

# Use of high-dose liposomal amphotericin B: efficacy and tolerance

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**Abstract.** Fungal infections have become increasingly prevalent over the past decade. Amphotericin B deoxycholate (AmBd) (Fungizone®) has been the treatment of choice despite its association with significant high adverse effects, and notably severe high nephrotoxicity. However, liposomal amphotericin B (L-AmB) (AmBisome®) has now become the first-line treatment due to its lower nephrotoxicity but without any loss of clinical efficacy. As illustrated in published reports, a higher dose of L-AmB may be prescribed in the case of unresponsiveness to treatment at normal dosage levels. Based on existing evidence from animal models of invasive fungal infections and the early clinical experience, L-AmB used at higher doses for invasive fungal infections is a new treatment option. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** AmBisome®, amphotericin, liposomal amphotericin B, fungal infections, high dose

## Introduction

Severe invasive fungal infections have become increasingly frequent and are recognized as a major cause of morbidity and mortality in immunocompromised patients. Amphotericin B deoxycholate (AmBd) (Fungizone®) has been the treatment of choice, but its nephrotoxicity is so great that mortality was high despite its therapeutic efficacy.

Since the initial studies, liposomal amphotericin (L-AmB) (AmBisome®) has demonstrated good clinical efficacy with less side-effects and has become the first-line treatment as an alternative to AmBd. The pharmacodynamic properties of AmBd has allowed a L-AmB dose escalation in patients with invasive fungal infections. Conventional AmBd and L-AmB have been shown to exhibit concentration-dependent pharmacodynamics against *Candida* species *in vivo*. Therefore, the antifungal efficacy of AmBd may be enhanced by maximization of the AmBd con-

centrations at the site/s of infection. L-AmB allows the use of higher doses to increase efficacy, yet with a reduced risk of both acute reactions and renal toxicity (1, 2).

## Efficacy of higher dosage levels of L-AmB

As illustrated in published reports, higher doses of L-AmB are prescribed in the case of unresponsiveness to treatment at normal dosage levels (3-5 mg/kg/day).

A typical case is the following. A patient with refractory Hodgkin's disease with a graft-versus-host-disease (GVHD) following a bone marrow transplant requiring severe immunosuppressive therapy developed invasive aspergillosis (3). The patient was initially treated unsuccessfully with L-AmB (5 mg/kg/day). Due to progression to disseminated aspergillosis, the dosage level of L-AmB was increased to 15

mg/kg/day in combination with itraconazole. The patient showed a good response and no increase in the abnormal baseline kidney function was observed. The treatment with high doses of L-Amb was well tolerated and did not result in additional renal toxicity.

An escalated dose of L-Amb was also successful in the eradication of zygomycosis in two severe immunosuppressed pediatric patients. The first patient had a relapse of his acute myeloid leukaemia (AML) after autologous bone marrow transplant and was treated with L-Amb 10 mg/kg/day with eradication of the infection. The second patient with pre-B-cell acute lymphoblastic leukemia treated by chemotherapy developed rhino-cerebral zygomycosis and was treated with 15 mg/kg/day with a satisfactory clinical response. No further treatment for the underlying diseases was required. No adverse events were observed in the first case. A supplement of potassium and magnesium was required for the second patient and an alteration in methotrexate excretion was evidenced (4).

A recent study demonstrated the efficacy of high dose L-Amb (10 mg/kg per dose once a week for 7 weeks) as antifungal prophylaxis in pediatric immunocompromised patients (5). In this study, the dose of 10 mg/kg/day was well tolerated and no toxicities were seen. Long-term prophylaxis may be useful in patients who do not tolerate oral therapy with azoles and is a simple treatment regimen which could be administered during outpatient consultation (5).

### **Brief description of two recent cases treated with high-dose L-Amb (AmBisome®) at the University Hospitals of Geneva**

#### *Case report 1*

A 59-year-old female under long-term corticoid therapy was hospitalized for falls and confusion. At admission, she was febrile and confused. A CT-scan of the head showed an expansive lesion compressing the left lateral ventricle. Broad spectrum antibiotic therapy was initiated and one week later she developed a right hemiparesis. A cerebral biopsy was performed and the diagnosis of fungal zygomycosis infection was

confirmed. L-Amb (5 mg/kg/day with a gradual increase to 7 mg/kg/day) was started in combination with voriconazole which was stopped due to an increase of liver enzymes levels and replaced by an investigational triazole. A control MRI showed a reduction of the size of the lesion, mainly in the peri-lesional edema. High-dose L-Amb was administered for 30 days and was well tolerated without experience of adverse events. A longer follow-up was not possible because the patient died due to bacterial pneumonia and sepsis.

#### *Case report 2*

A 10-year-old child with a history of acute myeloid leukaemia and bone marrow transplantation under immunosuppressive treatment developed fever and cough, followed by respiratory distress. The patient was treated with antibiotics, an increase in immunosuppressive therapy due to a chronic cutaneous and digestive GVHD, and antifungal treatment with voriconazole was also started. A control CT-scan showed a lung nodule and L-Amb (10 mg/kg/day) was added for 20 days. Surgical resection of the nodule was performed and a diagnosis of mucormycosis (zygomycosis) was confirmed by microbiological cultures. The clinical response for the fungal infection was good and no severe adverse events occurred.

### **Side-effects and tolerance to high-dose L-Amb (AmBisome®)**

The main concern in the use of AmBd is its well-known high nephrotoxicity which is lower with L-Amb but without any loss of clinical efficacy.

A total of 44 patients were enrolled in a study to evaluate the safety, tolerance and plasma pharmacokinetics of different doses of L-Amb (7.5, 10, 12.5, 15 mg/kg/day) in patients with infections due to *Aspergillus* spp. and other filamentous fungi (2). The treatment response was considered as a failure in only nine patients. The authors concluded that L-Amb as high as 15 mg/kg/day follows nonlinear saturation-like kinetics. However, despite their observation of high serum concentrations of L-Amb, no association between

dosage and increases in renal dysfunction or infusion-related reactions was observed; hypokaliemia was more frequent for doses over 10 mg/kg/day. This treatment regimen could be an effective therapy for these types of fungal infections.

In another large study, 115 patients underwent bone marrow or peripheral blood stem cell transplantation and were treated for fungal infections with L-AmB at doses up to 10 mg/kg (6). Results showed that antifungal treatment with L-AmB had a favorable response in 62.9% of cases with a low percentage of side-effects. The authors concluded that further dose-escalating studies should be conducted to confirm these positive study results.

Results of the study reported by Mehta and colleagues, in which a high dose of L-AmB (10 mg/kg) was administered once a week in immunocompromised children (n=14) undergoing hematopoietic stem cell transplantation (HSCT), showed an adequate protection for fungal prophylaxis (5). Plasma concentrations at 7 days were not significantly different after the first and fourth doses, thus suggesting no accumulation over the course of therapy (after one or seven weeks). Nevertheless, the drug plasma level was still detectable on the seventh day before re-dosing. This dosing was well tolerated with no renal, liver or other side-effects observed and could provide useful protection against fungal infections.

## Discussion

The pharmacodynamic properties of conventional AmB support escalation of the L-AmB dose given to patients with invasive mycoses. Conventional AmB and L-AmB have been shown to exhibit concentration-dependent pharmacodynamics against *Candida* species *in vivo* (7, 8). L-AmB allows the use of higher doses in order to increase its efficacy, yet with a reduced risk of both acute reactions and renal toxicity (1, 2). Therefore, the antifungal efficacy of AmB may be enhanced by maximization of the AmB concentrations at the site/s of infection.

In this context, it is important to recall that the peak level/MIC ratio was the parameter that is most strongly correlated with the efficacy of AmB (1).

Thus, at the end of the seventh day after a prophylactic dose, this ratio was respected and the MICs for *Aspergillus* and *Candida* were adequate (5). However, there are pharmacokinetic differences since the half-life of L-AmB is longer in adults (152 hours) than in children (45 hours). In addition, the volume of distribution is associated with body weight which is lower in pediatric patients. Both of these parameters can modify the efficacy in adult patients (5).

Finally, both the existing evidence from animal models of invasive fungal infections (8, 9) and the early clinical experience regarding the safety and the efficacy of L-AmB used at higher doses for invasive fungal infections (2-6, 10) suggest that this strategy deserves further study to confirm this new treatment option.

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