ORIGINAL ARTICLE

# Toxicity and efficacy of conventional amphotericin B deoxycholate versus escalating doses of amphotericin B deoxycholate–fat emulsion in HIV-infected patients with oral candidosis

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**Background:** Amphotericin B deoxycholate remains the treatment of choice for most systemic fungal infections; however, its clinical use can be limited by infusion-related side effects and nephrotoxicity. New formulations of amphotericin in lipid compounds have been shown to decrease toxicity. We previously showed that a lipid emulsion preparation of amphotericin B deoxycholate was better tolerated than the conventional preparation in dextrose. Therefore, we have now studied the clinical tolerance, renal toxicity and efficacy of higher doses of amphotericin B deoxycholate prepared and infused in a fat emulsion (Intralipid 20%). Thus, this report adds information to the previous publication.

**Methods:** Forty-two patients infected with HIV and suffering oral candidosis entered the study. The patients received either amphotericin B deoxycholate–glucose 1 mg/kg/day or amphotericin B deoxycholate–lipid emulsion 1 mg/kg/day for 4 days (randomized phase), or amphotericin B deoxycholate–lipid emulsion 2 mg/kg/day or 3 mg/kg/day (escalating-dose phase) for 5 days. Clinical (immediate) side effects and renal (creatinine) tolerance were assessed daily; efficacy against oral candidosis was measured by using a simple clinical score. Serum levels of amphotericin B were also measured.

**Results:** None of the patients receiving amphotericin B deoxycholate–lipid emulsion had treatment interrupted, as compared to four (36%) in the amphotericin B deoxycholate–glucose group ($p \leq 0.01$); chills during or after the infusions were significantly less frequent in the amphotericin B deoxycholate–lipid emulsion groups than in the amphotericin B deoxycholate-glucose group ($p=0.03$). The increase of creatininemia during treatment was significantly higher for patients receiving amphotericin B deoxycholate–glucose than for those receiving amphotericin B deoxycholate–lipid emulsion ($p=0.001$). The number of patients who had a creatininemia ≥18 mg/L during treatment was significantly higher in both the amphotericin B deoxycholate–glucose group (36%) and in the group receiving the highest dose of amphotericin B deoxycholate–lipid emulsion than in other groups ($p \leq 0.06$).

The serum concentrations of amphotericin B were lower for the amphotericin B deoxycholate–lipid emulsion regimen than for the amphotericin B deoxycholate–glucose regimen at the same dose of 1 mg/kg/day, but increased with the dose.

The change of the oral candidosis score was similar for the same dose of 1 mg/kg/day of amphotericin B deoxycholate infused in either glucose or lipid emulsion; higher doses of amphotericin B deoxycholate–lipid emulsion were more efficacious ($p=0.009$) and this efficacy seemed to increase with the dose ($p=0.06$).

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**Conclusions:** The clinical and renal tolerance of amphotericin B deoxycholate are improved when the drug is directly prepared and infused in lipid emulsion (Intralipid) and this preparation allows for greater dosage, up to 3 mg/kg/day, with resultant greater efficacy. This preparation is simple and cost-effective (approximately 7 US $ per 50 mg of amphotercin B) and could be clinically compared to other formulations of amphotericin B.

**Key words:** Amphotericin B, amphotericin B deoxycholate, fat emulsion, Intralipid, candidosis, HIV

## INTRODUCTION

Systemic and mucosal candidosis are conditions increasingly being recognized as causes of morbidity and mortality in patients with altered immunity [1–3]. In spite of the recent development of new antifungal agents, amphotericin B remains the treatment of choice for systemic candidosis. However, clinical use of amphotericin can be limited by infusion-related side effects, nephrotoxicity and electrolyte abnormalities [4–8]. Also, patients who require treatment with amphotericin B tend to be already seriously ill from their underlying diseases and thus particularly susceptible to drug toxicity.

New formulations of amphotericin in lipid compounds were shown to decrease toxicity [9]. Although most preparations have reduced efficacies when compared with amphotericin B deoxycholate on a dosage-for-dosage basis, their therapeutic indices are improved [9–11]. A preparation of amphotericin in parenteral lipid emulsion (Intralipid 20%) was demonstrated to reduce toxicity in both neutropenic and AIDS patients and in experimental models [12–19]. Several investigators have reported a similar therapeutic effect of amphotericin in lipid emulsion in comparison with the conventional preparation at the same dose [12,14,17].

Therefore, we planned an escalating-dose trial in HIV-infected patients with azole-resistant oral candidosis in order to investigate the therapeutic range of this fat emulsion preparation of amphotericin B deoxycholate. This study is a continuation of our previous study [16] and therefore the results of these two phases are given together in this paper.

## METHODS

Patients were eligible if they were aged 18 or over, infected with HIV, and had clinically azole-resistant oral candidosis. Patients were not included if they were pregnant or breast-feeding, had known intolerance to amphotericin or Intralipid, pancreatitis, arrythmia, hyperlipidemia or serum creatinine concentration above 12 mg/L, or if they had received treatment with amphotericin B deoxycholate in the previous 4 weeks. All eligible patients gave signed informed consent. The protocol was accepted by the local ethics committee. All the patients included in the study were hospitalized in our medical unit. For practical reasons, the treatment and the observers were not blinded.

### Treatment

The first phase, consisting of the comparison of amphotericin B deoxycholate diluted in 5% glucose with amphotericin B deoxycholate diluted in Intralipid 20%, has been described previously [16]. Briefly, the powder of amphotericin B deoxycholate (vials of 50 mg) was directly diluted in a syringe of 50–60 mL with 25 mL of Intralipid 20% (in case of dose >50 mg/day, 50 mL of Intralipid in one syringe are needed to dilute consecutively two vials of 50 mg of amphotericin B deoxycholate); thus the final concentration of 2 mg amphotericin B in 1 mL of Intralipid was used. This preparation was infused, without an in-line filter, by using a horizontal electric pump at a rate of 0.5 mg/kg/h.

The second phase consisted of an escalating dose trial of the lipid emulsion of amphotericin B. The same fat emulsion of amphotericin B deoxycholate was given at 2 mg/kg/day and 3 mg/kg/day for five consecutive days; the rate of infusion was 0.5 mg/kg/h. The doses of 2 and then 3 mg/kg/day were planned when the independent committee gave consent after examination of the results of the previous phase. Standard hydration and electrolyte supplementation were systematically given. No premedication was given before the infusions. Amphotericin B deoxycholate was infused into the peripheral or central vein. Concurrent drugs, including known nephrotoxic medications, were not stopped during this protocol.

### Assessment of tolerance

Clinical tolerance was monitored by using a standard data form which checked for sweating, chills, fever (rise of more than 1 °C), nausea, pulse rate and blood pressure. Biological tolerance was monitored by twice-daily electrolyte and creatinine measurements. In addition, a full blood count and electrocardiograms were obtained on days 1 and 6. Amphotericin B was stopped if severe clinical side effects occurred and if the creatinine concentration reached 18 mg/L. Paracetamol (1 g orally or intravenously) or dexamethasone (4 mg)

were given if severe chills or fever occurred during or after the infusion.

### Assessment of efficacy

We used a simple clinical score to monitor daily the state of the oral candidosis [16]. Briefly, every day, the following sites were inspected for the presence or the absence of candidosis: the upper, right and left sides of the tongue, the left and right jaws, the two tonsil regions and the smooth and hard palate (maximum=9). Each of these sites was rated for confluent (=3), patchy (=2) or scattered (=1) lesions. Thus, a clinical score could be determined daily. A regression line of the variation of the daily scores was constructed for each group by using the least squares method (curve fit $R^2 > 0.90$ for each group, $p<0.01$, data not shown). A swab of one or two lesions was taken for mycologic analysis.

### Pharmacokinetics

Serum samples obtained daily before (trough), 5 min after the end (peak) of the infusion and 12 h after the start of the infusion were stored at −20 °C until assayed. Amphotericin B was assayed by high-performance liquid chromatography [20], including samples of the first phase of the trial. The volume of initial distribution (L/kg) was calculated as follows: dose/concentration after the infusion.

### Statistics

As previously calculated [16], 10–11 patients were entered in each group. Results were expressed as mean ± SD. Statistical analysis was done by using the Mann–Whitney U test, the Scheffe test and the Kruskall–Wallis test as indicated. The data on time of the creatininemia, as continuous variables, were analyzed by using the ANOVA on repeated measures; the data on time to the development of renal impairment, defined as a creatinine blood ≥18 mg/L, were analyzed by the standard Kaplan–Meier method and compared by using the log-rank test. Significance was considered established if the $p$ value was less than 0.05 (two-tailed). Calculations were done by using SPSS software for Macintosh, Chicago.

An independent committee reviewed summary data of each phase of the protocol; the protocol specified that the immediate toxicity of amphotericin B deoxycholate–lipid emulsion should not be higher than that of conventional amphotericin B deoxycholate, and that the renal toxicity of amphotericin B deoxycholate–lipid emulsion should be less frequent than that of conventional amphotericin B deoxycholate. Therefore, this committee decided to terminate the trial at the dose of 3 mg/kg/day amphotericin B deoxycholate–Intralipid.

## RESULTS

The groups were comparable for demographic variables, status of HIV infection, renal function, total white blood cell and CD4 cell count, hemoglobin level, and the concomitant use of other nephrotoxic drugs (aminoglycosides, vancomycin, foscarnet, sulfonamides) (Table 1). However, the clinical score of oral candidosis was higher for the two groups with the highest doses of amphotericin B deoxycholate–lipid emulsion (Table 1).

The main results of the study are shown in Table 2. None of the patients receiving amphotericin B deoxycholate–fat emulsion had treatment interrupted,

**Table 1** Clinical and laboratory characteristics of the patients at entry

| | Fungizone–glucose | Fungizone–fat emulsion | | |
|---|---|---|---|---|
| Dose (mg/kg/day) | 1 | 1 | 2 | 3 |
| Number of patients | 11 | 11 | 10 | 10 |
| Number of patients with AIDS | 8 | 8 | 7 | 5 |
| Age (years) (mean ± SD) | 35 ± 7 | 34 ± 7 | 35 ± 8 | 35 ± 9 |
| Weight (kg) (mean ± SD) | 61 ± 8 | 53 ± 9 | 51 ± 7 | 51 ± 8 |
| Concurrent treatment (No. of patients) | | | | |
| Antiretroviral drugs | 5 | 7 | 5 | 9 |
| Nephrotoxic drugs | 5 | 6 | 5 | 9 |
| Creatinine (mg/L) (mean ± SD) | 9 ± 1.4 | 8.8 ± 2.2 | 7.3 ± 1.3 | 7.1 ± 1.1 |
| White cell count ($\times 10^6$/L) (mean ± SD) | 3.4 ± 1.7 | 2.8 ± 1.4 | 3.2 ± 1.2 | 3.4 ± 1.2 |
| CD4 count ($\times 10^6$/L) (mean ± SD) | 120 ± 161 | 48 ± 88 | 45 ± 88 | 23 ± 27 |
| Hemoglobin (g/L) (mean ± SD) | 10.9 ± 2.6 | 10.7 ± 2.1 | 11.7 ± 2 | 10.7 ± 2.2 |
| Platelet count ($\times 10^6$/L) (mean ± SD) | 155.1 ± 78 | 155.4 ± 105 | 135 ± 71 | 132 ± 71 |
| Clinical score of oral candidosis (mean ± SD) | 6 ± 7 | 6.3 ± 4.4 | 10.8 ± 7.5* | 12.6 ± 8.1* |
| Number of patients with *Candida albicans* strain | 9 | 10 | 9 | 7 |

*$p<0.05$ versus the two other groups.

**Table 2** Clinical and laboratory toxicity and efficacy

| | Fungizone–glucose | Fungizone–fat emulsion | | |
|---|---|---|---|---|
| Dose (mg/kg/day) | 1 | 1 | 2 | 3 |
| No. of patients | 11 | 11 | 10 | 10 |
| No. having interruption of treatment (%) | 4 (36%) | 0 | 0 | 0 |
| Fever per infusion (mean ± SD) | 0.3±0.3 | 0.02±0.07[a] | 0.3±0.3[a] | 0.46±0.25[b] |
| Chills per infusion (mean ±SD) | 0.4±0.3[c] | 0.02±0.07[c] | 0.2±0.3 | 0.24±0.26 |
| No of patients with creatinine >18 mg/L during the treatment (%) | 4 (36%) | 0 | 0 | 2 (20%)[d] |
| Change in leukocytosis ($\times 10^6$/L) (mean±SD) | 0.9±1.6 | 0.61±1.1 | −0.09±0.08 | 0.69±2.8 |
| Change in haemoglobin (g/L) (mean±SD) | −0.4±1.9 | −0.29±1.1 | −0.77±1.4 | −1.2±2 |
| Change in platelets ($\times 10^6$/L) (mean±SD) | −9.5±41 | −17.7±46 | −22±31 | −36.2±34 |
| Change of the clinical score of oral candidosis (*mean±SD of regression line*) | −1.1±1.7 | −1±1.5 | −2.5±1.9 | −2.7±2.2[e] |

[a] $p=0.05$; [b] $p=0.007$ versus the three other groups; [c] $p=0.03$.
[d] $p=0.21$ between fungizone–glucose and fungizone–fat emulsion 3 mg/kg/day and, $p=0.04$ and $p=0.06$ between fungizone–glucose and fungizone–fat emulsion 1 mg/kg/day and 2 mg/kg/day respectively.
[e] $p=0.05$.

as compared to four (36%) in the amphotericin B deoxycholate–glucose group ($p \leq 0.01$). Fever during infusions was less frequent in the amphotericin B deoxycholate-fat emulsion 1 mg/kg group than in the other groups ($p=0.007$); however, no difference was observed between the amphotericin B deoxycholate–glucose group and the highest dose with amphotericin B deoxycholate–Intralipid. Chills were significantly less frequent in the amphotericin B deoxycholate–lipid emulsion groups than in the amphotericin B deoxycholate–glucose group ($p=0.03$). Neither change nor abnormalities were detected during and after the infusions throughout the investigation in pulse rate, blood pressure, electrolytes, blood cell counts and electrocardiograms.

The evolution of renal function, measured as creatininemia, is depicted in Figure 1, upper panel. The increase of creatininemia during this protocol was significantly higher for patients receiving amphotericin B deoxycholate–glucose than for those receiving amphotericin B deoxycholate–lipid emulsion ($p=0.001$). Although the creatininemia increased more for the 3 mg/kg/day amphotericin B deoxycholate–fat emulsion group than for the 1 mg/kg/day and the 2 mg/kg/day amphotericin B deoxycholate–fat emulsion groups, a significant difference was only reached on day 5 of the treatment (the last infusion) ($p<0.05$). No differences were detected between the 1 mg/kg/day and the 2 mg/kg/day amphotericin B deoxycholate–fat emulsion groups ($p=0.72$); there was a significant difference in renal toxicity between the 2 mg/kg/day and the 3 mg/kg/day amphotericin B deoxycholate fat emulsion groups ($p=0.03$). The number of patients who had a creatininemia ≥18 mg/L was significantly higher in both the amphotericin B deoxycholate–glucose group (36%) and in the group receiving the highest dose of amphotericin B deoxycholate–lipid emulsion (20%) than in other groups ($p \leq 0.06$) (Table 2). The cumulative probability of this event is depicted in Figure 1, lower panel; clearly, the amphotericin B deoxycholate–glucose regimen caused a more frequent and more precocious renal impairment than the amphotericin B deoxycholate–fat emulsion regimens (log-rank test, $p=0.044$); furthermore, this cumulative probability for the highest dose of 3 mg/kg/day was significantly lower than that of amphotericin B deoxycholate-glucose (22% versus 54%, $p=0.05$). Since the cumulative probability for the 3 mg/kg/day amphotericin B deoxycholate–fat emulsion reached 20%, the independent committee did not allow the next step in the study which was planned to test higher dosage.

Although this study was not designed to investigate pharmacokinetics, serum amphotericin B concentrations were measured in 347 samples obtained from each group of patients (Figure 2). The concentrations of amphotericin B were lower for the amphotericin B deoxycholate–fat emulsion regimen than for the amphotericin B deoxycholate regimen at the same dose of 1 mg/kg/day. However, the concentrations of amphotericin B increased with the dose of amphotericin B deoxycholate–fat emulsion. Thus, the initial volume of distribution of amphotericin B was lower for the amphotericin B deoxycholate–glucose regimen than for the amphotericin B deoxycholate–fat emulsion regimens (0.71±0.24 L/kg versus 1.48±0.5 L/kg, 1.16±0.6 L/kg and 1.4±0.4 L/kg for the 1 mg/kg, 2 mg/kg and 3 mg/kg amphotericin B deoxycholate–fat emulsion regimens, respectively; $p=0.005$).

The efficacy of these amphotericin B regimens was evaluated clinically by using a simple score of the oral

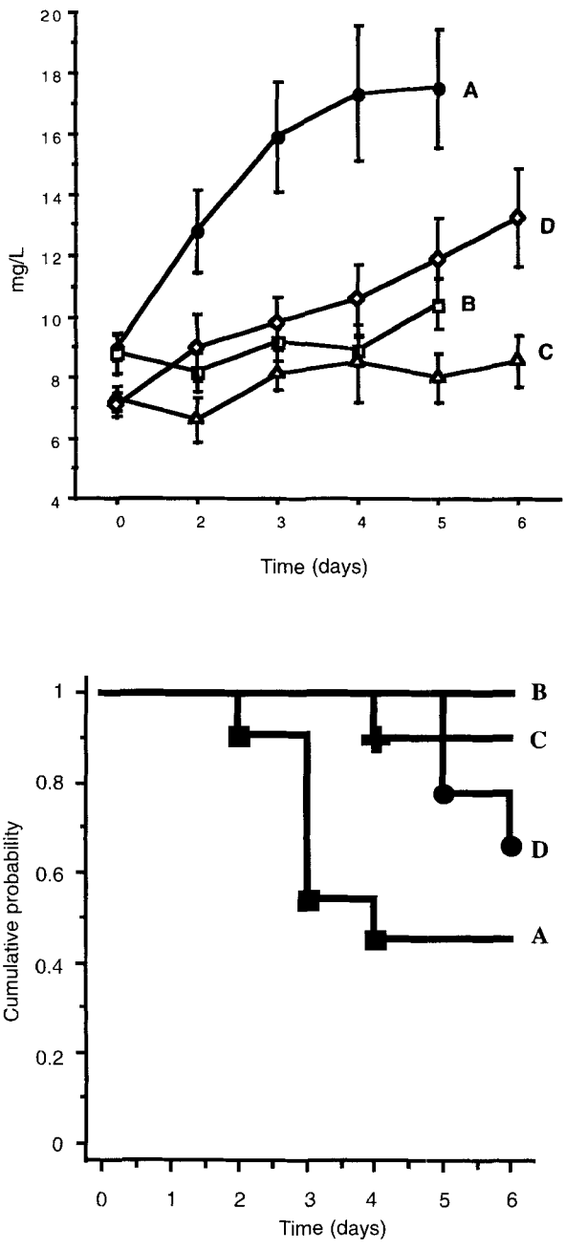


**Figure 1** Evolution of creatininemia during amphotericin B treatment (upper panel) and occurrence of the creatininemia above 18 mg/L according to treatment group (plotted with Kaplan–Meier curves) (lower panel):
A=amphotericin B deoxycholate–glucose 1 mg/kg/day;
B=amphotericin B–lipid emulsion 1 mg/kg;
C=amphotericin B–lipid emulsion 2 mg/kg;
D=amphotericin B–lipid emulsion 3 mg/kg.
Upper panel: ANOVA on repeated measures, $p=0.001$, and $p<0.05$ on day 5 for regimens A versus B or C. Lower panel: log-rank test, $p=0.0044$, and $p=0.05$ between regimens A and B.

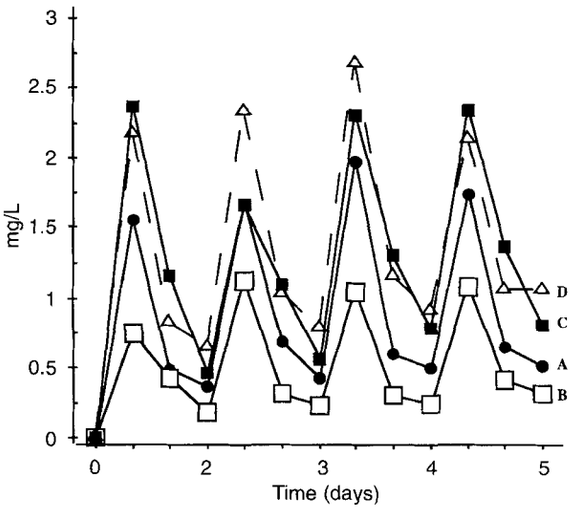


**Figure 2** Pharmacokinetics of amphotericin in serum (mean data of each group):
A=amphotericin B deoxycholate–glucose 1 mg/kg/day;
B=amphotericin B–lipid emulsion 1 mg/kg;
C=amphotericin B–lipid emulsion 2 mg/kg;
D=amphotericin B–lipid emulsion 3 mg/kg.

candidosis. The slope of change of this score over the 5 days of treatment was similar for the same dose of 1 mg/kg/day of amphotericin B deoxycholate infused either in glucose or in Intralipid (Table 2). Furthermore, higher doses of amphotericin B deoxycholate were more efficacious ($p=0.009$) and this efficacy seemed to increase with the dose of amphotericin B deoxycholate–fat emulsion ($p=0.06$).

## DISCUSSION

We and others have clearly shown that, at the same dose, amphotericin B deoxycholate prepared in a well-known lipid emulsion (Intralipid 20%) was less toxic than conventional amphotericin B deoxycholate [14–17,19,21–27]. However, several authors did not find this amelioration [28–30]. Although this issue remains controversial, one explanation could be that the modalities of both preparation (too large a volume of lipid emulsion) and infusion (vertical but not horizontal, non-calibrated rate of infusion) used by these authors were quite different from our recommendations (see Method). Therefore, taking into account our observations, we planned this study to investigate the possibility of increasing the dose of amphotericin B deoxycholate.

At the dose of 2 mg/kg/day, this lipid-based formulation of amphotericin B was as well tolerated as

the 1 mg/kg/day regimen; in particular, no differences in creatinine blood levels were seen between these two regimens. Furthermore, we found that a dosage of 3 mg/kg/day of amphotericin B deoxycholate–fat emulsion could be used. At this dose, no treatment courses were stopped, the immediate clinical side effects during or after the infusions were less frequent and, moreover, renal function impairment was less pronounced and occurred less frequently than with conventional 1 mg/kg/day amphotericin B deoxycholate.

The serum concentrations of amphotericin B were lower with the amphotericin B deoxycholate–lipid emulsion regimen than with the amphotericin B deoxycholate–glucose regimen at the same dose of 1 mg/kg/day but increased with the dose. Although we did not precisely investigate the pharmacokinetics of amphotericin B deoxycholate–lipid emulsion, our observations were concordant with previous data [16,19,31] which demonstrated an increase of the volume of distribution of amphotericin B when infused with this lipid emulsion. The serum concentrations of amphotericin B were lower with the amphotericin B deoxycholate–lipid emulsion regimen than with the amphotericin B deoxycholate–glucose regimen at the same dose of 1 mg/kg/day but increased with the dose. These lower concentrations could partly explain the lower rate of side effects observed with the amphotericin B deoxycholate–lipid emulsion. According to experimental data and clinical observations [24,33–36], it is quite probable that the diffusion of amphotericin B diluted in the lipid emulsion is wide and not limited to some rich reticuloendothelial system tissues [37].

Finally, the clinical activity (based on scoring the candidal lesions in the mouth) of amphotericin B deoxycholate–lipid emulsion was found, on a dosage-for-dosage basis, to be at least as effective as that of conventional amphotericin B deoxycholate and, furthermore, higher doses appeared to be more effective on mucosal candidal infection in immunocompromised patients. This finding is in complete accordance with in vitro and in vivo experimental data [38–41] and clinical experience [25,33,38]. However, this trial was a short-course treatment trial and was not planned to investigate precisely the efficacy of this preparation for the treatment of candidal tissue infections; further clinical studies are therefore warranted.

The possibility of high doses of amphotericin B is of interest for the treatment of resistant fungal infections [24,42–44]. Thus, our results warrant further clinical trials to compare the effectiveness of this formulation with other lipid-based formulations of amphotericin B [9]. In addition, the results of this study clearly show that the full dose of amphotericin B deoxycholate diluted in the lipid emulsion could be administered immediately and that the usual escalating-dose schedule could be omitted. These positive therapeutic results, combined with favorable pharmacokinetics and tolerance of amphotericin B deoxycholate–lipid emulsion, suggest that the use of loading doses or high doses for short courses of treatment could be realizable.

We conclude that the clinical and renal tolerance of amphotericin B deoxycholate is improved when the drug is directly prepared and infused in lipid emulsion (Intralipid) and that this preparation allows for higher dosage, up to 3 mg/kg/day. In addition, its therapeutic index on candidal infection is not altered versus conventional amphotericin B deoxycholate and increases with the dose. This preparation is simple and cost-effective (approximately 7 US $ per 50 mg of amphotercin B) and should be clinically compared to other formulations of amphotericin B.

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