HomeMed staff members are responsible for providing patient education, drug information, and compliance assessment, as well as assisting with management of infusion-related complications. Study patients

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were identified using a computerized database maintained by HomeMed. The study was approved by the institutional review boards of both the University of Michigan Health System and the Veterans Affairs Ann Arbor Healthcare System.

All patients included in the study were followed in UMHS clinics during the period in which they received AmB home infusion. All patients had a long-term venous access device, either a peripherally inserted central catheter line or a surgically placed device, such as a Hickman catheter or an infusion port. Laboratory studies were monitored a minimum of twice/week.

Amphotericin B Formulations

The formulations of AmB prescribed were amphotericin B deoxycholate (AmBd), amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), and liposomal amphotericin B (L-AmB).

Study Design and Data Collection

For each patient, the medical chart, HomeMed record, pharmacy dispensing information, and microbiology data were reviewed. Information collected included demographic data, underlying medical conditions, concomitant drugs, and frequency of patient visits and laboratory testing. Indications for antifungal therapy were categorized as definite, probable, or possible invasive fungal infection (in accordance with the European Organization for Research and Treatment of Cancer–Mycoses Study Group criteria),¹² empiric, or prophylactic. The AmB formulation, dosage, duration of therapy, and occurrence of adverse events during treatment were recorded. Hospital admissions were documented, along with a determination of whether these were a direct result of complications of AmB infusion.

Definitions of Adverse Events

Nephrotoxicity was defined as an increase in serum creatinine level of at least 1 mg/dl or a doubling of serum creatinine level compared with the baseline value on day 1 of AmB therapy. Electrolyte imbalance was defined as hypokalemia (serum potassium level < 3.5 mEq/L) or hypomagnesemia (serum magnesium level < 1.5 mEq/L) occurring during the course of outpatient therapy with AmB. Infusion reactions were chills, fever, nausea, vomiting, dyspnea, chest

Table 1. Underlying Conditions Among 105 Patients Who Received 113 Courses of Home Infusion Therapy with Amphotericin B

Condition ^a	No. (%) of Patients
Hematologic malignancy	51 (49)
Neutropenia (< 500 cells/mm ³)	51 (49)
Allogeneic stem cell transplant	28 (27)
Solid organ transplant	22 (21)
Renal insufficiency ^b	22 (21)
Graft vs host disease	16 (15)
Diabetes mellitus	11 (11)
Hemodialysis	6 (6)
Solid tumor	5 (5)
Autologous stem cell transplant	3 (3)
Cirrhosis	3 (3)
Acquired immunodeficiency syndrome	1 (1)

^aMost patients had more than one condition.

^bFor adults, defined as a serum creatinine level of 2 mg/dl or greater; for children, defined as less than 50% of the normal value for each child's age group.

pain, hypotension, and muscle spasm occurring during or immediately after AmB infusion. Venous access device complications consisted of deep vein thrombosis, accidental removal of a device, pump malfunction, leaking, and infection.

Statistical Analysis

The χ^2 test was used to compare dichotomous variables, and the Student *t* test was used to compare continuous variables. A *p* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patient Characteristics

A total of 105 evaluable patients received 113 courses of AmB through HomeMed Services from January 1997–July 2002. The mean \pm SD age was 40.5 \pm 21.8 years (range 2 mo–82 yrs); 63 (60%) were males. Fifteen (14%) of the patients who received 17 courses were younger than 13 years of age, including seven infants who were 1 year old or younger. Twenty-two (21%) of the patients who received 24 courses were 60 years of age or older. Most patients had two or more underlying medical conditions (Table 1). The most common underlying conditions were hematologic malignancy, neutropenia, and stem cell transplantation. As shown in Table 2, indications for therapy were definite or probable invasive fungal infection (55 [49%] courses [one patient had two simultaneous infections]), possible invasive fungal infection (32 [28%]

Table 2. Indications for Home Infusion Therapy with Amphotericin B in 105 Patients Who Received 113 Courses

Indication	No. (%) of Courses ^a
Definite or probable fungal infection	
Candidiasis	25 (22)
Aspergillosis	23 (20)
Other filamentous fungi ^b	5 (4)
Histoplasmosis or coccidioidomycosis	3 (3)
Possible fungal infection	32 (28)
Empiric therapy	13 (12)
Prophylaxis	13 (12)

^aOne patient had both candidiasis and aspergillosis.

^bIncludes zygomycoses (two courses), *Fusarium* (two courses), and *Scedosporium* (one course).

courses), empiric therapy (13 [12%] courses), and prophylaxis (13 [12%] courses).

Amphotericin B Therapy

The most frequently administered AmB preparation was L-AmB, which was given as the sole AmB preparation for 41 (36%) courses. It was followed by AmBd and ABLC, which were each the sole AmB preparation in 31 (27%) courses. In three (3%) courses, ABCD was the sole AmB preparation (Table 3). Sixteen patients received two AmB formulations sequentially during their course of therapy. However, nine of the 16 patients received AmBd for less than 3 days before switching to a lipid formulation; adverse events in these patients were ascribed to the lipid formulation, which constituted almost all of their therapy. The remaining seven of the 16 patients received AmBd for at least 4 days (range 4–44 days) before being given a lipid formulation. These patients were considered to have been treated with both drugs for purposes of analysis of adverse events.

The mean \pm SD duration of outpatient AmB therapy was 33 \pm 37 days (range 1–257 days). For ABLC, the mean duration was 38 \pm 31 days versus 31 \pm 30 days for L-AmB, 31 \pm 49 days for AmBd, and 17 \pm 14 days for ABCD. The mean duration of earlier inpatient AmB therapy was 10 \pm 9 days for AmBd, 12 \pm 15 days for ABLC, 13 \pm 13 days for L-AmB, and 10 \pm 10 days for ABCD. Infusion times were targeted for 3 hours for AmBd and ABCD, and 2 hours each for ABLC and L-AmB. Mean daily doses were AmBd 0.7 \pm 0.3 mg/kg, ABLC 4.5 \pm 0.9 mg/kg, L-AmB 4 \pm 1 mg/kg, and ABCD 4 \pm 1 mg/kg.

The number of patients receiving community-based AmB therapy increased over the study

Table 3. Nephrotoxicity and Electrolyte Abnormalities Related to Different Amphotericin B Formulations in 105 Patients Who Received 113 Courses of Therapy

Formulation	No. of Courses	No. (%) of Courses	
		Nephrotoxicity	Electrolyte Imbalance
AmBd	31	12 (39)	11 (36)
AmBd + lipid ^a	7	4 (57)	4 (57)
ABLC	31	14 (45)	12 (39)
L-AmB	41	13 (32)	13 (32)
ABCD	3	3 (100)	0

AmBd = amphotericin B deoxycholate; ABLC = amphotericin B lipid complex; L-AmB = liposomal amphotericin B; ABCD = amphotericin B colloidal dispersion.

^aThese seven patients received AmBd for at least 4 days before treatment with ABLC (four patients) or L-AmB (three patients).

period. In the second half of the study, a larger proportion of patients started therapy with a lipid formulation. Only 5 (50%) of 10 courses began with a lipid formulation in 1997, compared with 42 (81%) of 52 courses from January 2001–July 2002. The seven patients who had received AmBd for at least 4 days before being given a lipid formulation were evenly distributed from 1997–2002. Laboratory values were monitored twice/week for 66 (58%) courses and 3 times/week for 47 (42%) courses.

Adverse Events

The overall rate of adverse events was 72% (81 of 113 courses). Nephrotoxicity was associated with 46 (41%) courses of AmB therapy. In these patients, mean \pm SD baseline serum creatinine level was 1.0 ± 0.5 mg/dl, which increased to a mean peak of 2.4 ± 0.7 mg/dl. The mean \pm SD number of days of therapy before development of nephrotoxicity was 25 ± 25 (range 4–105). The overall rate of nephrotoxicity in the outpatient setting did not differ between patients receiving standard AmB versus lipid formulations (Table 3). The lowest rate of nephrotoxicity (32%) was noted with L-AmB (13 of 41 courses), but this was not statistically different from that noted with ABLC (14 [45%] of 31 courses, $p=0.36$) or with AmBd (12 [39%] of 31 courses, $p=0.71$). When children younger than 13 years are excluded from the analysis, the rate of nephrotoxicity with AmBd increases to 50%.

Sodium loading with normal saline before infusion of AmB was ordered on day 1 and continued throughout outpatient AmB treatment for 43 (38%) of 113 courses. Sodium loading was performed in approximately one half of the courses in which AmBd or L-AmB were used, but only in 34% of courses of ABLC. Thirteen (30%)

of the 43 courses in which sodium loading was prescribed were associated with nephrotoxicity, compared with 33 (47%) of the 70 courses in which sodium loading was not prescribed ($p=0.11$).

During 40 (35%) of the 113 courses of therapy, hypokalemia and/or hypomagnesemia developed. Electrolyte abnormalities occurred irrespective of the AmB formulation used (Table 3). Furthermore, electrolyte abnormalities persisted despite aggressive oral supplementation in 27 (24%) courses of therapy, and two patients required hospitalization for intravenous potassium supplementation.

We also compared the various AmB formulations with regard to the time until nephrotoxicity or electrolyte disturbances were recorded. Similar intervals were noted with AmBd (18 ± 19 days) and ABLC (19 ± 19 days). The interval was shortest for the few patients receiving ABCD (14 ± 8 days). The longest interval until nephrotoxicity or electrolyte disturbances occurred was noted with L-AmB (23 ± 19 days); however, this interval was not significantly different compared with ABLC ($p=0.43$) or AmBd ($p=0.39$).

In patients aged 60 years or older, 16 (67%) of 24 AmB courses were associated with nephrotoxicity, and 13 (54%) with electrolyte abnormalities. Nephrotoxicity was associated with seven (78%) of nine ABLC courses, five (56%) of nine L-AmB courses, two (50%) of four AmBd courses, and in one course each of ABCD or AmBd followed by a lipid formulation. Only eight courses of AmB in older adults were preceded with sodium loading. Nephrotoxicity occurred in four (50%) of eight patients in this group versus 12 (75%) of the 16 patients not given sodium loading ($p=0.44$).

Among 17 courses of AmB given in children

younger than 13 years old, nine were with AmBd. Only one (11%) course of AmBd was associated with nephrotoxicity, and two courses were associated with electrolyte abnormalities. In children treated with lipid formulations (eight courses), one course was associated with nephrotoxicity and three courses were associated with electrolyte abnormalities. Sodium loading was prescribed in eight of all 17 courses administered to children. Overall, nephrotoxicity occurred in only 12% of courses of AmB given to children younger than 13 years of age. Nephrotoxicity was significantly lower in this population (12%) than in patients aged 60 years or older (67%) ($p=0.002$).

Twenty-four AmB courses were given to 22 solid organ transplant recipients. In this group, there were 14 lung, four liver, three kidney, and one heart transplants. The mean \pm SD age of the recipients was 52 ± 10 years. The AmB formulations were ABLC (11 [46%] courses), L-AmB (six [25%] courses), AmBd (three courses), ABCD (three courses), and AmBd followed by a lipid formulation (one course). Of the 24 courses of AmB therapy, 21 were given to patients receiving cyclosporine and three to patients receiving tacrolimus. Nephrotoxicity developed during 15 (63%) of the 24 courses, and eight (33%) courses were accompanied by electrolyte abnormalities.

Thirty-three courses of therapy with AmB were given to 31 stem cell transplant recipients. Twenty-two of these patients also received tacrolimus, and one was given cyclosporine. The mean \pm SD age of this group was 34 ± 19 years. The preferred formulation in this population was L-AmB, which was given for 22 (67%) of 33 courses. Other formulations used were ABLC (five courses), AmBd (five courses), and AmBd followed by ABLC (one course). Only eight (24%) of AmB courses in stem cell transplant recipients were associated with nephrotoxicity; similarly, eight courses were associated with electrolyte abnormalities.

In the total transplant population, those receiving ABLC had more nephrotoxicity (eight [47%] of 17 courses) than those receiving L-AmB (eight [29%] of 28 courses). Courses given with concomitant cyclosporine were associated with greater nephrotoxicity (14 [64%] of 22 courses) than courses given with concomitant tacrolimus (8 [32%] of 25 courses, $p=0.06$).

Infusion-related events were noted during 13 (12%) courses. Rigors or chills were noted in 11 of these courses, hypotension in one, and severe

back spasms in one. These events were primarily seen in patients receiving ABLC (nine patients), followed by L-AmB (three patients), and AmBd (one patient). Physician responses to infusion reactions included adding meperidine or hydrocortisone to the regimen, slowing the infusion rate, and switching to a different lipid formulation of AmB. Three patients had AmB discontinued solely because of infusion-related reactions that could not be controlled with prophylactic drugs given before the AmB.

Venous access device complications were noted in 12 (11%) courses in 11 patients. Problems with peripherally inserted central catheter lines consisted of inadvertent removal (four courses), purulence at the exit site (two courses), improper insertion (one course), and leakage at the exit site (one course). One patient had a malfunctioning pump device. Two patients with peripherally inserted central catheter lines developed upper-extremity deep vein thrombosis that required anticoagulation, and another patient developed a *Staphylococcus aureus* catheter-related infection. Two of the 11 patients had AmB discontinued solely because of venous access problems.

Thirteen (12%) courses in 13 patients resulted in hospital admission due to their AmB-related adverse events. Reasons for hospitalization were adverse events related to nephrotoxicity (seven patients), venous access device complications (catheter infection, deep vein thrombosis, peripherally inserted central catheter placement; four patients), and correction of electrolyte abnormalities (two patients).

Overall, 28 (25%) outpatient courses of AmB were stopped because of adverse events. Of the 28, 24 were associated with nephrotoxicity, but eight were also associated with electrolyte abnormalities, and six involved infusion reactions.

Discussion

During the past 2 decades, the use of community-based antimicrobial infusion has burgeoned. With improving support networks and the growing pressure to decrease hospital lengths of stay, an increasing number of patients are sent home to complete their course of antimicrobial therapy. At the same time, the ability to treat previously fatal conditions has resulted in large numbers of immunocompromised patients who often require prolonged therapy with potentially toxic agents. Many of these agents, including AmB, are now given in the home setting.

We sought to determine how frequently toxicity is associated with community-based therapy with AmB and whether recommendations for monitoring patients appear adequate. To do this, we focused on adverse events that occurred in the outpatient, rather than the inpatient, setting for a large number of patients receiving AmB therapy. It is important to note that we included only adverse events that met our study definitions. Eleven courses of AmB in 11 patients resulted in toxicity before the start of outpatient therapy; these courses were not counted as having toxicity associated with home AmB infusion therapy. It is likely that some patients experienced mild toxicity as inpatients but did not meet our definition for toxicity. However, as outpatients, this toxicity continued, and they were then included in our analysis as experiencing an adverse event during home AmB infusion therapy. Overall our findings demonstrate that home infusion of AmB was associated with adverse events related to 81 (72%) of 113 courses of therapy. This adverse-event rate is similar to that noted in a small study consisting of 10 patients who received AmB at home.⁷

Not surprising, nephrotoxicity, occurring with 41% of the AmB courses, was the most common adverse event. Although the rate of nephrotoxicity was high, this was not unexpected. Twice-weekly evaluation of kidney function appeared to identify this toxicity appropriately. A total of seven hospital admissions were required for symptomatic renal dysfunction, but no patient required dialysis. In 21% of the courses, however, nephrotoxicity led to discontinuation of AmB.

The highest rates of nephrotoxicity were observed in patients who were 60 years of age or older, those who had received a solid organ transplant, and those who were taking concomitant cyclosporine. However, it is not clear which of these factors played the most important role or whether, as is most likely, a combination of all of these factors led to nephrotoxicity. Unfortunately, the small sample size of patients receiving different formulations of AmB limited our ability to perform statistical analyses that would help determine causality. An age-related increase in AmB-associated nephrotoxicity seems intuitive, but this has not been noted as a major factor in several studies that looked at risk factors for AmB-associated nephrotoxicity in hospitalized patients.¹³⁻¹⁶

One review article reported a high rate of AmB-induced nephrotoxicity among transplant recipients.¹³ That review differs from our study

in that nephrotoxicity was higher in patients who received stem cell transplants than in those who received solid organ transplants. The predominant use of tacrolimus rather than cyclosporine in our stem cell transplant recipients may have helped obviate nephrotoxicity; the concomitant use of cyclosporine and AmB has been shown to be highly predictive of the subsequent need for hemodialysis in stem cell transplant recipients.¹³

In our study, lipid formulations of AmB did not appear to protect against nephrotoxicity. These results differ from those noted in hospitalized patients.¹⁷⁻²⁰ However, several characteristics of our study help explain the lack of differences in nephrotoxicity found among the various AmB formulations. First, nearly 30% of the AmB courses were given to children, and children are known to experience fewer toxicities from AmB than adults; this decreased the nephrotoxicity rate in the AmBd group below that usually noted.^{13, 15, 18} In fact, if children are removed from that group, the rate of nephrotoxicity becomes 50%, which is higher than that noted with ABLC or L-AmB.

Second, it is likely that patients deemed to be at higher risk for nephrotoxicity were preferentially prescribed lipid formulations of AmB. Thus, a protective effect on nephrotoxicity could have been lost, as higher risk patients were given these formulations. It did appear that less nephrotoxicity occurred with L-AmB than ABLC, as previously noted,²¹ but this could also be because different patient populations, who were treated with different calcineurin inhibitors, received these two formulations. Our study was not designed to show that one formulation of AmB was less toxic than another, but rather to assess adverse events and determine if our method for following patients in the home setting was adequate to monitor for these events. To determine differing risks for nephrotoxicity among several AmB formulations would require much larger numbers of patients and control over the use of concomitant nephrotoxic agents and adjuvant measures, such as sodium loading.

There was a trend toward less nephrotoxicity when sodium loading was used, but the differences were not statistically significant. Previous studies in hospitalized patients have shown a beneficial effect of sodium loading with AmBd therapy.^{22, 23} It is likely that sodium loading was not as aggressively followed in the home setting as it could be in the hospital. No trials have assessed the effect of sodium loading with lipid formulations of AmB, and it is left to

the clinician to decide whether this might be appropriate. Thus, in our population, sodium loading was only prescribed for 38% of the courses of therapy. Others have shown that volume loading (massive hydration) effectively decreases AmB-associated nephrotoxicity,²⁴ but this practice does not lend itself to home infusion therapy.

Therapy for hypokalemia and hypomagnesemia was problematic in many patients. Intravenous potassium supplementation can sometimes be given in the home setting, but the patient must be carefully monitored. Even oral potassium supplementation can be dangerous in the setting of fluctuating renal function. One patient who received oral potassium supplementation for refractory hypokalemia and was monitored twice/week still developed hyperkalemia when AmB-related renal dysfunction occurred. Serum potassium levels in several patients were difficult to maintain despite aggressive oral supplementation, and two patients required hospitalization to correct hypokalemia.

Conclusion

Due to the burgeoning use of community-based antimicrobial infusion, it is important to consider the adverse effects of home infusion therapy with AmB and to specify how patients who receive this therapy should be monitored. We found that significant rates of four types of adverse events occurred: nephrotoxicity was associated with 46 (41%) of the 113 AmB courses, electrolyte abnormalities with 40 (35%) courses, infusion reactions with 13 (12%) courses, and venous access device complications with 13 (12%) courses. The overall rate of adverse events was 72%.

New antifungal agents, including second-generation triazoles and echinocandins, are redefining the role of AmB, especially for long-term use in immunocompromised hosts.^{20, 25, 26} Given the high rate of adverse events and the frequency of monitoring that is required, the indications for the use of AmB in this community-based setting must be weighed carefully. Even seemingly minor adverse events, such as infusion reactions, pose a risk that makes AmB less attractive now that suitable less toxic alternatives are available.

For those patients who require long-term AmB therapy in the outpatient setting, recommendations call for twice-weekly monitoring of blood urea nitrogen, serum creatinine, and potassium levels

and weekly monitoring of complete blood count and magnesium level. Our study corroborates these recommendations and also leads us to suggest that older adults should be monitored more frequently than younger patients. For AmB to be safely used in the community-based setting, it is essential to have an infrastructure in place that can both monitor and manage the complications associated with AmB administration.

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