Alternative dosing regimens of liposomal amphotericin B (AmBisome) effective in treating murine systemic candidiasis

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Objectives: This study was done to determine whether high dose AmBisome (4–20 mg/kg), given intermittently, could reduce the frequency of dosing needed to treat murine systemic candidiasis when compared with conventional daily treatment.

Methods: Mice were immunosuppressed with cyclophosphamide every 3 days, beginning day −3 before challenge with log_{10} 5.0 cfu *Candida albicans*. Treatment was begun 48–72 h post-challenge with daily or intermittent dose regimens of AmBisome, followed by determination of kidney cfu for up to 1 month post-treatment.

Results: A single AmBisome dose of 4 mg/kg was as effective as four daily, 1 mg/kg treatments. A total of 8 mg/kg, given as 4 mg/kg on days 2 and 4, or as 5 mg/kg on day 2 followed by 1 mg/kg on days 3, 4, and 5, also produced comparable efficacy. While 20 mg/kg given day 2, 4 and 6 post-challenge as a 1 week loading dose, followed by one 10 mg/kg treatment on day 13, decreased the fungal burden by up to 5 logs compared with controls (log_{10} 2.3 cfu/g and log_{10} 7.5 cfu/g, respectively), 20 mg/kg given Monday, Wednesday and Friday for 5 weeks, reduced the fungal burden to undetectable levels (i.e. log_{10} 1.0 cfu).

Conclusions: Significant reduction or clearance of kidney cfu, following intermittent, high dose AmBisome treatment, indicated that non-daily dosing regimens could be successfully used instead of conventional daily dosing to treat established *C. albicans* infection in immunosuppressed mice.

Keywords: AmBisome loading dose, antifungal therapy, intermittent AmBisome dosing

Introduction

Amphotericin B deoxycholate (AMB) has long been considered one of the most effective treatments for life-threatening, systemic fungal infections although infusion-related side effects and severe nephrotoxicity have limited the daily dose of AMB to about 1 mg/kg. To minimize this problem, lipid formulations of amphotericin B have been developed which are significantly less toxic than AMB even at doses as high as 5 mg/kg and are now considered by some to be the polycene standard for treating systemic fungal infections in immunosuppressed patients.

When compared with other amphotericin B lipid formulations, AmBisome (liposomal amphotericin B) is the least toxic, and doses of AmBisome as high as 15 mg/kg have been shown to be well tolerated by patients. Doses of 4 mg/kg or higher have been reported to be associated with good drug penetration into animal tissues as well as maintenance of therapeutic drug levels in the animal tissues for several weeks following treatment. This is probably related to the unique composition and pharmacodynamics of AmBisome (i.e. high AUC, high $C_{max}$ and non-linear pharmacokinetics) resulting in elevated levels of amphotericin B concentrations in the blood of patients and animals, as well as in the reticuloendothelial system (RES) and non-RES tissues of animals which include important sites of fungal dissemination, such as the brain and the kidneys.

Although treatment regimens for AmBisome, like those for AMB, have nearly always utilized daily dosing, some non-clinical studies have shown that AmBisome can be given every other day to significantly reduce fungal burdens and significantly improve survival compared with untreated controls. Thus, intermittent dosing of AmBisome may be just as effective as conventional daily dosing. In addition, the drug’s pharmacokinetic profile suggests that administration of a high loading dose of AmBisome at the beginning of treatment might provide...
an improved treatment outcome. Loading dose regimens are already routinely used with other antifungal drugs, such as itraconazole,\textsuperscript{20} and caspofungin.\textsuperscript{21,22} The focus of this study was to use a severe, systemic Candida mouse infection model to investigate these different approaches to AmBisome dosing. High dose AmBisome (4–20 mg/kg), was given intermittently and as a 1 week loading dose, to try to reduce the number of drug treatments needed to effectively treat systemic candidiasis in continually immunosuppressed mice.

**Materials and methods**

**Animals**

Female C57BL/6N mice (18–20 g) were obtained from Charles River (Indianapolis, IN, USA) or B&K Universal (Fremont, CA, USA) and maintained in micro-isolator boxes with standard rodent diet (Lab Mouse Diet #5015, PMI Nutrition International, Brentwood, MO, USA) and water ad libitum. All animal research procedures were approved by the Institutional Animal Care and Use Committee of California State Polytechnic University, Pomona.

**Test substance**

AmBisome (Gilead Sciences, Inc., San Dimas, CA, USA), a lyophilized liposomal preparation of amphotericin B, was reconstituted with 12 mL of sterile water for injection (WFI) and shaken vigorously for 1 min, and filtered according to the manufacturer’s instructions. This resulted in a 4 mg/mL solution of amphotericin B.

**Immunosuppression**

Mice to be immunosuppressed were given cyclophosphamide at 100 mg/kg intraperitoneally (Sigma Chemical Co., St Louis, MO, USA) 3 days before fungal challenge. Maintenance doses of 75 mg/kg cyclophosphamide were given on the day of challenge and then every third day for the duration of each study (32–33 or 62–65 days). Although the animals transiently lost an average of 0.5 g on the day following each cyclophosphamide treatment, no secondary bacterial infections were observed. Blood cell counts in mice immunosuppressed with 75 mg/kg cyclophosphamide every 72 h for 1 week were compared with non-immunosuppressed mice and the white blood cells (WBC) in the non-treated mice were 2.6 times greater than the WBC in the cyclophosphamide-treated animals (4.2 x 10^9 cells/mL versus 1.6 x 10^9 cells/mL, respectively; \(P<0.05\)).

Cyclophosphamide is reported to produce decreased numbers of granulocytic cells, monocytic cells, lymphoid cells and myeloid blast cells.\textsuperscript{21}

**Fungal inocula**

*Candida albicans* (California State Polytechnic University, strain CP620) was passaged through mouse kidneys as used in our previous studies of systemic candidiasis.\textsuperscript{35} It was maintained as a frozen stock culture in Sabouraud’s dextrose broth containing 20% glycerol. Three days before challenge, a 0.5 mL aliquot of the stock was thawed and subcultured initially at 35°C and then at room temperature, for two more days in Sabouraud’s dextrose broth without shaking. On the day of challenge, the blastospore subculture was pelleted, and rinsed twice with 0.01 M phosphate buffered saline, pH 7.2 (PBS). The final pellet was resuspended in 15 mL of PBS, the concentration of viable blastospores determined by 1% Methylene Blue staining and the suspension adjusted with PBS to approximately 1 x 10^7 cells/mL for non-immunosuppressed mice and 1 x 10^9 cells/mL for cyclophosphamide immunosuppressed mice. At the time of challenge, non-immunosuppressed mice were injected intravenously (iv) via the tail vein with approximately 0.7 x 10^7 cells and immunosuppressed mice were injected intravenously with approximately 0.6–1 x 10^7 cells.

**Treatment regimens**

To compare daily dosing with intermittent dosing, immunosuppressed *Candida*-infected mice were divided into the following four AmBisome treatment groups (\(n=7\) mice/group): 1 mg/kg (4 mg/kg total dose) for four consecutive days (days 2, 3, 4 and 5); 4 mg/kg given once on day 2 (4 mg/kg total dose); alternate day dosing (days 2 and 4) at 4 mg/kg (8 mg/kg total dose); and 5 mg/kg given once on day 2 followed by 1 mg/kg on days 3, 4 and 5 (8 mg/kg total dose). AmBisome was given intravenously via the tail vein. Seven control infected mice were treated intravenously with 5% dextrose (D5W) on days 2, 3, 4 and 5. An additional seven infected mice were killed 48 h post-challenge to determine the fungal burden in the kidneys at the initiation of treatment (log\textsubscript{10} 6.13 cfu/g, range 5.18–6.78). Thirty-two days post-treatment, surviving animals in the AmBisome groups and the control group were killed, and then both kidneys were removed from each mouse, weighed and the pair of kidneys homogenized in 1.0 mL of PBS using a Tissue Tearor (Biospec Products Inc., Bartlesville, OK, USA). The kidneys were assayed for cfu because the primary site of infection in murine systemic candidiasis is the kidneys.\textsuperscript{37} Following serial dilutions of the kidney homogenates, 0.2 mL aliquots of each dilution were plated in duplicate on Sabouraud dextrose agar plates and incubated at 35°C for 24 h to determine cfu per gram of kidney; the diluting procedures eliminated drug carryover. The cfu for each treatment group was expressed as the mean log\textsubscript{10} cfu for that group of mice.

To determine the efficacy of high dose, intermittent therapy, groups of immunocompetent (\(n=20\)) and immunosuppressed (\(n=20\)) *Candida*-infected mice were given 20 mg/kg AmBisome intravenously on Mondays, Wednesdays and Fridays for 5 weeks, beginning 48 h post-challenge. Control groups of *Candida*-infected immunocompetent (\(n=25\)) and immunosuppressed (\(n=25\)) mice were given D5W using the same injection schedule. The mice in each group (immunocompetent or immunosuppressed) were pre-assigned to a subgroup of five mice, and the surviving mice in a given subgroup were killed on days 9, 24, 38 or 65 (1 month after the last treatment). The extra five mice in the immunocompetent and immunosuppressed control mouse groups were killed 48 h post-challenge to determine the fungal burden in the kidneys at the initiation of treatment (log\textsubscript{10} 5.25 cfu/g; range, 4.66–6.68 for the immunocompetent mice and log\textsubscript{10} 5.68 cfu/g; range, 5.25–6.04 for the immunosuppressed mice). On the day of sacrifice, both kidneys from each mouse were collected and processed as described above for determination of cfu/g kidneys.

To study the efficacy of a 1 week loading dose, we intravenously administered 5, 10 or 20 mg/kg AmBisome on days 2, 4 and 6, or on days 3, 5 and 7 post-challenge to immunosuppressed mice (\(n=7\)/group), followed by once a week dosing for 2 weeks with 5, 10 or 20 mg/kg. The total dose of drug delivered to the 5, 10 and 20 mg/kg groups was 25, 50 or 100 mg/kg, respectively. Control mice were treated with D5W on days 2, 4, 6, 13 and 20 or on days 3, 5, 7, 14 and 21 post-challenge. Immunosuppression was maintained throughout the studies as described above. Surviving mice were killed on day 32 when the loading dose was given on days 2, 4 and 6, or on day 33 when the loading dose was given on days 3, 5 and 7. In these experiments, an additional seven control mice were killed 48 or 72 h post-challenge to determine the fungal burden in
the kidneys at the initiation of treatment ($\log_{10} 5.95$ cfu/g; range, 5.30–6.94 for 48 h and $\log_{10} 6.45$ cfu/g; range, 5.94–7.76 for 72 h). On the day of sacrifice, both kidneys from each mouse were collected and processed as described above for determination of cfu/g kidneys. In a subsequent study of the 1 week loading dose, we treated 56 Candida-infected, continually immunosuppressed mice with 20 mg/kg AmBisome intravenously on days 2, 4 and 6 post-challenge and then divided the mice into four AmBisome treatment groups ($n = 14$/group) which were further subdivided into two subgroups ($n = 7$/subgroup). Each subgroup for a given AmBisome treatment was to be killed on a different day (i.e. day 32 or day 62). The four AmBisome regimens were as follows: 2.5 mg/kg on days 13, 20, 27 and 34; 5 mg/kg on days 13 and 20; 10 mg/kg on day 13; and 20 mg/kg on days 13, 20, 27 and 34. The first three regimens delivered the same total dose of drug to the mice (i.e. 70 mg/kg) and the latter regimen gave a total dose of 140 mg/kg. On day 32 post-challenge, surviving mice in one subgroup from each AmBisome treatment were killed, and surviving mice in the remaining four AmBisome subgroups were killed approximately 1 month after treatment termination (day 62 post-challenge). Control Candida-infected, immunosuppressed mice were divided into two subgroups of seven mice each to be killed on day 32 and day 62 following treatment with D5W on days 2, 4, 6, 13 and 20. An additional seven immunosuppressed control mice were killed 48 h post-challenge (day 2) to determine the fungal burden in the kidneys at the initiation of treatment ($\log_{10} 5.95$ cfu/g; range, 5.30–6.94). For all killed mice, both kidneys from each mouse were collected and processed as described above for determination of cfu/g kidneys.

**Statistical analysis**

For cfu/g kidneys, a Kruskal–Wallis test (analogous to a one-way ANOVA) was applied to all groups and where differences occurred, a two-tailed Mann–Whitney test was done on paired groups. 

![Figure 1. Log$_{10}$ cfu/g kidneys of immunosuppressed C. albicans infected mice treated with daily or intermittent AmBisome regimens.](image1)

**Results**

Results of the experiment to compare daily versus intermittent dosing with AmBisome are given in Figure 1. A single AmBisome dose of 4 mg/kg was as effective as four consecutive daily treatments at 1 mg/kg ($P = 0.318$). Likewise, intermittent dosing with a total of 8 mg/kg (AmBisome at 4 mg/kg days 2 and 4) was as effective ($P = 0.456$) as the same 8 mg/kg total dose given as 5 mg/kg, followed by daily dosing with 1 mg/kg. In comparison, a total dose of 8 mg/kg given as 4 mg/kg days 2 and 4 was significantly more effective ($P = 0.038$) than a total dose of 4 mg/kg delivered as four daily 1 mg/kg treatments. All of the AmBisome treatment regimens significantly reduced cfu in the kidneys compared with the control group ($P < 0.001$) and at the time of sacrifice, there were four control mice alive, one moribund and two dead. The animals which had died were assigned a value of $\log_{10} 7.5$ cfu/g since this was the fungal burden observed for most control mice killed in a moribund condition. Thus, the results indicated that, in this model, the frequency of treatment could be reduced from daily to intermittent treatment without loss of efficacy.

In the subsequent study, we investigated the use of high dose, intermittent AmBisome therapy in immunosuppressed and immunocompetent mice to define an optimum treatment regimen that might lead to clearance of the infection. We selected a 20 mg/kg AmBisome dose for treatment of the immunocompetent and immunosuppressed Candida-infected mice, and this dose was administered Mondays, Wednesdays and Fridays, for 1 week ($n = 5$), 3 weeks ($n = 5$) or 5 weeks ($n = 5$). Control mice ($n = 5$/timepoint) were treated similarly with D5W. We collected tissue samples at weekly intervals during treatment to follow the progress of therapy over time and to see if extended AmBisome treatments would clear the infection. As shown in Figure 2, the fungal burden in the kidneys of immunocompetent mice given

![Figure 2. Log$_{10}$ cfu/g kidneys in immunocompetent mice at various time points post-AmBisome treatment.](image2)
AmBisome was significantly reduced compared with control mice at the end of just 1 week of therapy (log$_{10}$ 3.16 cfu/g versus log$_{10}$ 5.50 cfu/g, respectively; $P=0.008$). Efficacy was further improved after 3 weeks of treatment (log$_{10}$ 2.84 cfu/g versus log$_{10}$ 6.80 cfu/g, respectively; $P=0.008$), and by the end of 5 weeks, only one animal in the AmBisome group had detectable yeast in their kidneys (log$_{10}$ 1.20 cfu/g). The lower limit of detection in this model was log$_{10}$ 1.0 cfu/g. Kidney cfu/g of surviving mice was also determined 4 weeks post-treatment (9 weeks post-challenge). At this time, there was only one AmBisome-treated animal with any detectable fungi in their kidneys (log$_{10}$ 1.31 cfu/g) and there were no surviving mice in the control group.

In immunosuppressed mice (Figure 3), as in the immunocompetent mice, cfu/g also decreased after 1 week (log$_{10}$ 3.70 cfu/g, $P=0.008$) and 3 weeks (log$_{10}$ 1.85 cfu/g, $P=0.008$) of AmBisome therapy, compared with control mice (log$_{10}$ 5.54 cfu/g and log$_{10}$ 6.80 cfu/g, respectively). After 5 weeks of intermittent treatment, all animals in the control group were still alive, with a mean fungal burden of log$_{10}$ 4.90 cfu/g but the cfu were significantly higher than that of the AmBisome-treated mice ($P=0.031$) which had no detectable cfu in their kidneys at this time. Four weeks later, when the remaining group of AmBisome-treated animals was killed, there were also no detectable fungi in the kidneys. In comparison, all of the control mice were dead by day 65 and these animals were assigned a value of log$_{10}$ 7.5 cfu/g kidneys.

Based on the observation that only 1 week of intermittent, high dose AmBisome therapy would significantly reduce the cfu compared with controls in continually immunosuppressed mice, we investigated whether or not an initial 1 week loading dose of AmBisome on Monday, Wednesday and Friday, with weekly follow-up treatments, would produce comparable or better efficacy than just 1 week of intermittent therapy. When 5, 10 or 20 mg/kg was given as a loading dose on days 3, 5 and 7, with follow-up treatments on days 14 and 21 (Figure 4), all three regimens produced similar reduced fungal burdens by day 33 (log$_{10}$ 4.05 cfu/g, log$_{10}$ 3.74 cfu/g and log$_{10}$ 3.41 cfu/g, respectively), which were significantly lower than that of the controls (log$_{10}$ 7.54 cfu/g, $P=0.0006$, for all AmBisome groups). At the time of sacrifice, three of the control mice were dead, and the remaining four mice in the group were moribund. When the same dose regimens were used, but treatment was given on days 2, 4, 6, 13 and 20, the results following sacrifice on day 32 (data not shown) were very similar to those seen in Figure 4. It should be noted that comparable efficacy was achieved with these different AmBisome dosing regimens, even though different total amounts of drug were administered (25, 50 and 100 mg/kg, respectively).

In a follow-up experiment, we selected 20 mg/kg as the 1 week loading dose on days 2, 4 and 6. This was followed by weekly treatments with the same dose to deliver a total dose of 140 mg/kg or a range of lower drug doses which would each deliver a cumulative drug dose of 70 mg/kg. Fungal burdens in the kidneys were evaluated on day 32 (Figure 5) and again on day 62, which was 28 days after the last treatment (Figure 6). On day 32, four of seven control mice were alive, two were moribund and one had died. The dead animal was assigned a kidney fungal burden of log$_{10}$ 7.5 cfu/g kidneys (# indicates $P=0.0006$ for all AmBisome treatments versus control).

![Figure 3](image_url)  
**Figure 3.** Log$_{10}$ cfu/g kidneys in immunosuppressed mice at various time points post-AmBisome treatment. The mice were immunosuppressed on day 3 with 100 mg/kg cyclophosphamide and immunosuppression was maintained with 75 mg/kg cyclophosphamide given every third day. Mice were challenged iv with $0.62 \times 10^5$ C. albicans/mouse and iv treatments were begun 72 h later. DSW control (group 1) or AmBisome at 5 mg/kg (group 2), 10 mg/kg (group 3) or 20 mg/kg (group 4) was given iv on day 3, 5 and 7 post-challenge, and then once weekly for 2 weeks (day 14 and 21). Mice were killed on day 33 and evaluated for log$_{10}$ cfu/g kidneys. Horizontal lines indicate the mean log$_{10}$ cfu/g kidneys for each group. When early deaths occurred in the control group, dead animals were assigned a kidney fungal burden of log$_{10}$ 7.5 cfu/g kidneys (# indicates $P=0.008$; ## indicates $P=0.031$ for treatment versus control).

![Figure 4](image_url)  
**Figure 4.** Efficacy of 1 week loading dose using different AmBisome doses (5, 10 or 20 mg/kg). Immunosuppressed mice ($n=7/group$) were challenged iv with $0.67 \times 10^5$ C. albicans/mouse and treatments were begun 72 h later. DSW control (group 1) or AmBisome at 5 mg/kg (group 2), 10 mg/kg (group 3) or 20 mg/kg (group 4) was given iv on day 3, 5 and 7 post-challenge, and then once weekly for 2 weeks (day 14 and 21). Mice were killed on day 33 and evaluated for log$_{10}$ cfu/g kidneys. Horizontal lines indicate the mean log$_{10}$ cfu/g kidneys for each group. When early deaths occurred in the control group, dead animals were assigned a kidney fungal burden of log$_{10}$ 7.5 cfu/g kidneys (# indicates $P=0.0006$ for all AmBisome treatments versus control).
Efficacy of 1 week loading dose with 20 mg/kg AmBisome evaluated day 32 post-challenge. Immunosuppressed mice (n = 7/group) were challenged iv with 0.70 x 10^5 cfu/g C. albicans/mouse and treatments were begun 48 h later. Treatment groups were: group 1a, fungal burden at initiation of treatment; group 2a, D5W control; group 3a, 10 mg/kg AmBisome on days 2, 4, and 6 followed by 3 weekly doses of 10 mg/kg; group 4a, 20 mg/kg AmBisome on days 2, 4, and 6 followed by 2 weekly doses of 5 mg/kg; group 5a, 20 mg/kg AmBisome on days 2, 4, and 6 followed by one dose of 10 mg/kg; and group 6a, 20 mg/kg AmBisome on days 2, 4, and 6 followed by 3 weekly doses of 10 mg/kg. Except for group 1a, all animals were killed on day 32 and evaluated for log_10 cfu/g kidneys. Horizontal lines indicate the mean log_10 cfu/g kidneys for each group (# indicates P < 0.004 for all AmBisome treatments versus control).

Figure 5.

Efficacy of 1 week loading dose with 20 mg/kg AmBisome evaluated day 62 post-challenge. Immunosuppressed mice (n = 7/group) were challenged iv with 0.70 x 10^5 cfu/g C. albicans/mouse and treatments were begun 48 h later. Treatment groups were: group 1b, fungal burden at initiation of treatment; group 2b, D5W control; group 3b, 20 mg/kg AmBisome on days 2, 4, and 6 followed by 2 weekly doses of 5 mg/kg; group 4b, 20 mg/kg AmBisome on days 2, 4, and 6 followed by 1 weekly dose of 10 mg/kg; group 5b, 20 mg/kg AmBisome on days 2, 4, and 6 followed by 4 weekly doses of 20 mg/kg. When early deaths occurred in a group, dead animals were assigned a kidney fungal burden of log_10 7.5 cfu/g kidneys. Except for group 1b, all animals were killed on day 62 and evaluated for log_10 cfu/g kidneys. Horizontal lines indicate the mean log_10 cfu/g kidneys for each group (# indicates P < 0.05 for group 5b or group 6b versus group 3b).

Figure 6.

Discussion

AmBisome is unique compared with other commercial amphotericin B lipid formulations because of its high Cmax, elevated AUC and non-linear pharmacokinetics. In this study, we took advantage of these characteristics to compare the efficacy of AmBisome given as intermittent high doses with that of a series of repeated low, daily doses. Other investigators have reported that every other day dosing with 3–20 mg/kg AmBisome was efficacious in treating several preclinical infections, including coccidioidomycosis,17 cryptococcosis18 and histoplasmosis.19 In this study, the data showed that one or two high doses of AmBisome had at least comparable efficacy with daily low doses of AmBisome for the treatment of murine systemic candidiasis.

One of the reasons that daily treatments with polyenes and other antifungal drugs have become the convention is that patients with fungal infections are often immunosuppressed requiring intensive therapy to treat any established infection. However, when we used a Monday, Wednesday, Friday dosing schedule with high dose (20 mg/kg) AmBisome to treat an established systemic Candida infection in continually immunosuppressed mice, the regimen was effective in significantly reducing infection after only 1 week of treatment. After 5 weeks of treatment, it had reduced the infection to undetectable levels. The absence of fungi in the kidneys 1 month after treatment had terminated, indicated that this intermittent high dose regimen had probably cleared the infection. It is likely that there were therapeutic levels of AmBisome remaining in the tissues at this time since there are several reports of therapeutic levels of AmBisome being detected in infected tissues 7 days26 and even 103 days27 post-treatment. The sustained presence of AmBisome has also been noted in several prophylactic studies which measured the amount of AmBisome in the target tissues (including kidneys) at the time of challenge as well as in other experiments where treatment was terminated and yet the cfu continued to decrease in the kidneys29 and spleens30 of AmBisome-treated animals.

To reach therapeutic drug levels quickly, loading doses are used with the antifungal drugs itraconazole and caspofungin and the data in this study indicate that this may also be an effective strategy for AmBisome. In our study, a 1 week loading dose of 5, 10 or 20 mg/kg, was able to significantly reduce the fungal burden in immunosuppressed mice even when the Candida infection was well-established at the start of treatment. We also observed that if a 60 mg/kg loading dose of AmBisome was followed by weekly treatment(s) with 2.5, 5, 10 or 20 mg/kg of AmBisome, the fungal burden in the kidneys was significantly reduced.
lower with follow-up doses of 10 or 20 mg/kg when compared with the lower, follow-up drug dosing regimens. This observation is consistent with the non-linear pharmacokinetics of AmBisome\textsuperscript{12,13,14} which is associated with more drug being delivered to non-reticuloendothelial system tissues, such as the kidneys, when the dose is higher. In conclusion, intermittent high dose treatments with AmBisome, given over a 5 week period, were able to clear the Candida infection from the kidneys of immunosuppressed mice. These data indicate that alternative dosing regimens, like those discussed in this paper have the potential to decrease the clinical cost and time required to administer the drug by reducing the total number of treatments needed. Given AmBisome’s markedly better safety profile compared with other amphotericin B formulations, the results of the present experiments support the idea of further investigation of alternative dosing schedules which take advantage of the non-linear pharmacokinetics and the sustained drug tissue levels of high dose (4–20 mg/kg) AmBisome.

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