ADIS DRUG EVALUATION

Drugs 1998 Apr; 55 (4): 585-612
0012-6667/98/0004-0585/$28.00/0

© Adis International Limited. All rights reserved.

Liposomal Amphotericin B

Therapeutic Use in the Management of Fungal Infections and Visceral Leishmaniasis

Allan J. Coukell and *Rex N. Brogden*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

J.D. Berman, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C., USA; ***C. Carbon,*** Assistance Publique, CHU Bichat Claude Bernard, Paris, France; ***R.J. Hay,*** St John's Institute of Dermatology, Guy's Hospital, London, England; ***W. Krüger,*** Knochenmarktransplantation, Abteilung Onkologie / Hämatologie, Universitäts-Krankenhaus Eppendorf, Hamburg, Germany; ***O. Ringdén,*** Department of Immunology, Microbiology, Pathology and Infectious Diseases, Huddinge University Hospital, Karolinska Institutet, Huddinge, Sweden; ***J. Tollemar,*** Departments of Transplantation Surgery and Clinical Immunology, Huddinge University Hospital, Karolinska Institutet, Huddinge, Sweden; ***G.G. Zhanel,*** Faculties of Medicine and Pharmacy, University of Manitoba, Department of Medicine, Health Sciences Centre, Winnipeg, Manitoba, Canada.

Contents

Summary

Synopsis

Incorporation of amphotericin B into small unilamellar liposomes (AmBisome®) alters the pharmacokinetic properties of the drug, but allows it to retain significant in vitro *and* in vivo *activity against fungal species, including* Candida, Aspergillus *and* Cryptococcus, *and parasites of the genus* Leishmania.

Used as prophylaxis against fungal infections in immunocompromised patients, liposomal amphotericin B appeared to reduce the incidence of both fungal colonisation and proven fungal infections, but did not affect overall survival.

Empirical therapy with liposomal amphotericin B in immunocompromised adults or children with suspected fungal infections was at least as effective as therapy with conventional amphotericin B. In the largest noncomparative studies, liposomal amphotericin B produced mycological eradication in 40 and 83% of patients with proven Candida *infections and 41 and 60% with proven* Aspergillus *infections; however, these studies included relatively few patients. Mycological eradication rates of 67 to 85% in patients with cryptococcal meningitis have been reported.*

Liposomal amphotericin B is an effective treatment for visceral leishmaniasis in immunocompetent adults and children, including those with severe or drug-resistant disease. The drug also produces good response rates in immunocompromised patients; however, relapse rates in these patients are high.

Liposomal amphotericin B is generally well tolerated. Few patients require discontinuation or dose reduction of the drug because of adverse events. The most frequently reported adverse events are hypokalaemia, nephrotoxicity and infusion-related reactions; however, these occur significantly less often after liposomal amphotericin B than after the conventional formulation of the drug.

The acquisition cost of liposomal amphotericin B is higher than that of conventional amphotericin B. Cost-effectiveness analyses did not clearly show an economic benefit for empirical liposomal amphotericin B antifungal therapy in adults; however, one model suggested that initial empirical therapy with the liposomal formulation in children may cost less per cure than initial therapy with the conventional formulation.

Liposomal amphotericin B appears to be an effective alternative to conventional amphotericin B in the management of immunocompromised patients with proven or suspected fungal infections. Use of the drug is facilitated by its greatly improved tolerability profile compared with conventional amphotericin B. Because of this, liposomal amphotericin should be preferred to conventional amphotericin B in the management of suspected or proven fungal infections in immunocompromised patients with pre-existing renal dysfunction, amphotericin B–induced toxicity or failure to respond to conventional amphotericin B. Liposomal amphotericin B may also be considered for first- or second-line treatment of immunocompetent patients with visceral leishmaniasis.

Pharmacodynamics

Amphotericin B is a macrocyclic polyene antibiotic which acts via inhibition of membrane function in susceptible fungal and *Leishmania* cells. Liposomal amphotericin B (AmBisome®) – produced by incorporation of amphotericin B into small, unilamellar liposomes – accumulates at sites of fungal infection, binding directly to fungal cells and causing cell death. Drug and liposome remain closely associated in circulation, permitting the administration of higher doses with reduced toxicity relative to conventional amphotericin B.

Liposomal amphotericin B is active *in vitro* and *in vivo* against a variety of

© Adis International Limited. All rights reserved.

pathogenic fungi and *Leishmania* species. In rodent models of *Candida*, *Aspergillus* and *Cryptococcus* infection, liposomal amphotericin B was administered in higher doses than the conventional drug, generally producing greater reductions in fungal burden. Survival rates were generally similar between the 2 formulations, although liposomal amphotericin B improved cure rates and survival compared with lower doses of conventional amphotericin B in some studies. When the 2 formulations were administered in identical milligram per kilogram dosages, they had similar effects on survival in infected animals, and conventional amphotericin B tended to produce a greater reduction in fungal burden. Against murine visceral leishmaniasis, liposomal amphotericin B was considerably more effective than conventional amphotericin B or meglumine antimonate, and it produced clinical improvement with significantly fewer doses than the latter agent.

Pharmacokinetics

After intravenous administration, liposomal amphotericin B achieves a higher peak serum concentration and larger area under the serum concentration-time curve than conventional amphotericin B. The drug appears to be taken up extensively by the reticuloendothelial system. High concentrations of drug are detected in liver and spleen, with lower concentrations found in brain, CSF, bone marrow, heart and lung.

The apparent mean half-life of liposomal amphotericin B is approximately 6 to 7 hours. Elimination of liposomal amphotericin B, like that of the conventional formulation, is poorly understood. No metabolites are known.

Therapeutic Use in Fungal Infections

Liposomal amphotericin B fungal prophylaxis was more effective than placebo in immunocompromised patients. The drug significantly reduced rates of invasive fungal infection in liver transplant recipients; among bone marrow transplant recipients, liposomal amphotericin B reduced the rate of fungal colonisation, but not invasive fungal infection. Overall survival was not affected.

Empirical therapy with liposomal amphotericin B in immunocompromised adults and children with suspected fungal infections was at least as effective as therapy with conventional amphotericin B in randomised studies. Evidence from noncomparative studies confirms the effectiveness of empirical liposomal amphotericin B in patients with suspected fungal infections, including patients who had experienced prior inefficacy or toxicity with conventional amphotericin B.

Limited data from noncomparative studies suggest that liposomal amphotericin B is effective against invasive *Candida* and *Aspergillus* infection and oral candidosis. However, fewer than 20 patients with each infection were evaluable in most studies. In the largest available studies, liposomal amphotericin B produced mycological eradication in 41 and 60% of patients with *Aspergillus* infection and 40 and 83% of patients infected by *Candida* spp. 67 to 85% of patients with AIDS and cryptococcal infection (primarily meningitis) who received liposomal amphotericin B achieved mycological eradication.

Therapeutic Use in Visceral Leishmaniasis

Liposomal amphotericin B is an effective treatment for visceral leishmaniasis (*kala azar*) in immunocompetent adults and children, clearing parasites in 100% of patients in several studies. The drug is also effective in patients with severe or pentavalent antimonial-resistant disease; however, response rates appear to be lower. In most immunocompetent patients, symptomatic improvement and objective response are detectable within 1 week of starting therapy. Liposomal

© Adis International Limited. All rights reserved.

amphotericin B also produces good response rates in immunocompromised patients; however, relapse rates are high. No comparative data are available.

Tolerability

Liposomal amphotericin B was generally well tolerated. The drug was discontinued because of adverse events in <5% of patients. Liposomal amphotericin B recipients experienced fewer adverse events than patients who received conventional amphotericin B. The most frequently reported adverse events in the liposomal amphotericin B group included hypokalaemia, nephrotoxicity and infusion-related fever and rigors. Increased serum liver enzymes have been noted in a substantial proportion of liposomal amphotericin B recipients. However, these patients may have been predisposed to elevations in liver enzymes by concomitant drugs or disease states; causality is unclear.

Dosage and Administration

Liposomal amphotericin B is administered as a single daily dose by slow intravenous infusion. Premedication is not required.

Used for empirical antifungal therapy in immunocompromised patients, the recommended (US) liposomal amphotericin B dosage is 3 mg/kg/day. Patients with proven systemic fungal infections should receive 3 to 5 mg/kg/day (US) or 1 to 3 mg/kg/day (UK). The optimum duration of antifungal therapy is not well defined. In neutropenic patients, treatment is generally continued until the recovery of neutrophil counts. A dosage of liposomal amphotericin B 1 mg/kg/day has been used for fungal prophylaxis after bone marrow or liver transplantation.

In immunocompetent patients with visceral leishmaniasis, liposomal amphotericin B 3 mg/kg should be administered on days 1 to 5, 14 and 21. In immunocompromised patients, the recommended dosage is 3 mg/kg/day on days 1 to 5 and 4 mg/kg/day on days 10, 17, 24, 31 and 38. Other regimens of 21 to 30 mg/kg administered over 10 to 21 days may also be appropriate.

Pharmacoeconomic Implications of Liposomal Amphotericin B

The acquisition cost of liposomal amphotericin B is considerably higher than that of the conventional formulation. Because of this, the prophylactic use of liposomal amphotericin B may be difficult to justify. One cost-effectiveness analysis of empirical liposomal amphotericin B therapy suggested that savings associated with the reduced toxicity and improved efficacy of the liposomal formulation in immunocompromised adults with proven or suspected fungal infections were not enough to offset its increased acquisition cost compared with the conventional formulation. Another model suggested that initial empirical therapy with liposomal amphotericin B may cost less per complete cure than the conventional formulation in children, but not in adults. No pharmacoeconomic data are available for the use of liposomal amphotericin B in patients with visceral leishmaniasis.

Amphotericin B is a macrocyclic polyene antibiotic derived from *Streptomyces nodosus*.[1] Administered in its conventional formulation – that is, complexed with deoxycholate – it remains the drug of choice for many fungal infections and has been studied in the treatment of visceral leishmaniasis. However, use of the conventional formulation is limited by its poor tolerability profile.

Incorporation of amphotericin B into liposomes (Ambisome®) alters the pharmacokinetic profile of the drug, leading to changes in tissue distribution, antifungal activity and, importantly, tolerability.

Several lipid-based formulations of amphotericin B exist; however, only 1 available formulation – that reviewed in this article – may truly be described as liposomal amphotericin B (table I). This product is a lyophilised formulation consisting of liposomal amphotericin B incorporated into small,

© Adis International Limited. All rights reserved.

unilamellar liposomes (mean diameter <100nm) composed of hydrogenated soy phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol combined in a molar ratio of 2 : 1 : 0.8. Liposomal amphotericin B is administered intravenously, and dosage is always expressed in terms of amphotericin B content.

1. Pharmacodynamics

1.1 Mechanism of Action of Amphotericin B

Amphotericin B acts by binding to ergosterol, the principal sterol in the membrane of susceptible fungal and parasite cells.[1,4] This impairs membrane function, causing metabolic disturbance, loss of cell constituents and, eventually, cell death.

Liposomal encapsulation of amphotericin B alters the pharmacokinetic profile of the drug (section 2), but does not appear to alter its mechanism of antifungal activity.

In vitro and *in vivo*, amphotericin B remains closely associated with the liposome structure. Whereas conventional amphotericin B (1 μg/ml) incubated with red blood cells caused 95% cell lysis, the liposomal formulation (100 μg/ml), incubated under identical conditions, caused only 5% lysis, suggesting that little amphotericin B (<1%) was released from the liposomes.[5] Similarly, amphotericin B was not released from liposomes in circulation: 1 to 24 hours after injection of [^{14}C]phosphatidylcholine-containing liposomal amphotericin B into mice, the ratio of drug to ^{14}C in plasma remained near 1 (range 0.91 to 1.18).[5]

Intact liposomes accumulate at sites of fungal infection. Sectioned tissues from mice killed 17 hours after treatment with liposomes containing sulforhodamine dye (with or without amphotericin B) fluoresced brightly at sites of fungal infection. Both empty and amphotericin B–containing liposomes bound as intact liposomes to *Candida albicans* in suspension.[5]

The binding of amphotericin B liposomes to fungal cells leads to cell death. Initially, both amphotericin B liposomes and empty liposomes bound to *C. albicans* cells in suspension.[5] After 15 hours' incubation, however, disruption of the drug-containing liposomes had occurred, and the fungus showed a loss of viability. In contrast, empty liposomes remained intact and did not reduce fungal viability. Similar results were observed in cultures of *Candida*-infected murine peritoneal macrophages.[5]

1.1.1 Effects on Neutrophils and Lymphocytes

Effective phagocytic cell function is often crucial for successful antifungal therapy. It is therefore of interest that higher concentrations of liposomal than conventional amphotericin B are required to reduce neutrophil phagocytic function.[6] In *in vitro* cell cultures, liposomal amphotericin B, at concentrations ≥20 mg/L, caused a significant reduction in neutrophil uptake of *C. albicans* blastospheres. Similar effects were seen with conventional amphotericin B at concentrations ≥1 mg/L.

Similarly, clinically relevant concentrations of amphotericin B (0 to 16 mg/L) impaired *in vitro* proliferation of B- and T-lymphocytes from immune-normal and immunocompromised mice, but the same concentrations of liposomal amphotericin B did not affect immune function.[7]

Table I. Comparative properties of amphotericin B formulations[2,3]

Particle properties	Conventional amphotericin B	Liposomal amphotericin B (AmBisome®)	Amphotericin B colloidal dispersion	Amphotericin B lipid complex
Shape	Micelle	Liposome	Lipid disc	Lipid sheet
Size (nm)	<25	90	100	500-5000
Lipid/carrier composition	Deoxycholate	Cholesterol soy lecithin plus distearoylphosphatidylcholine	Cholesteryl sulphate	Dimyristoylphosphatidylcholine plus dimyristoylphosphatidylglycerol
Amphotericin concentration (mol/L)	340	100	50	330

© Adis International Limited. All rights reserved.

1.2 Overview of Antimicrobial Activity

1.2.1 Antifungal Activity

Encapsulation of amphotericin B in liposomes did not appear to reduce its activity against fungal isolates *in vitro* (table II). Indeed, minimum inhibitory concentrations of the liposomal drug were generally one dilution lower than those of conventional amphotericin B. However, *in vitro* fungal susceptibility testing may not reliably predict the clinical activity of antifungal drugs.[8,9] Because of this, and because clinical assessment of antifungal activity is complicated by difficulties in identifying and proving fungal infections (section 3), studies of *in vivo* activity are of particular importance in the evaluation of the antifungal activity of liposomal amphotericin B. Unless otherwise indicated, the drug was administered intravenously in all of these studies.

Candida spp.

In *C. krusei*-infected neutropenic mice, intermediate and high dose liposomal amphotericin B (15 and 30 mg/kg/day) produced a greater reduction in fungal burden than low doses of the drug (8 to 10 mg/kg/day), conventional amphotericin B (1 or 2 mg/kg/day) or fluconazole (100 mg/kg/day).[11,12] High dose liposomal amphotericin B was associated with increased mortality, probably secondary to toxicity, but survival improved in mice treated with low and intermediate doses of liposomal amphotericin B and conventional amphotericin B compared with that in untreated and fluconazole-treated mice.[11,12] No difference in survival was detected between mice treated with low or intermediate dose liposomal amphotericin B or conventional amphotericin B.[11,12]

Similarly, liposomal amphotericin B 8 to 30 mg/kg/day was as effective as conventional amphotericin B 1 or 2 mg/kg/day in prolonging survival in immunosuppressed mice infected with amphotericin B–susceptible *C. lusitaniae*, and produced greater reductions in fungal titres.[11] However, no advantage was detected for any dose of the liposomal compared with the conventional formulation in mice infected with amphotericin B–resistant *C. lusitaniae*.[11]

Conventional and liposomal amphotericin administered in maximum tolerated dosages (0.4 and 7 mg/kg/day, respectively) and fluconazole (0.4 to 64 mg/kg/day) caused a reduction in the numbers of *C. albicans* colony-forming units in the kidneys of immunocompetent mice.[13] (Maximum tolerated dosages for the 2 amphotericin B formulations were determined in noninfected mice in a dose-ranging study in which end-points were death or renal/hepatic dysfunction.) In infected mice, both formulations of amphotericin B prevented relapse of infection after the completion of treatment; fluconazole did not. Similarly, in leucopenic mice infected with *C. albicans*, conventional amphotericin B (0.3 mg/kg/day) and fluconazole (64 mg/kg/day) reduced the number of colony-forming units in the liver, spleen and lungs, but failed to reduce the number of colony-forming units in the kidney, which led to relapse after the completion of treatment.[13] In contrast, liposomal amphotericin B (7 mg/kg/day) significantly reduced the number of colony-forming units in all organs, including the kidney, and prevented relapse.[13] In a similar study published in abstract form,[14] liposomal amphotericin B, but not conventional amphotericin B or conventional amphotericin B in lipid 10% (a formulation not available commercially), significantly

Table II. Representative study of the *in vitro* activity of liposomal and conventional amphotericin B against various fungal isolates tested using microbroth dilution assays[10]

Organism[a] (no. of isolates)	Minimum amphotericin B concentration required to inhibit 90% of isolates (mg/L) [MIC_{90}]	
	liposomal	conventional
Aspergillus spp.[b] (13)	1.25	2.50
Candida spp.[c] (72)	0.62	1.25
Cryptococcus neoformans (32)	0.62	1.25
Fusarium spp.[d] (8)	2.50	2.50

a For species tested, MIC_{90} values did not differ within genus.

b Tested isolates included *A. fumigatus* (4), *A. flavus* (4), *A. terreus* (3), *A. niger* (2).

c Tested isolates included *C. albicans* (32), *C. tropicalis* (20), *C. parapsilosis* (20).

d Tested isolates included *F. solani* (4), *F. moniliforme* (2), *F. oxysporum* (1), *F. equiseti* (1).

© Adis International Limited. All rights reserved.

reduced the amount of fungus in liver tissue from mice which were infected with *C. albicans* (mouse strain, immune status not reported) [all drugs administered at 1 mg/kg/day].[14] Conventional and liposomal amphotericin B, both administered at 0.75 mg/kg, produced equivalent reductions of yeasts in the kidney tissue of *C. albicans*-infected mice.[15]

Aspergillus spp.

In immunosuppressed rabbits and rats, liposomal amphotericin B (5 and 10 mg/kg/day, respectively) was more effective than conventional amphotericin B 1 mg/kg/day against pulmonary *Aspergillus fumigatus*.[16,17] In rabbits, the liposomal formulation caused less nephrotoxicity, improved survival more and produced a greater reduction in the number of viable fungal organisms than the conventional formulation.[16] In rats, both formulations delayed and reduced mortality, but only the liposomal formulation reduced the number of colony-forming units in the inoculated lung and prevented the dissemination of infection from the infected to the noninfected lung.[17]

In a rabbit model of *A. fumigatus* endocarditis (immune status not reported), conventional amphotericin B, the liposomal formulation and amphotericin B lipid complex had similar effects on survival when administered at 2 mg/kg/day; however, the conventional formulation produced the greatest reduction in colony-forming units.[18] At higher doses (6 mg/kg/day), the liposomal and lipid-based formulations were as effective as the conventional formulation administered at 2 mg/kg/day.

Cryptococcus neoformans

In a murine model of *Cryptococcus neoformans* meningitis (ICR outbred mice), therapy every second day with liposomal amphotericin B 1 mg/kg or conventional amphotericin B 0.3 mg/kg produced similar and significant prolongation of survival compared with that in untreated mice.[19] Both drugs significantly reduced fungal burden compared with controls; however, the reduction was significantly greater in mice which received the conventional formulation (p value not reported). Over the dosage range of 1 to 30 mg/kg, liposomal amphotericin B dose-dependently reduced fungal burden, with brain cultures negative in 78% of animals at the highest dose. Similar dose-response effects of liposomal amphotericin B in murine cryptococcosis have been noted elsewhere (C57BL/6 mice).[15]

Other Fungal Pathogens

Liposomal amphotericin B was active in several murine models of systemic fungal infection, including pulmonary infection by *Paracoccidioides brasiliensis*,[20] *Blastomyces dermatitidis*[21] and *Coccidioides immitis*,[22] and disseminated *Trichosporon beigelii*[23] and *Histoplasma capsulatum*.[24] Against paracoccidiomycosis[20] and blastomycosis (in BALB/c and CD-1 mice, respectively),[21] conventional amphotericin B was more active than the liposomal formulation on a milligram-per-kilogram basis; however, higher doses of the liposomal drug could be administered safely and were curative. Against coccidiomycosis (in ICR mice)[22] and histoplasmosis (in athymic *nu/nu* BALB/c mice),[24] both formulations were effective and equally active at the same dosage. In addition, aerosolised liposomal amphotericin B has been shown to be effective in the treatment and prophylaxis of murine cryptococcosis (data reviewed by Gilbert).[25]

1.2.2 Activity Against Leishmania

Against *Leishmania major* promastigotes (the form of the parasite which occurs in the vector) in culture and amastigotes (as found in an infected lesion) in murine macrophages, liposomal amphotericin B was 3 to 6 times less active than the conventional formulation.[26] However, in *L. major*–infected (BALB/c) mice, liposomal amphotericin B (6.25 to 50 mg/kg) reduced the lesion size in a dose-dependent fashion, whereas the conventional formulation was ineffective in subtoxic doses (≤1 mg/kg).[26] Sodium stibogluconate, even at a daily dose of 400mg antimony (Sb^V)/kg, was also ineffective *in vivo*.

Liposomal amphotericin B (12 mg/kg) and amphotericin B lipid complex (12 mg/kg) were both completely successful in eradicating *L. infantum* in

© Adis International Limited. All rights reserved.

Table III. Pharmacokinetics of liposomal amphotericin B, conventional amphotericin B and amphotericin B in lipid 20% after single-dose intravenous administration in 10, 6 and 8 patients, respectively (disease states not reported)[32]

Drug (dose)	C_{max} (mg/L)	Vd (L/kg)	CL (L/h/kg)	$t_{½\alpha}$ (h)	$t_{½\beta}$ (h)[a]	AUC (mg/L • h)
Liposomal amphotericin B (3 mg/kg)	29.0	0.37	0.02	1.74	23.6	423
Conventional amphotericin B (1 mg/kg)	3.57	1.59	0.04	0.67	34.7	34.2
Amphotericin B in lipid 20% (1 mg/kg)	1.40	2.80	0.08	1.99	33.3	19.7

a Analyses were limited to 24h; therefore, these are apparent values only.

Abbreviations: AUC = area under the serum concentration-time curve; C_{max} = peak serum drug concentration; CL = total plasma clearance; $t_{½\alpha}$, $t_{½\beta}$ = first, second elimination half-life; Vd = volume of distribution.

a (BALB/c) murine model of visceral leishmaniasis.[27] Conventional amphotericin B (0.8 mg/kg), amphotericin B in lipid 20% (1.2 mg/kg) and meglumine antimonate 200mg Sb^V/kg were considerably less effective. Similarly, 3 consecutive daily doses of liposomal amphotericin B 3 mg/kg were enough to clear *L. infantum* parasites from the livers of infected (BALB/c) mice, but meglumine antimonate 28mg Sb^V/kg/day did so only after 21 days.[28] In dogs naturally infected with *L. infantum*, 3 to 5 doses of liposomal amphotericin B 3 to 3.3 mg/kg were as effective as 14 to 21 doses of meglumine antimonate in producing clinical improvement; however, neither agent produced parasitological cures.[29]

1.3 Murine Toxicity: Comparison with Conventional Amphotericin B

In rodents, as in humans (section 5), liposomal amphotericin B was considerably less toxic than conventional amphotericin B.[30] In single-dose studies, the amount of liposomal amphotericin B required to cause death in 50% of mice (LD_{50}) was >76-fold higher with the liposomal than the conventional formulation (>175 *vs* 2.3 mg/kg). Rats were more sensitive to the lethal effects of both drugs; however, the ratio of LD_{50} values remained high (50 *vs* 1.6 mg/kg). In multiple-dose studies, only 2 of 10 mice died after liposomal amphotericin B 75 mg/kg daily for 14 days, whereas a single dose of conventional amphotericin B >2.6 mg/kg was lethal in 100% of mice.

2. Pharmacokinetics

The pharmacokinetics of liposomal amphotericin B after single- and multiple-dose intravenous administration are summarised in tables III and IV, respectively. After single-dose intravenous administration, the drug achieves high peak serum concentrations (C_{max}) and a large area under the serum concentration-time curve (AUC) [table III]. In multiple dose data reviewed elsewhere,[31] C_{max} after the second once daily dose of liposomal amphotericin B was approximately twice that measured after the first dose; thereafter, C_{max} remained constant. The first-phase elimination half-life ($t_{½}\alpha$) of liposomal amphotericin B is ≤2 hours, indicating rapid distribution to the tissue compartment and/or uptake by the reticuloendothelial system. The second-phase elimination half-life is 24 to 35 hours

Table IV. Steady-state pharmacokinetics of liposomal amphotericin B administered intravenously once daily over 1-2h to febrile neutropenic cancer and bone marrow transplant patients[34]

Dosage (mg/kg/day)	No. of evaluable pts	C_{max} (mg/L)	Vd (L/kg)	$t_{½}$ (h)	CL (L/h/kg)	$AUC_{0–24}$ (mg/L • h)
1.0	7	12.2	0.14	7.0	0.039	211
2.5	7	31.4	0.16	6.3	0.022	419
5.0	9	83.0	0.10	6.8	0.011	523

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24h; C_{max} = peak serum drug concentration; CL = total plasma clearance; $t_{½}$ = mean elimination half-life; Vd = volume of distribution.

© Adis International Limited. All rights reserved.

(table III); the apparent mean half-life is 6 to 7 hours (table IV).

With increasing doses of liposomal amphotericin B, AUC values increased in a nearly linear fashion, suggesting that clearance was not saturable at the doses reported (table IV). The linear relationship was less clear in a study carried out in febrile neutropenic patients (AUC values 69, 206 and 713 mg/L · h at 1, 2.5 and 5 mg/kg/day).[33] As mentioned in section 1, amphotericin B does not tend to dissociate from the liposomes in circulation.[31]

After administration of the liposomal formulation, amphotericin B is detected mainly in spleen and liver tissue, reflecting the extensive reticuloendothelial uptake of the drug (fig. 1). Substantial amounts of drug were recovered in kidney and lung tissue; concentrations in brain, CSF, thyroid, bone marrow, heart and muscle tissue were low (generally <25 mg/kg).[35] In patients with AIDS-related cryptococcal meningitis, no amphotericin B was detectable in the CSF after 7, 14 and 21 days' treatment with liposomal amphotericin B 4 mg/kg/day (n = 15) or conventional amphotericin B 0.7 mg/kg/day (n = 13). In contrast, a case report does exist of the CSF concentration reaching 56% of the serum concentration (0.36 and 0.64 mg/L, respectively) after administration of liposomal amphotericin B (dose not specified) for presumed fungal sepsis after bone marrow transplant (BMT) in a patient with acute myeloid leukaemia.[36]

In rabbits, liposomal amphotericin B 5 mg/kg produced 7-fold higher drug concentrations in the liver than conventional amphotericin B 1 mg/kg (239 *vs* 33 μg/g; p = 0.002); however, accumulation of the liposomal formulation in kidney tissue was 14 times lower (0.87 *vs* 12.7 μg/g; p = 0.04).[37] No drug was detectable in CSF after administration of liposomal amphotericin B, amphotericin B colloidal dispersion, amphotericin B lipid complex (each at 5 mg/kg) or conventional amphotericin B (1 mg/kg) in rabbits.[38] Brain amphotericin B concentrations were 4 to 7 times higher after the liposomal formulation than after the other 3 formulations (p < 0.005).

The pharmacokinetic profile of liposomal amphotericin B is substantially different from that of

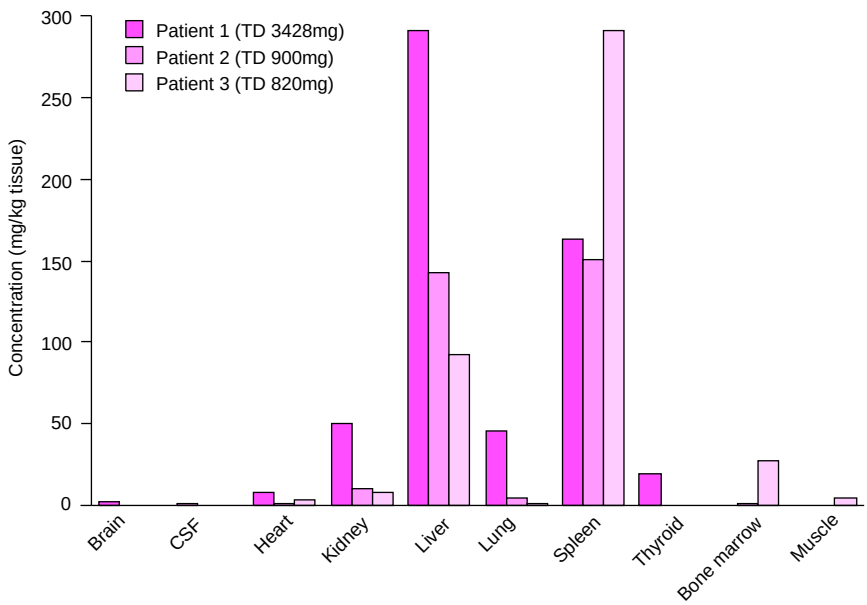

Fig. 1. Tissue concentrations of liposomal amphotericin B in 3 patients.[35] TD indicates total cumulative dose.

© Adis International Limited. All rights reserved.

the conventional drug or amphotericin B in lipid 20% (table III). Liposomal amphotericin B distributes in a smaller volume of distribution than the other formulations and, correspondingly, the C_{max} is substantially higher after administration of the liposomal formulation (table III).

The second elimination half-life of liposomal amphotericin B is approximately 24 hours (table III). No metabolite of amphotericin B has been identified and the elimination of both conventional and liposomal formulations of the drug is poorly understood.[31] After administration of conventional amphotericin B, only about 2 to 5% of a dose is recovered in the urine within 24 hours, and tissue accumulation appears to account for most drug distribution.[31] Clearance of the liposomal formulation is slower than that of the conventional formulation (table III).

Haemodiafiltration in a patient receiving liposomal amphotericin B (1 to 2 mg/kg/day) removed drug at a constant rate of approximately 0.5 mg/h (zero-order removal); dosage adjustment was not required.[39] Liposomal amphotericin B was not removed by short term (4-day) continuous venous-venous haemofiltration.[40]

3. Therapeutic Use in Fungal Infections

Evaluation of antifungal therapy in immunosuppressed patients is notoriously difficult. Mycotic disease is not easy to identify accurately and may present clinically like other (nonfungal) infections or similar noninfectious presentations. Even with invasive investigations, fungal pathogens are infrequently isolated, may be isolated only after death and may be indistinguishable from colonisation or contamination of cultures.[1,41]

3.1 Empirical Antifungal Therapy in Immunocompromised Patients

3.1.1 Use as Prophylactic Therapy

Two randomised double-blind placebo-controlled studies have assessed the benefit of prophylactic liposomal amphotericin B in transplant patients (table V). Liposomal amphotericin B appeared to reduce the post-transplant incidence of proven fungal infections in both BMT (allogeneic or autologous)[42] and liver transplant[43] recipients, although the apparent effect reached statistical significance only in the latter study. This post–liver transplant difference in incidence of proven fungal infections between liposomal amphotericin B and placebo recipients remained significant even after 1 year (11 *vs* 29%; p = 0.05). Cultured organisms in these 2 studies included *Candida* spp.[42,43] and *Aspergillus* spp.[43] No difference in survival was noted between placebo and liposomal amphotericin B recipients in either trial.

Among BMT patients, significantly fewer liposomal amphotericin B than placebo recipients were colonised by *Candida* spp. by study end (p = 0.05).[42] During the study, fungal colonisation decreased in liposomal amphotericin B recipients (from 55% of patients at baseline to 33% at study

Table V. Prophylaxis against fungal infections with liposomal amphotericin B (LAB): randomised, double-blind, placebo-controlled studies in immunocompromised patients (pts)

Reference	Underlying condition	No. of evaluable pts	Treatment (mg/kg/day) [duration]	Outcomes (% of pts)			
				fungal colonisation	suspected fungal infection	proven fungal infections at ≤30 days	survival at 1y
Tollemar et al.[42]	Bone marrow transplant[a]	36	LAB 1 [until ANC >0.5][b]	33*	14	3	62
		40	Placebo	62	18	8	73
Tollemar et al.[43]	Liver transplant	40	LAB 1 [5 days]	NR	NR	0**	80
		37	Placebo	NR	NR	16	78

a 82% of enrolled pts received allogeneic transplants; 18% received autologous transplants.

b Treatment was begun when ANC decreased to <0.5 and continued until >0.5 on 2 successive days.

Abbreviations and symbols: ANC = absolute neutrophil count ($\times 10^9$/L); NR = not reported; * p = 0.05, ** p < 0.01 *vs* placebo.

© Adis International Limited. All rights reserved.

Table VI. Use of liposomal amphotericin B (LAB) in immunocompromised patients (pts) with suspected or proven fungal infections. Studies were nonblind, except as indicated

Reference (study design)	No. of clinically evaluable pts	LAB dosage (mg/kg/day) [median duration of treatment; range (days)]	Clinical response[a] (% of pts)	
			success	failure
Noncomparative studies, generally in patients with underlying, or conventional amphotericin B (C-AmB)–induced, renal failure or previously unsuccessful C-AmB treatment				
Berenguer et al.[46] (pro)	10	2.5-4 [mean 17; 3-33]	50	50
Böhme & Hoelzer[47] (pro)	19[b]	3-5 every other day [NR]	84	16
Heinemann et al.[48]c (ret)	100	200 mg/day[d] [15]	NR	42
Krüger et al.[49]	50	1-5 [13; 1-55]	54	46
Mills et al.[50] (ret)	133[e]	NR [12; 2-96]	61[f]	19
Nowoczyn et al.[51]c	10	1.5-2.5 [15; 4-35]	70	10
Ringdén et al.[52]	15	0.5-3 [15; 3-55]	87	NR
Ringdén et al.[35] (pro, mc)	99	0.5-5 [18; 1-97]	81	19
Randomised comparisons with C-AmB				
Leenders et al.[53]c (pro, mc)	32	LAB 5 [NR]	50*	NR
	34	C-AmB 1 [NR]	24	NR
Prentice et al.[45] (pro, mc)	118	LAB 1 [NR][g]	58	NR
	118	LAB 3 [NR][g]	64*	NR
	102	C-AmB 1 [NR][g]	49	NR
Walsh et al.[44]c (pro, mc, db)	343	LAB 3 [mean 10.8]	50	14[h]
	344	C-AmB 0.6 [mean 10.3]	49	19[h]

a Response definitions varied between studies. Success includes pts with clinical cure or improvement including, in some studies,[35,46,47] radiographic improvement.

b Pts in this study had pneumonia. Those with pulmonary infiltrates characteristic of *Aspergillus* received 5 mg/kg every second day; others received 3 mg/kg every second day.

c Abstract.

d Median dose.

e 133 treatment episodes in 116 enrolled pts.

f A further 20% of pts were found to have a nonfungal source of illness.

g Study end was defined as resolution of fever, recovery of neutrophils, patient death, unresolved toxicity or patient/physician request to withdraw.

h Withdrawal of study drug because of toxicity or lack of efficacy.

Abbreviations: db = double-blind; mc = multicentre; NR = not reported; pro = prospective; ret = retrospective; * $p < 0.05$ *vs* C-AmB.

end), but increased in placebo recipients (from 41 to 62%).[42]

3.1.2 Use in Patients with Suspected Infections

In large, randomised comparative trials, liposomal amphotericin B was at least as efficacious as conventional amphotericin B in the treatment of neutropenic patients with pyrexia of unknown origin (table VI).[44,45]

Combined efficacy data from 2 comparative studies which included 134 adults and 204 children who received liposomal amphotericin B 1 or 3 mg/kg/day or conventional amphotericin B 1 mg/kg/day showed successful outcome in 58, 64 and 49% of patients, respectively.[45] Successful outcome, defined as resolution of fever for ≥3 days without the development of new fungal infection, occurred significantly more frequently in recipients of liposomal amphotericin B 3 mg/kg than in recipients of conventional amphotericin B ($p = 0.03$). However, a Kaplan-Meier analysis of time to defervescence showed that there were no significant differences between the treatments.[45]

In 687 neutropenic patients [absolute neutrophil count (ANC) $<0.5 \times 10^9$/L] with persistent fever (>96 hours while on antibacterial therapy), the composite success rates (not defined) for lipo-

© Adis International Limited. All rights reserved.

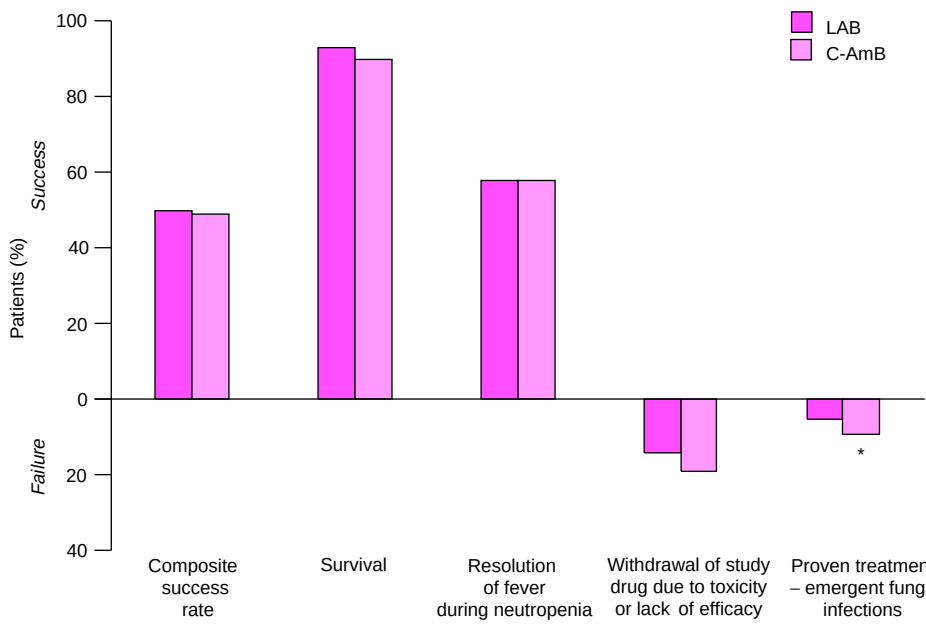

Fig. 2. Clinical outcomes of empirical antifungal therapy with liposomal amphotericin B (LAB) 3 mg/kg/day versus conventional amphotericin B (C-AmB) 0.6 mg/kg/day in persistently febrile, neutropenic patients (n = 343 and 344, respectively). * p = 0.021 *vs* LAB.[44]

somal and conventional amphotericin B (3 and 0.6 mg/kg/day, respectively) were 50 and 49% (fig. 2).[44] Overall survival, resolution of fever during neutropenia and premature withdrawal of study drug because of poor efficacy or tolerability were similar between the 2 groups. Significantly fewer proven fungal infections emerged during treatment in the group which received the liposomal formulation (5 *vs* 9% of patients; p = 0.02).

In a small comparative study in neutropenic patients (n = 66) published in abstract form,[53] liposomal amphotericin B 5 mg/kg/day produced a higher clinical success rate (complete or partial response) than conventional amphotericin B 1 mg/kg/day (50 *vs* 24%) [table VI]. Complete response (total resolution of pretreatment signs and symptoms plus progressive improvement of chest x-rays) also occurred more often in recipients of the liposomal formulation in this study (44 *vs* 18%; p = 0.03).

The empirical use of liposomal amphotericin B for suspected fungal infections in immunocompromised adults produced complete clinical resolution ('clinical cure') or significant clinical improvement in 50 to 87% of patients in noncomparative studies (table VI). Definitions of clinical response and 'proven fungal infection' varied widely in these studies, as did patient inclusion criteria. Clinical cure was generally defined as resolution of all symptoms of infection, possibly including fever, infected wounds, stomatitis, cough and chest infiltrates. Most studies included heterogeneous patients with very different case histories and reasons for enrolment.

The predominant underlying medical condition of patients in several of these studies was neutropenia secondary to haematological malignancy.[47,50,51] Other major underlying conditions included neutropenia secondary to treatment for solid tumours, bone marrow or peripheral blood progenitor cell transplantation and organ (mainly liver) transplantation.[35,47,49,54] One study[35] included 12 patients with AIDS; however, use of the drug in this population is discussed in section 3.2.1.

© Adis International Limited. All rights reserved.

In several studies, a large proportion of patients (36 to 100%) had received conventional amphotericin B before being switched to the liposomal drug because of toxicity or progression of fungal infection.[35,49-52]

In the largest noncomparative study, 137 episodes of suspected fungal infection in 126 patients were treated with liposomal amphotericin B.[35] Of 99 clinically evaluable patients (64 with proven infection, 24 with presumed infection and 11 with superficial fungal infection) who received the drug for ≥8 days, 60% achieved clinical cure and a further 21% improved clinically. Cure, in this study, was defined as complete disappearance of all symptoms, including infiltrates on x-ray and fever. Improvement was defined as clearance of some, but not all, symptoms.

Similarly, of 133 episodes of suspected or proven mycosis among 116 patients in a large retrospective analysis who received liposomal amphotericin B, clinical resolution resulted in 61% (table VI).[50] In 17 of 25 patients who deteriorated and died despite liposomal amphotericin B treatment, there was microbiological evidence of *Aspergillus* in 8 patients and *Candida* in 9.

Compared with 72 historical controls (neutropenic patients with haematological malignancies and febrile pulmonary infiltrates) who received conventional amphotericin B or itraconazole (not shown in table VI), 23 patients who received liposomal amphotericin B for suspected *Aspergillus* pneumonia experienced higher response rates and lower lethality.[47] 89 and 68%, respectively, of liposomal and conventional amphotericin B recipients responded to initial treatment (or, for 1 liposomal amphotericin recipient, a dosage increase) [difference not statistically significant]. Mortality in the 2 groups was 5 and 32%, respectively ($p = 0.01$).

High dose liposomal amphotericin B did not appear to be superior to lower doses in the treatment of suspected or confirmed invasive aspergillosis in neutropenic cancer patients according to preliminary data published in an abstract.[55] In a dose-finding study, 68% of patients who received liposomal amphotericin B 1 mg/kg/day, compared with 49% who received 4 mg/kg/day, had complete or partial clinical response (n = 70). Corresponding values for radiological response were 63 and 54% (no statistical analyses reported).

Paediatric Patients

Paediatric patients (median age 7 to 14 years) were included in both randomised[45] and noncomparative studies.[51,52] Case reports and published abstracts further document the use of liposomal amphotericin B in immunocompromised children, including those under 1 year.[56-59]

3.2 Efficacy Against Proven Fungal Infections

3.2.1 Cryptococcosis and Other Infections in Patients with AIDS

Liposomal amphotericin B was active against *Cryptococcus* infection (primarily cryptococcal meningitis) in several small trials in patients with AIDS (table VII). Mycological eradication was complete in 67 to 85% of patients, including, in some instances,[60-62] patients in whom previous amphotericin B had been ineffective or unacceptably toxic.

Urine, stool, blood, skin and oral secretion cultures positive for *C. neoformans* cleared within 7 days' therapy with liposomal amphotericin B in all 9 patients in 1 study.[2] The time to clearance of CSF cultures generally appeared to be longer: CSF cultures cleared in 1 patient after 14 days' therapy, whereas in 3 others cultures had not cleared after 42 days. Reported times to negative fungal CSF cultures in other studies were 7 to 15,[60] 1 to 35 (mean 21)[61] and 7 to 36 (median 11) days.[62] No proven clinical relapses occurred in either group during ≥6 months' follow-up.

In a small, randomised comparison in patients with cryptococcal meningitis, liposomal amphotericin B 4 mg/kg/day produced mycological eradication in 73% of patients, compared with a 38% clearance rate in conventional amphotericin B 0.7 mg/kg/day recipients (21-day follow-up).[64] Liposomal amphotericin B produced more rapid mycological eradication than the conventional drug:

© Adis International Limited. All rights reserved.

Table VII. Summary of nonblind studies of liposomal amphotericin B (LAB) in patients (pts) with AIDS and confirmed *Cryptococcus neoformans* or other fungal infections

Reference	No. of evaluable pts	Primary pathogen (site of infection)	Treatment (mg/kg/day)[a] [mean duration of treatment; range (days)]	Clinical outcome	
				clinical cure (%)[b]	mycological eradication (%)[c]
Noncomparative studies					
Codeluppi et al.[63]d	11	5 *Cryptococcus* (meningitis)	LAB 1-2 [35]	100	NR
		6 *Candida* (oesophageal)	LAB 1-2 [16; 10-22]	50	NR
Coker et al.[62]	23	*Cryptococcus* (19 meningitis)	LAB 3 [27; 2-43]	61	67
Lazar & Ksionski[60]d	9	*Cryptococcus* (8 meningitis; 1 CSF and pulmonary)	LAB ≤3 [NR; 1-59]	89	75
Mota-Miranda et al.[61]	20[e]	10 *Cryptococcus* (9 meningitis; 1 pulmonary) 7 *Candida* (oesophageal; 1 disseminated *C. glabrata*) 3 *Aspergillus* (pulmonary)	LAB 2-3 [17; 3-35]	85[f]	85[f]
Viviani et al.[2]	9	*Cryptococcus* (2 extraneural disease, 6 disseminated with meningeal involvement, 1 meningitis refractory to other antifungals)	LAB 3 [33; 21-42]	67	67
Randomised comparison with conventional amphotericin B (C-AmB)					
Leenders et al.[64]	15	*Cryptococcus* (meningitis)	LAB 4 [21][g]	80	73[h]
	13	*Cryptococcus* (meningitis)	C-AmB 0.7 [21][g]	86	38[h]

a Excluding initial dose titrations and test doses.

b Clinical cure, where defined, generally included disappearance of all signs and symptoms of infection.[2,61,62,64]

c Clearance of (initially positive) fungal cultures during treatment,[60] by the end of treatment[61] or in 2 consecutive cultures.[2,62,64]

d Abstract.

e 19 pts with AIDS and 1 immunocompromised pt with bladder neoplasm who had undergone prolonged treatment with broad spectrum antibiotics.

f 'Cure' in this study included both remission of clinical manifestations of infection and absence of positive fungal cultures.

g Followed by maintenance therapy with fluconazole 400mg daily for 7wk.

h Assessed at 21 days. At 14 days, 67 and 11%, respectively, of liposomal and conventional amphotericin B recipients had complete mycological responses (p = 0.01).

Abbreviation: NR = not reported.

Kaplan-Meier estimates suggested median times to CSF culture conversion of 7 to 14 versus >21 days ($p < 0.05$).

Similarly, sterilisation of CSF was achieved after liposomal amphotericin B in 12 of 19 patients who had positive CSF cultures for *C. neoformans*.[62] Clinically, the majority of patients were either cured or improved (63 and 11%, respectively); 3 patients (16%) died of cryptococcosis, 2 within the first 2 weeks of therapy.

Extrapulmonary cryptococcosis is less common in paediatric than adult patients with AIDS;[65] however, a case report suggests that liposomal amphotericin B may also be effective in this population.[66]

Liposomal amphotericin B produced a good clinical response and a remission of dysphagia in 3 of 6 patients with AIDS who had oesophageal *Candida* infection which was previously unresponsive to high doses of fluconazole, with or without additional topical antifungals (table VII).[63] In 6 other patients with oesophageal candidosis,[61] dysphagia and retrosternal pain disappeared 4 to 6 days after the initiation of liposomal amphotericin B.

3.2.2 Proven Fungal Infections in Other Immunocompromised Patients

Data on the use of liposomal amphotericin B against proven fungal infections in immunocompromised patients come mainly from noncomparative studies, generally with few clinically evaluable patients per organism (table VIII). However, 1 small comparative study is available (n = 66; 26 documented infections), in which liposomal

© Adis International Limited. All rights reserved.

amphotericin B 5 mg/kg/day produced higher complete response rates than conventional amphotericin B 1 mg/kg/day (64 *vs* 17%; p = 0.02).[53] The identity of the fungal pathogens in this study was not reported.

Candida Infections

Liposomal amphotericin B appears to be active against both invasive and superficial infection by *Candida* spp. Overall response rates (clinical cure plus improvement) in patients with confirmed candidosis in noncomparative studies were 20 to 84% (table VIII).

Of 25 patients with proven invasive candidosis, 19 (76%) were cured.[35] Correspondingly, mycological eradication occurred in 83% of evaluable patients.[35] In another study, mycological eradication of confirmed *Candida* infection occurred in 40% of evaluable patients (table VIII).[48]

Mucosal, oesophageal or gastrointestinal *Candida* infection was cured by liposomal amphotericin B in 100% of patients in 2 studies (n = 6[35] and 3[68]). However, *Candida* was isolated in 11 of 48 other patients with oral candidosis, despite 7 days' liposomal amphotericin B therapy, and in 3 of 5 patients who had not received prior systemic anti-

Table VIII. Liposomal amphotericin B (LAB) in the treatment of proven fungal infections in immunocompromised patients (pts); nonblind, noncomparative studies

Reference	No. of confirmed fungal infections (site of infection/positive culture)	Clinical response[a] (% of pts)		Mycological eradication (%)
		success	failure	
Berenguer et al.[46]	4 *Aspergillus* (3 pulmonary; 1 disseminated)	75	25	NR
	4 *Candida* (2 fungaemia; 1 disseminated; 1 endocarditis)	25	75	NR
	2 *Rhizopus* spp. (1 rhinosinusal; 1 surgical wound)	50	50	NR
Böhme & Hoelzer[47]	8 *Aspergillus* (pulmonary)	75	25	NR
Fisher et al.[67]	5 *Aspergillus* (4 sputum; 1 peritoneal fluid)	20	80	NR
Heinemann et al.[48][b]	10 *Aspergillus* (NR)	NR	NR	60
	90 *Candida*[c] (NR)	NR	NR	40
Krüger et al.[49]	2 *Aspergillus* (1 pulmonary; 1 sinus)	0	100	0
	5 *Candida* (4 pulmonary/sepsis; 1 sepsis)	20	80	NR
Mills et al.[50]	21 *Aspergillus* (pulmonary)	62	38	NR
	2 *Candida* (septicaemia)	50	50	NR
Ng & Denning[68]	17 *Aspergillus* (NR)	59	41	NR
	6 *Candida*[d] (NR)	33	67	NR
	4 other (2 rhinocerebral, 1 pulmonary zygomycosis; 1 *Cryptococcus neoformans* meningitis)	75	25	NR
Ringdén et al.[52]	3 *Aspergillus* (NR)	67	33	67
	6 *Candida* (NR)	83	17	83
Ringdén et al.[35]	28 *Aspergillus* (24 pulmonary; 1 intracavitary fungus ball; 1 hepatic; 1 endocardial; 1 air sinus)	61[e]	39	41[e]
	25 *Candida* (13 blood; 4 hepatic; 4 abdominal; 1 pulmonary; 1 mediastinal; 1 air sinus and eye; 1 nasopharynx and face)	84[e]	16	83[e]
	11 others (7 *Cryptococcus neoformans*; 1 *Mucor* spp.; 1 *Coccidioides immitis*; 1 *Trichosporon capitatum*; 1 NR)	100	0	78

a Response definitions varied between studies. Success includes pts with clinical cure or improvement.

b Abstract.

c In 54 other pts, relevance of a *Candida* isolate to systemic disease was unknown.

d Excludes 3 pts with mucosal candidosis.

e A statistically significant difference was detected between the complete clinical response rate of invasive candidosis and aspergillosis (76 *vs* 32%; p < 0.01) and also between rates of mycological eradication (p < 0.01).

Abbreviation: NR = not reported.

© Adis International Limited. All rights reserved.

fungal therapy, the clinical and microbiological signs of oropharyngeal candidosis were not resolved by liposomal amphotericin B.[50]

Aspergillus Infections

Liposomal amphotericin B produced clinical cure or improvement in 60 to 70% of patients with confirmed invasive *Aspergillus* infection in most studies (table VIII); however, numbers of confirmed infections in these noncomparative studies were small. In 2 studies which included >20 patients with confirmed aspergillosis, clinical responses were observed in 61[35] and 62%[50] of patients. Most *Aspergillus* infections were pulmonary,[35,46,47,49,50] although small numbers of patients had other foci, including intracavitary fungus ball,[35] sinusitis[35,49] and endocardial,[35] hepatic[35] or disseminated infection.[46]

Of 28 proven invasive *Aspergillus* infections in 1 study, 9 (32%) were cured; this clinical cure rate was significantly lower than that reported in the same study for candidosis (76%; $p < 0.01$).[35] Similarly, mycological eradication of *Aspergillus* (41%) was lower than that of *Candida* (83%; $p < 0.01$). Of 10 confirmed *Aspergillus* infections in another study,[48] liposomal amphotericin B produced mycological eradication in 6 (60%).

Results from the large retrospective analysis discussed previously (section 3.1.2) indicate that 36 of 116 liposomal amphotericin B recipients had suspected aspergillosis; 21 further patients had confirmed *Aspergillus* infections.[50] Of these 21, 13 (62%) obtained complete or excellent partial clinical and radiological resolution with liposomal amphotericin B (table VIII). Of the 8 nonresponders, 4 had refractory malignancy and 4 died before assessment of clinical efficacy was possible. Median initial and day-14 ANCs were higher among responders than nonresponders ($ANC_{initial}$ and $ANC_{14days} = 0.25 \times 10^9$ and 1.2×10^9 cells/L for responders *vs* 0.1×10^9 and $\leq 0.2 \times 10^9$ cells/L for nonresponders; $p = 0.003$ for both comparisons). Nevertheless, there were 8 patients in whom signs of infection did not recur when the drug was discontinued despite continued neutropenia.

A higher response rate (92%) and lower lethality (41%) were seen among patients with suspected or proven pulmonary *Aspergillus* infection who received liposomal amphotericin B (n = 12) than in historical controls (n = 17) who received itraconazole or conventional amphotericin B (41 and 59%, respectively; $p = 0.008$ for both outcomes).[47] However, the differences between the active treatment and historical control groups, including a longer median duration of neutropenia in the latter group, limit the value of this finding.

Other Fungal Infections

Liposomal amphotericin B appeared to be active against infections other than candidosis or aspergillosis (table VIII). A *Fusarium pori* mycetomatous lesion improved in 1 patient, but cultures remained positive despite 65 days of liposomal amphotericin B treatment.[35] Three patients with rhinocerebral zygomycosis [one identified as *Rhizopus arrhizus (oryzae)*][69] responded to liposomal amphotericin B; 1 with pulmonary zygomycosis died despite treatment.[68,69]

Case reports suggest that liposomal amphotericin may also be effective in immunocompromised patients infected by *Fusarium* spp.,[70,71] disseminated *Histoplasma*[72] and *Curvularia* spp.[73]

4. Therapeutic Use in Visceral Leishmaniasis

Liposomal amphotericin B, administered in a variety of regimens over 7 to 21 days, is a generally effective treatment for visceral leishmaniasis (*kala azar*) in immunocompetent adults and children, including those aged <2 years (table IX). In most studies, 97 or 100% of patients experienced complete response (clearance of *Leishmania* parasites from bone marrow or splenic aspirates). With the exclusion of 2 studies discussed below, variation of the liposomal amphotericin B regimen, within the studied dosage range (table IX), appeared to have little effect on outcome. Few immunocompetent patients in any study relapsed during 12 months' follow-up.

Low response rates were reported in a study of patients with either severe or pentavalent anti-

© Adis International Limited. All rights reserved.

Table IX. Summary of studies of liposomal amphotericin B (LAB) in patients (pts) with visceral leishmaniasis; nonblind studies in immunocompetent patients infected with *Leishmania infantum*, unless otherwise indicated

Reference (study design)	No. of evaluable pts	LAB dose (mg/kg/day) [days administered]	Clinical outcome				Comments
			complete response (% of pts)[a]	time of assessment (days)	relapse (% of pts)	duration of follow-up (mo)	
Davidson et al.[74] (mc)	10	1-1.38 [1-21]	100	21	0	12	Group included 6 children; objective response assessed in 5 pts
	10	3 [1-10]	100	21	0	12	Group included 9 children; objective response assessed in 10 pts on microscopy, 3 on culture
	11	100mg[b] [1-21]	82	21	82	NR	Immunocompromised (HIV-infected) adults; relapses occurred between 2 and 22mo
Davidson et al.[75] (mc)	13	4 [1-5,10]	100	21	0	12	Group included 10 children; 3 pts lost to follow-up
	42	3 [1-5,10]	100	21	0	12	Group included 26 children
	32	3 [1-4,10]	97	21	9	12	Group included 19 children
	1	3 [1-3,10]	100	21	0	12	
di Martino et al.[76] (mc)	11	1 [1-21]	100	21	0	12	Pts were children, mean age 2.2y
	13	3 [1-10]	100	21	0	12	Pts were children, mean age 2.3y
	66	3 [1-5,10]	100	21	2[c]	12	Pts were children, mean age 3.0y
	16	3 [1-3,5,10]	94[c]	21	20[c]	12	Pts were children, mean age 2.7y; relapses occurred 3mo after treatment
Russo et al.[77] (mc)	8	4 [1-5,10,17,24, 31,38]	88	45	100	NR	Immunocompromised (HIV-infected) adults; relapses occurred between 2 and 7mo
Seaman et al.[78]	16	3-5 [0,3,10]	50[d]	21	NR	NR	Sudanese pts with *L. donovani*; all had Sb^V-resistant or severe disease; median age 8.5y
	16	3-5 [0,3,6,8,10,13]	88	21	NR	NR	As above; median age 18y
	12	4-5 [0,2,5,7]	64	14	NR	NR	Sudanese pts with *L. donovani*; median age 10.5y
Thakur et al.[79] (r)	10	2 [1-6,10]	100	24	0	12	Indian pts with *L. donovani*
	10	2 [1-4,10]	100	24	0	12	As above
	10	2 [1,5,10]	100	24	0	12	As above

a Negative culture and microscopy on repeat bone marrow or spleen aspirate.

b A fixed dose, not based on pt weight, was used.

c Pts in this study who failed to respond to initial treatment (1) or relapsed within 12 months' follow-up (4) were cured with additional LAB.

d Three further pts achieved complete response with additional LAB.

Abbreviations: mc = multicentre; NR = not reported; r = randomised; Sb^V = pentavalent antimonial compounds.

monial-resistant disease (table IX).[78] In these patients, liposomal amphotericin B 3 to 5 mg/kg on days 0, 3 and 10 was less effective than a longer regimen (6 doses over 13 days) [complete response rate 50 *vs* 88%].[78] Similarly, in a dose-ranging study in children,[76] liposomal amphotericin B 3 mg/kg on days 1 to 3, 5 and 10 appeared to be less effective than the same dose administered on days 1 to 5 and 10 (statistical comparison not performed). Furthermore, in both these studies, several patients who did not achieve good initial clinical response did respond to additional liposomal amphotericin B.[76,78] It should be noted, however, that patients with severe disease (body mass index

© Adis International Limited. All rights reserved.

<13 in adults, age >50 years, bleeding, intractable vomiting or moribund condition) may respond differently to treatment than patients with antimonial-resistant disease (i.e. patients who relapse after, or have incomplete response to, combined Sb^V and aminosidine treatment). Therefore, caution must apply when grouping these 2 patient subsets together.

Symptomatic improvement was generally rapid after the initiation of liposomal amphotericin B in patients with visceral leishmaniasis.[74-76,79] Most patients reported improved appetite and well-being by the third day of treatment.[75] Objective signs also improved rapidly: splenomegaly decreased and elevated erythrocyte sedimentation rate (ESR) fell by days 5 to 7,[74-76] haemoglobin concentration and platelet count increased by days 5 to 14 and peripheral blood leucocyte count by days 5 to 7.[74,76] Serum albumin (<35 g/L in most patients before treatment) rose toward normal values by day 5[75] or days 10 to 14.[74] Fever receded or was absent by day 3 in most patients in whom it had been present initially.[76]

In immunocompromised adults, liposomal amphotericin B administered over 21 to 38 days produced good initial clinical and parasitological responses (table IX), albeit more slowly than in immunocompetent individuals;[74] however, the majority of patients relapsed after the end of therapy.[74,77]

5. Tolerability

Liposomal amphotericin B is well tolerated by the majority of patients. Generally, the drug was discontinued because of suspected adverse events in 0 to <5% of patients in clinical studies.[49,74,75,77,80]

The tolerability profile of liposomal amphotericin B is clearly superior to that of conventional amphotericin B. Recipients of the liposomal formulation experience fewer adverse events and fewer severe adverse events than recipients of the conventional formulation (fig. 3). In a comparative study, liposomal amphotericin B 1 and 3 mg/kg/day was discontinued or dose-reduced in 7.6 and 5.1% of patients, respectively, compared with 34.3% of patients who received conventional amphotericin B 1 mg/kg/day ($p < 0.01$).[45] Adverse events commonly associated with conventional amphotericin B, including renal tubular damage, potassium wasting, mild anaemia and infusion-related reactions such as fever, chills, rigors, nausea and vomiting,[1,81] were significantly reduced in liposomal amphotericin B recipients.[44,45] Even patients who had previously experienced adverse events with the conventional formulation have been able to tolerate the liposomal formulation.[82]

5.1 Nephrotoxicity and Hypokalaemia

Liposomal amphotericin B recipients experienced nephrotoxicity less often (fig. 3)[44,45] and later[45] than those receiving conventional amphotericin B in comparative studies. Nephrotoxicity, defined as twice the baseline serum creatinine level in paediatric patients or twice the baseline and >106 μmol/L (>1.2 mg/dl) in adults, occurred in 19% of liposomal amphotericin B recipients compared with 34% of patients who received the conventional drug in a large, double-blind, randomised study.[44]

Changes in serum creatinine levels did not appear to correlate with cumulative dose of liposomal amphotericin B during 121 episodes of use at cumulative doses relatively evenly distributed over <1 to >5g.[82] Concomitant nephrotoxic drug use also appeared to have little effect on increases or decreases in serum creatinine. Among patients who received conventional amphotericin B before receiving the liposomal formulation, 13% with normal initial serum creatinine levels had increases during liposomal amphotericin B therapy, but 41% with high initial concentrations had decreases.[82]

No clinically significant increase in serum urea or creatinine levels occurred in 116 patients who received liposomal amphotericin B for a median 12 days (median dose 1684mg, range 180 to 10 440mg).[50] In 187 patients receiving concomitant cyclosporin A, mean serum creatinine level increased 20% from baseline after the start of liposomal amphotericin B therapy, but this increase

© Adis International Limited. All rights reserved.

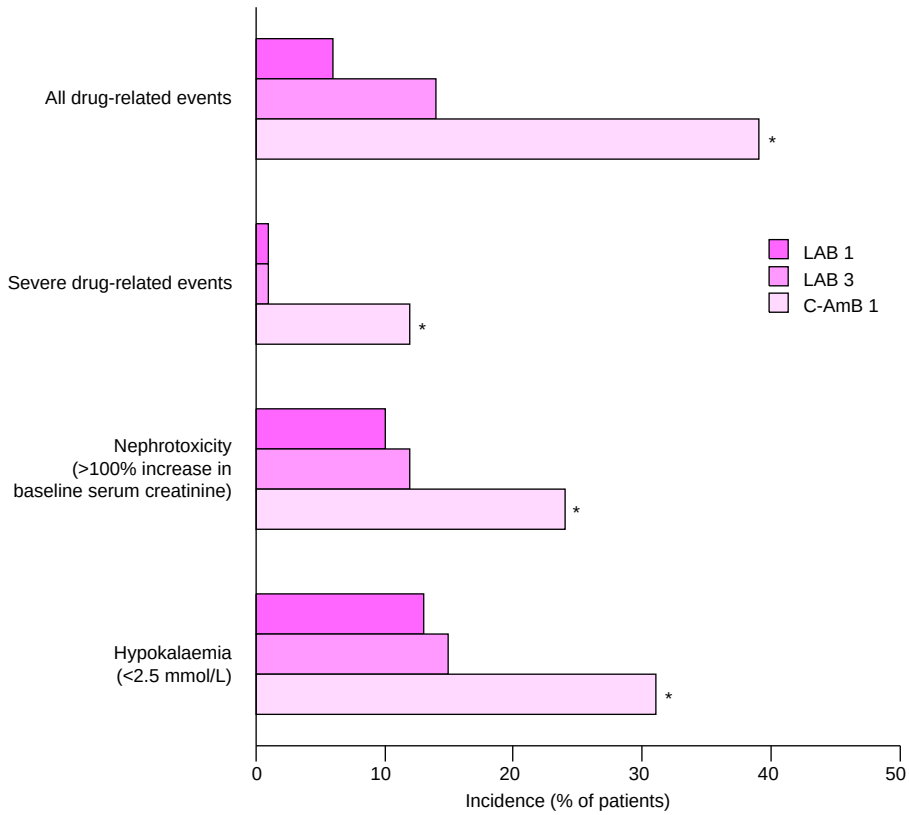

Fig. 3. Overall incidence and incidence of selected adverse events in febrile neutropenic recipients of liposomal amphotericin B 1 mg/kg/day (LAB 1), 3 mg/kg/day (LAB 3) or conventional amphotericin B 1 mg/kg/day (C-AmB 1) [n = 118, 118 and 102, respectively].[45] * $p < 0.01$ between conventional and liposomal amphotericin B.

was not statistically significant (median duration of liposomal amphotericin B treatment, 11 days).[80]

5.2 Hypersensitivity and Infusion Reactions

The incidence of infusion-related fever and rigors is significantly lower after liposomal amphotericin B than after the conventional formulation.[44,45] Compared with conventional amphotericin B recipients, patients who received liposomal amphotericin B experienced fewer episodes of infusion-related fever (44 *vs* 17%), chills or rigors (54 *vs* 18%) and cardiorespiratory events (dyspnoea, hypotension, tachycardia, hypertension and hypoxia; 46 *vs* 13%) [$p < 0.01$ for each comparison].[44] Allergic reactions occurred during 27 of 1146 and 25 of 3431 doses, respectively, of conventional and liposomal amphotericin B (2 *vs* 0.7%; $p < 0.01$).

First-dose reactions (chills and rigors) were among the most common adverse events in a randomised comparison of liposomal and conventional amphotericin B; however, the specific incidence of these reactions with either drug was not reported.[45] Anaphylaxis occurring within less than 1 minute of the first infusion of liposomal amphotericin B has been reported in several patients.[83,84] Symptoms resolved after the infusion was stopped, with or without supportive medications. Acute dyspnoea and chest tightness (not ac-

© Adis International Limited. All rights reserved.

companied by other symptoms) occurred during the first 15 minutes of the initial liposomal amphotericin B infusion in 2 patients; symptoms disappeared within minutes of stopping the infusion.[85] Mild to severe hypersensitivity reactions have also occurred in patients after 2 to 7 liposomal amphotericin B infusions.[86,87] Because in many instances these reactions occur during the first infusion in patients who had previously tolerated conventional amphotericin B, it seems likely that they represent a hypersensitivity to the liposomal formulation.

Ventricular fibrillation and fatal cardiac arrest during the seventh dose of liposomal amphotericin B (200mg over 3 hours) has also been reported in 1 patient.[88]

5.3 Other

Liposomal amphotericin B has been associated with increases in the levels of liver enzymes. Alkaline phosphatase and aspartate aminotransferase, respectively, increased and, in some instances, became elevated in 22 and 17% of liposomal amphotericin B recipients; however, these patients may have been predisposed to elevations of liver enzymes by other medications and underlying diseases.[82] No differences were noted between conventional and liposomal amphotericin recipients (n = 102 and 236) in the incidence of elevated serum bilirubin, alkaline phosphatase or serum transaminase levels.[45] Although hepatotoxicity of liposomal amphotericin B has been reported in mice and rats,[30] similar reactions in humans have not been noted.

Normocytic, normochromic anaemia, which develops in most patients during conventional amphotericin B therapy,[81] appears to occur in fewer than 10% of liposomal amphotericin B recipients.[34]

5.3.1 Increased Cyclosporin Levels

Concomitant administration of liposomal amphotericin B and cyclosporin in 187 transplant patients resulted in increased cyclosporin levels (from mean 275 μg/L before, to 328 μg/L during, liposomal amphotericin B treatment; $p < 0.001$).[80]

6. Dosage and Administration

The recommended dosage and administration schedules for liposomal amphotericin B are summarised in table X. Dose is based on bodyweight, and adult and paediatric dosage recommendations are identical. The drug is administered by slow intravenous infusion. Premedication is of questionable benefit with conventional amphoteri-

Table X. Recommended dosage and administration of liposomal amphotericin B in adult and paediatric patients

	US[34]	UK[91]
Dosage (mg/kg/day)		
Empirical antifungal treatment	3[a]	
Proven systemic fungal infections (*Aspergillus*, *Candida*, *Cryptococcus*)	3-5[a]	1-3[ab]
Visceral leishmaniasis: immunocompetent patients	3 on days 1-5, 14, 21[c]	21-30 mg/kg over 10-21 days
Visceral leishmaniasis: immunocompromised patients	3 on days 1-5 and 4 on days 10, 17, 24, 31, 38	
Administration		
Administered intravenously over 60-120min in a concentration of 1-2 mg/ml[d] (US)[34] or over 30-60min in 0.2-2.0 mg/ml (UK)[91]		
Premedication is generally not required		
The liposomal formulation is physically incompatible with saline solutions and other electrolytes		

a The optimum duration of antifungal therapy is not well defined.
b A 1 mg/kg/day initial dose is recommended, increased stepwise to 3 mg/kg/day as necessary.
c If parasites are not cleared, a repeat course of therapy may be useful.
d Concentrations of 0.2-0.5 mg/ml may be appropriate in children.

© Adis International Limited. All rights reserved.

cin B[89,90] and is not required with the liposomal drug.

In the empirical management of patients with fungal infections, clinical studies have used daily doses from 0.5 to 5 mg/kg/day (section 3). A dosage of 3 mg/kg/day was effective in comparative studies. The optimum duration of empirical liposomal amphotericin B in these patients is not known. At present, there is no recommended maximum cumulative dose of liposomal amphotericin B. In neutropenic patients, treatment is generally continued to recovery of neutrophil counts. In patients with AIDS and *Cryptococcus neoformans* infection, liposomal amphotericin B has been administered at 2 to 4 mg/kg/day (section 3.2.1).

No dosage recommendations are available for fungal prophylaxis with liposomal amphotericin B in immunocompromised patients, but a 1 mg/kg daily dose has been studied in both liver transplant and BMT recipients (section 3.1.1)

In the treatment of visceral leishmaniasis, it is recommended that a total dose of intravenous liposomal amphotericin B of 21 to 30 mg/kg be administered over 10 to 21 days (table X).[91,92] A variety of regimens have been used in clinical studies (section 4).

Although use of the drug in paediatric patients has been studied (section 3), safety and effectiveness have not been established in infants below the age of 1 month.[34] However, in neonates of very low birth weight, the drug has been used at an initial dosage of 1 mg/kg/day, increased after a week to 1.25 mg/kg/day.[93] Other investigators have used dosages of 1.5 to 5[94] or 3 to 7 mg/kg/day[95] in 2 and 14, respectively, very low birth weight infants with disseminated fungal infections.

Dosage adjustment in patients on continuous venous-venous haemofiltration or haemodiafiltration appears to be unnecessary (section 2); however, administration of liposomal amphotericin B should begin only after the completion of dialysis.[91]

7. Pharmacoeconomic Implications of Liposomal Amphotericin B

The acquisition cost of liposomal amphotericin B is substantially higher than that of the conventional formulation (£145 *vs* £3.70 for 50mg; 1997 UK prices).[96]

Using clinical data from 9 published studies in immunocompromised patients with proven fungal infections, Tollemar and Ringdén[97] calculated the mean acquisition cost of liposomal amphotericin B per course. Mean cost per patient per course in these studies ranged from $US3248 to $US20 416 (median $US12 992) [1995 UK costs]. However, as discussed previously (section 3), fungal infection is difficult to diagnose and only a small proportion of patients who receive empirical antifungal therapy have proven fungal infections. Therefore, acquisition cost of the drug per patient with proven fungal infection may be a less useful measure than acquisition cost per patient with suspected fungal infection (i.e. acquisition cost of the drug per course of empirical use).

Two cost-effectiveness analyses (both from the hospital perspective) compared the use of liposomal and conventional amphotericin B in immunocompromised patients.[98,99] In a Swedish retrospective comparison of liposomal and conventional amphotericin B in the treatment of proven systemic mycoses in bone marrow, liver or kidney and/or pancreas transplant recipients, savings produced by liposomal amphotericin B (including increased life expectancy and reduced toxicity) were not enough to offset the acquisition cost of the drug.[98] It was concluded that use of liposomal amphotericin B was associated with an extra cost of about SEK150 000 per life-year gained in recipients of bone marrow or kidney and/or pancreas transplants (1991 currency; $US1 = SEK6). In patients who received liver transplants, the extra cost was estimated at SEK195 000. These amounts were comparable to accepted costs per year of life saved with other medical and nonmedical interventions.[98] Efficacy rates used in calculations in this study were based on mean survival rates in Sweden, discounted at 5% for each additional year of

© Adis International Limited. All rights reserved.

life gained. Costs considered included standard cost per treatment day plus cost of antifungal therapy and other expensive drugs estimated separately. It must be noted that patients in the conventional amphotericin B group in this study were historical controls, having been treated mostly in 1987 to 1989. Patients who received the liposomal formulation were generally treated during 1989 to 1991. However, the authors state that the improved survival is likely to be a result of the change in antifungal treatment, as no major improvements in patient or graft survival were obtained during the study period.

A Dutch model of cost effectiveness, published in abstract form,[99] showed that initial therapy with liposomal amphotericin B in neutropenic adults with presumed fungal infections may cost more per complete cure than initial therapy with the conventional formulation. Three regimens were compared, each consisting of initial antifungal therapy followed, if unsuccessful, by a second-line regimen. Conventional amphotericin B followed by liposomal amphotericin B 1 mg/kg/day cost $13 674 per cure after 15 days. Initial therapy with liposomal amphotericin B 1 mg/kg/day (increased if necessary to 3 mg/kg/day) cost $15 509 per cure; initial liposomal amphotericin B 3 mg/kg/day (increased if necessary to 5 mg/kg/day) cost $20 024.[99] These cost differences are primarily a result of the higher acquisition cost of the liposomal formulation. Although unstated, the currency reported in this study was presumably $US; the year of costs was not reported. These estimates assume efficacy for the 3 initial regimens of 46, 49 and 64%, respectively, and efficacy of 58% for all second-line regimens.

In contrast with the finding in adults, the same model applied to paediatric patients suggested that the regimen of liposomal amphotericin B 1 mg/kg/day (increased as necessary to 3 mg/kg/day) was most cost effective.[99] In this analysis, first-line efficacy estimates for the 3 regimens were 51, 46 and 63%, respectively; the same second-line efficacy estimate (58%) was used for all regimens.[99] In both adults and children, however, an initial dose of liposomal amphotericin B 1 mg/kg/day is lower than that recommended in the US (table X).

The cost of liposomal amphotericin B prophylaxis (2 mg/kg 3 times per week) against oropharyngeal fungal colonisation or infection in BMT recipients was higher than the cost of either oral fluconazole or oral polyenes over the 12-week post-transplant period (£53 225, £28 956 and £32 768, respectively).[100] This cost-minimisation model was conducted from the perspective of the UK National Health Service (1995). It was based on retrospective efficacy data from noncomparative studies, and the time of onset of colonisation was assumed to be evenly distributed across the 12-week period. Costs included were those related to hospitalisation and treatment, including medication administration costs and the cost of acute antifungal treatment (conventional and liposomal amphotericin B in 75 and 25% of patients, respectively) in patients for whom prophylaxis was unsuccessful. Sensitivity analysis showed that liposomal amphotericin B remained a more expensive prophylactic regimen, even when efficacy of liposomal amphotericin B was varied between 0 and 100% and when the acquisition cost of the drug was assumed to be zero. This result, although counterintuitive, reflects the assumption made in this model that failure during liposomal amphotericin B therapy resulted in a change to a medication with a lower acquisition cost.

No studies have examined the pharmacoeconomic implications of liposomal amphotericin B use in patients with visceral leishmaniasis.

8. Place of Liposomal Amphotericin B in the Management of Fungal Infections and Visceral Leishmaniasis

Incorporation of amphotericin B into unilamellar liposomes significantly ameliorates the toxicity of the parent drug, permitting the administration of well tolerated and effective dosage regimens. Liposomal amphotericin B is active *in vitro* and *in vivo* against *Leishmania* parasites and a variety of fungal organisms.

© Adis International Limited. All rights reserved.

Table XI. Factors contributing to an increased prevalence of fungal infections[102]

Increased numbers, and overall survival, of patients with AIDS
More aggressive cancer chemotherapy, including increased bone marrow transplantation
Increased numbers of solid organ transplants
Greater numbers of other immunocompromised patients
More aggressive intensive care medicine
Increased usage of broad spectrum antibiotics
Increased exposure of persons to foci of endemic mycoses as a result of international travel
Increased use of parenteral nutrition and lipid suspensions

Fungal Infections. Worldwide, the prevalence of fungal infection, especially by opportunistic organisms [principally *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans* and *Rhizopus arrhizus (oryzae)*], is increasing.[1,101-103] The rate of infection by the true pathogenic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*,[101] is also increasing. In the US, the rate of fungal infections nearly doubled between 1980 and 1990 (from 2 to 3.8 infections per 1000 hospital discharges).[103] Some reasons for this increase are summarised in table XI.

Morbidity and mortality secondary to invasive fungal infections in immunocompromised patients are high. Haematogenous *Candida* infection causes death in 38 to 76% of infected patients.[104,105] Survival of patients with invasive *Aspergillus* infection ranges from 0 to 35%.[106] *Cryptococcus* infection is rarely cured in patients with AIDS;[107] cryptococcal meningitis has been associated with 7 to 29% mortality,[108] and long term maintenance therapy is routine in patients who respond to initial therapy.[107]

Management of invasive fungal infections is complicated by difficulties in obtaining precise and timely diagnoses (section 3). In neutropenic patients with persistent fever (≥72 hours), not responding to antibacterial therapy, antifungal therapy should be initiated without delay.[1,101]

For suspected or proven invasive fungal infections in neutropenic patients, conventional amphotericin B remains – 30 years after its introduction – the treatment of choice for many invasive clinical infections,[1,3,109] but its use is limited by its poor tolerability profile. Fluconazole and other azoles may have a role in the management of several infections, particularly in maintenance therapy.[110,111]

Empirical use of liposomal amphotericin B produced clinical improvement in a majority of patients with suspected or proven infections in noncomparative studies and has been shown, in randomised comparative studies, to be as effective as conventional amphotericin B.

Against proven fungal infections, liposomal amphotericin B produced clinical cure or improvement in 20 to 80% of patients in most studies. Mycological eradication rates of 41 and 60% against invasive *Aspergillus* infections and 40 and 83% against invasive *Candida* in immunocompromised patients have been reported in relatively large studies. Mycological cure in 67 to 85% of *Cryptococcus* infections in patients with AIDS appears extremely promising, and limited comparative data suggest that the drug may be more effective than conventional amphotericin B in these patients. Despite the noncomparative nature of most of these data, and the small sample sizes in most studies, liposomal amphotericin B may be considered a good choice for systemic antifungal therapy in patients with proven fungal infections who are unable to tolerate, or do not respond to, therapy with conventional amphotericin B. Whether liposomal amphotericin B has advantages over other available lipid-based amphotericin B formulations is, as yet, unknown.

Prophylaxis with systemic antifungal drugs in immuocompromised patients may reduce or delay the development of fungal infections; however, it may also encourage the emergence of drug-resistant strains.[101] Moreover, a recent meta-analysis[112] was unable to demonstrate any convincing benefit for prophylactic or empirical antifungal therapy in patients with cancer complicated by neutropenia.

Prophylactic therapy with liposomal amphotericin B in immunocompromised patients appears to reduce the incidence of proven fungal infections

© Adis International Limited. All rights reserved.

and fungal colonisation compared with placebo; however, no survival benefit has been demonstrated. Therefore, routine antifungal prophylaxis with the drug cannot be recommended.

The acquisition cost of liposomal amphotericin B is considerably higher than that of the conventional formulation (section 7). Cost-effectiveness analyses of empirical liposomal amphotericin B therapy in immunocompromised patients with suspected fungal infections suggest that savings associated with reduced toxicity and increased efficacy of the liposomal formulation did not offset its increased costs. However, 1 model suggested that initial use of the liposomal formulation in children may cost less per complete cure than use of the conventional formulation. Interestingly, despite the improved tolerability profile of liposomal amphotericin B compared with conventional amphotericin B (section 5), no quality-of-life analyses have yet been conducted.

Visceral Leishmaniasis. Infections caused by *Leishmania* spp. are prevalent in regions where sandfly vectors and mammalian reservoirs are present in adequate numbers to facilitate transmission of the parasite.[4,113] *L. infantum* infection occurs sporadically in the Mediterranean region, particularly in children and immunocompromised patients. Visceral leishmaniasis caused by *L. donovani* is epidemic in Sudan and India and endemic in parts of China.[4,113,114] Elsewhere, other species are also implicated, including *L. major* and *L. chagasi*. Large outbreaks in South America have been attributed to the latter organism. Worldwide, at least 100 000 cases of visceral leishmaniasis were estimated to exist in 1992,[115] and the global incidence is increasing.[4,114]

Symptomatic visceral leishmaniasis (*kala azar*) is commonly fatal if untreated; even with treatment, 1 to 11% of patients may die.[4] Pentavalent antimonial compounds, including meglumine antimoniate and sodium stibogluconate, have long been the standard treatment for visceral leishmaniasis.[4,114] These drugs, however, require long treatment courses (3 to 5 weeks) to be effective, and are increasingly associated with microbial resistance and treatment failure.[113] Cure rates range from 57 to 100%, with relapse occurring in up to 22% of patients within 6 months. Treatment-induced toxicities, including chemical pancreatitis, myalgias, arthralgias, abdominal symptoms and headache, are common, but not usually treatment limiting.[4,113] Conventional amphotericin B has been studied in patients with visceral leishmaniasis, but its use has been limited by the high incidence of toxicities.[4]

Although no comparative data with either conventional amphotericin B or the pentavalent antimonials are available, complete response rates associated with liposomal amphotericin B appear promising (section 4). In several studies, cure rates in immunocompetent patients approached 100%. Complete response rates were lower in immunocompromised patients and in those with severe visceral leishmaniasis or pentavalent antimonial-resistant disease. Relapse up to 1 year is rare in immunocompetent patients, but common in patients with AIDS. Furthermore, the drug appears to have significant clinical activity in patients with visceral leishmaniasis that is resistant to pentavalent antimonial agents. Therefore, liposomal amphotericin B represents a suitable choice for first- or second-line therapy of visceral leishmaniasis.

Pharmacoeconomic analyses of liposomal amphotericin B use in patients with visceral leishmaniasis have not been conducted. Given the high rates of poverty in some of the countries where the disease is endemic,[78] the high acquisition cost of the drug may limit its use.

Tolerability. In patients with suspected or proven fungal infections or visceral leishmaniasis, liposomal amphotericin B is generally very well tolerated. Discontinuation because of adverse events is generally necessary in fewer than 5% of patients. Compared with the conventional drug, the liposomal formulation is very well tolerated. Nephrotoxicity, in particular, occurs far less often after liposomal amphotericin B than after the conventional drug. Hypokalaemia, anaemia and infusion reactions are also less common after liposomal amphotericin B.

© Adis International Limited. All rights reserved.

Conclusion. Liposomal amphotericin B appears to be an effective alternative to conventional amphotericin B in the management of fungal infections, particularly invasive *Candida* and *Aspergillus* infections, in immunocompromised patients. Liposomal amphotericin B is also clearly effective against *C. neoformans* infections in patients with AIDS. The chief advantage of the liposomal drug is its greatly improved tolerability profile compared with conventional amphotericin B. Liposomal amphotericin B is more costly than the conventional formulation and pharmacoeconomic considerations will undoubtedly affect how it is used in clinical practice. Nevertheless, cost implications aside, liposomal amphotericin should be preferred to conventional amphotericin B in the management of suspected or proven fungal infections in immunocompromised patients with pre-existing renal dysfunction, amphotericin B–induced toxicity or failure to respond to conventional amphotericin B. Liposomal amphotericin B may also be considered a reasonable first- or second-line regimen in the management of visceral leishmaniasis in immunocompetent patients.

References

1. Richardson MD, Warnock DW. Fungal Infection: diagnosis and management. Oxford: Blackwell Scientific Publications, 1993
2. Viviani MA, Rizzardini G, Tortorano AM, et al. Lipid-based amphotericin B in the treatment of cryptococcosis. Infection 1994 Mar-Apr; 22: 137-42
3. de Marie S, Janknegt R, Bakker-Woudenberg IAJM. Clinical use of liposomal and lipid-complexed amphotericin B. J Antimicrob Chemother 1994 May; 33: 907-16
4. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis 1997; 24: 684-703
5. Proffitt RT, Adler-Moore J, Fujii G, et al. Stability and mode of action of Ambisome® (liposomal amphotericin B). J Control Release 1994 Jan; 28: 342-3
6. Pallister CJ, Johnson EM, Warnock DW, et al. In-vitro effects of liposome-encapsulated amphotericin B (AmBisome) and amphotericin B-deoxycholate (Fungizone) on the phagocytic and candidacidal function of human polymorphonuclear leucocytes. J Antimicrob Chemother 1992 Sep; 30: 313-20
7. Schindler JJ, Warren RP, Allen SD, et al. Immunological effects of amphotericin B and liposomal amphotericin B on splenocytes from immune-normal and immune-compromised mice. Antimicrob Agents Chemother 1993 Dec; 37: 2716-21
8. Working Party of the British Society for Antimicrobial Chemotherapy. Working Party report: antifungal drug susceptibility testing. J Antimicrob Chemother 1995; 36: 899-909
9. Cormican MG, Pfaller MA. Standardization of antifungal susceptibility testing. J Antimicrob Chemother 1996; 38: 561-78
10. Anaissie E, Paetznick V, Proffitt R, et al. Comparison of the in vitro antifungal activity of free and liposome-encapsulated amphotericin B. Eur J Clin Microbiol Infect Dis 1991 Aug; 10: 665-8
11. Karyotakis NC, Anaissie EJ. Efficacy of escalating doses of liposomal amphotericin B (AmBisome) against hematogenous *Candida lusitaniae* and *Candida krusei* infection in neutropenic mice. Antimicrob Agents Chemother 1994 Nov; 38: 2660-2
12. Karyotakis NC, Anaissie EJ, Hachem R, et al. Comparison of the efficacy of polyenes and triazoles against hematogenous *Candida krusei* infection in neutropenic mice. J Infect Dis 1993 Nov; 168: 1311-3
13. van Etten EW, van den Heuvel-de-Groot C, Bakker-Woudenberg IA. Efficacies of amphotericin B-desoxycholate (Fungizone), liposomal amphotericin B (AmBisome) and fluconazole in the treatment of systemic candidosis in immunocompetent and leucopenic mice. J Antimicrob Chemother 1993 Nov; 32: 723-39
14. Kretschmar M, Nichterlein T, Hof H. Ambisome is superior to amphotericin B in lipid suspensions for treatment of murine candidiasis [abstract]. 7th Eur Congr Clin Microbiol Infect Dis 1995: 155
15. Adler-Moore JP, Chiang S-M, Satorius A, et al. Treatment of murine candidosis and cryptococcosis with a unilamellar liposomal amphotericin B formulation (AmBisome). J Antimicrob Chemother 1991 Oct; 28 Suppl. B: 63-71
16. Francis P, Lee JW, Hoffman A, et al. Efficacy of unilamellar liposomal amphotericin B in treatment of pulmonary aspergillosis in persistently granulocytopenic rabbits: the potential role of bronchoalveolar D-mannitol and serum galactomannan as markers of infection. J Infect Dis 1994 Feb; 169: 356-68
17. Leenders ACAP, de Marie S, ten Kate MT, et al. Liposomal amphotericin B (AmBisome) reduces dissemination of infection as compared with amphotericin B deoxycholate (Fungizone) in a rat model of pulmonary aspergillosis. J Antimicrob Chemother 1996 Aug; 38: 215-25
18. Vassiloyanakopoulos A, Boutsikakis J, Mylonakis EE, et al. Comparative therapeutic efficacy of two amphotericin B liposomal forms in aspergillus fumigatus (AF) experimental endocarditis [abstract]. Clin Infect Dis 1995 Sep; 21: 779
19. Albert MM, Stahl-Carroll TL, Luther MF, et al. Comparison of liposomal amphotericin B to amphotericin B for treatment of murine cryptococcal meningitis. J Mycol Med 1995; 5 (1): 1-6
20. Clemons KV, Stevens DA. Comparison of a liposomal amphotericin B formulation (AmBisome) and deoxycholate amphotericin B (Fungizone) for the treatment of murine paracoccidioidomycosis. J Med Vet Mycol 1993; 31 (5): 387-94
21. Clemons KV, Stevens DA. Therapeutic efficacy of a liposomal formulation of amphotericin B (AmBisome) against murine blastomycosis. J Antimicrob Chemother 1993 Sep; 32: 465-72
22. Albert MM, Adams K, Luther MJ, et al. Efficacy of AmBisome in murine coccidioidomycosis. J Med Vet Mycol 1994 Dec; 32: 467-71
23. Anaissie EJ, Hachem R, Karyotakis NC, et al. Comparative efficacies of amphotericin B, triazoles, and combination of both as experimental therapy for murine trichosporonosis. Antimicrob Agents Chemother 1994 Nov; 38: 2541-4

© Adis International Limited. All rights reserved.

24. Graybill JR, Bocanegra R. Liposomal amphotericin B therapy of murine histoplasmosis. Antimicrob Agents Chemother 1995 Aug; 39: 1885-7
25. Gilbert BE. Liposomal aerosols in the management of pulmonary infections. J Aerosol Med 1996; 9 (1): 111-22
26. Yardley V, Croft SL. Activity of liposomal amphotericin B against experimental cutaneous leishmaniasis. Antimicrob Agents Chemother 1997; 41 (4): 752-6
27. Gangneux J-P, Sulahian A, Garin YJ-F, et al. Lipid formulations of amphotericin B in the treatment of experimental visceral leishmaniasis due to Leishmania infantum. Trans R Soc Trop Med Hyg 1996 Sep-Oct; 90: 574-7
28. Gradoni L, Davidson RN, Orsini S, et al. Activity of liposomal amphotericin B (AmBisome) against *Leishmania infantum* and tissue distribution in mice. J Drug Target 1993; 1 (4): 311-6
29. Oliva G, Gradoni L, Ciaramella P, et al. Activity of liposomal amphotericin B (AmBisome) in dogs naturally infected with *Leishmania infantum*. J Antimicrob Chemother 1995 Dec; 36: 1013-9
30. Proffitt RT, Satorius A, Chiang S-M, et al. Pharmacology and toxicology of a liposomal formulation of amphotericin B (AmBisome) in rodents. J Antimicrob Chemother 1991 Oct; 28 Suppl. B: 49-61
31. Janknegt R, de Marie S, Bakker-Woudenberg IAJM, et al. Liposomal and lipid formulations of amphotericin B: clinical pharmacokinetics. Clin Pharmacokinet 1992 Oct; 23: 279-91
32. Heinemann V, Kähny B, Debus A, et al. Pharmacokinetics of liposomal amphotericin B (AmBisome) versus other lipid-based formulations. Bone Marrow Transplant 1994; 14 Suppl. 5: S8-9
33. Walsh TJ, Bekersky I, Yeldandi V, et al. Pharmacokinetics of AmBisome in persistently febrile neutropenic patients receiving empirical antifungal therapy [abstract no. A13]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC): 1995 Sep 17-20; 3
34. NeXstar Pharmaceuticals Inc. AmBisome(R) (amphotericin B) lipossome for injection: prescribing information. Deerfield, IL, USA, Aug 1997
35. Ringdén O, Meunier F, Tollemar J, et al. Efficacy of amphotericin B encapsulated in liposomes (Ambisome) in the treatment of invasive fungal infections in immunocompromised patients. J Antimicrob Chemother 1991 Oct; 28 Suppl. B: 73-82
36. Tollemar J, Ringden O, Tyden G. Liposomal amphotericin-B (Ambisome) treatment in solid organ and bone marrow transplant recipients. Efficacy and safety evaluation. Clin Transpl 1990 Jun; 4: 167-75
37. Lee JW, Amantea MA, Francis PA, et al. Pharmacokinetics and safety of a unilamellar liposomal formulation of amphotericin B (AmBisome®) in rabbits [abstract]. Antimicrob Agents Chemother 1994 Apr; 38: 713-8
38. Gonzalez C, Sein T, Bacher J, et al. Penetration of lipid formulations of amphotericin B into cerbrospinal fluid and brain tissue [abstract no. A-90]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC): 1997 Sep 28-Oct 1; Toronto, 19
39. Tomlin M, Priestley GS. Elimination of liposomal amphotericin by hemodiafiltration [letter]. Intensive Care Med 1995 Aug; 21: 699-700
40. Humphreys H, Oliver DA, Winter R, et al. Lipososmal amphotericin B and continuous venous-venous haemofiltration [letter]. J Antimicrob Chemother 1994 May; 33: 1070-1
41. Meunier F. Targeting fungi: a challenge. Am J Med 1995 Dec 29; 99 Suppl. 6A: 60S-7S
42. Tollemar J, Ringdén O, Andersson S, et al. Randomized double-blind study of liposomal amphotericin B (Ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. Bone Marrow Transplant 1993 Dec; 12: 577-82
43. Tollemar J, Höckerstedt K, Ericzon B-G, et al. Prophylaxis with liposomal amphotericin B (AmBisome) prevents fungal infections in liver transplant recipients: long term results of a randomized, placebo-controlled trial. Transplant Proc 1995 Feb; 27: 1195-8
44. Walsh T, Bodensteiner D, Hiemenz J, et al. A randomized, double-blind trial of AmBisome (liposomal amphotericin B) versus amphotericin B in the empirical treatment of persistently febrile neutropenic patients [abstract no. LM-90]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC): 1997 Sep 28-Oct 1; Toronto, 381
45. Prentice HG, Hahn IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. Br J Haematol 1997; 98: 711-8
46. Berenguer J, Muñoz P, Parras F, et al. Treatment of deep mycoses with liposomal amphotericin B. Eur J Clin Microbiol Infect Dis 1994 Jun; 13: 504-7
47. Böhme A, Hoelzer D. Liposomal amphotericin B as early empiric antimycotic therapy of pneumonia in granulocytopenic patients. Mycoses 1996; 39: 419-26
48. Heinemann V, Pyka S, Bosse D, et al. Liposomal amphotericin B (AmBisome): clinical safety and efficacy [abstract]. Onkologie 1995 Oct; 18 Suppl. 2: 198
49. Krüger W, Stockschläder M, Rüssmann B, et al. Experience with liposomal amphotericin-B in 60 patients undergoing high-dose therapy and bone marrow or peripheral blood stem cell transplantation. Br J Haematol 1995 Nov; 91: 684-90
50. Mills W, Chopra R, Linch DC, et al. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: a single-centre experience of 133 episodes in 116 patients. Br J Haematol 1994 Apr; 86: 754-60
51. Nowoczyn V, Ritter J, Boos J, et al. Liposomal amphotericin B (ambisome) in neutropenic children with hematological malignancies and systemic fungal infections [abstract]. Med Pediatr Oncol 1992; 20 (5): 376
52. Ringdén O, Tollemar J, Dahllöf G, et al. High cure rate of invasive fungal infections in immunocompromised children using ambisome. Transplant Proc 1994 Feb; 26: 175-7
53. Leenders ACAP, Daenen S, Jansen RLH, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B in the treatment of neutropenia-associated invasive fungal infections [abstract]. Trends in Invasive Fungal Infections 4: 1997 Nov 5; Barcelona
54. Tollemar J, Ringdén O, AmBisome(Rm) Users Group. Early pharmacokinetic and clinical results from a noncomparative multicentre trial of amphotericin B encapsulated in a small unilamellar liposome (Ambisome(Rm)). Drug Invest 1992; 4 (3): 232-8
55. Ellis M, Spence D, Meunier F, et al. Randomised multicentre trial of 1 mg/kg (LD) versus 4 mg/kg (HD) liposomal amphotericin B (AmBisome) (LAB) in the treatment of invasive aspergillosis (IA): EORTC protocol 19923 [abstract no. LM39]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), American Society for Microbiology: 1996 Sep 15-19; New Orleans

© Adis International Limited. All rights reserved.

56. Devecioglu Ö, Özgen Ü, Agaoglu L, et al. Clinical experience with amphotericin B (conventional & liposomal) in febrile neutropenic children [abstract]. Can J Infect Dis 1995 Jul; 6 Suppl. C: 365C
57. Dornbusch HJ, Urban CE, Pinter H, et al. Treatment of invasive pulmonary aspergillosis in severely neutropenic children with malignant disorders using liposomal amphotericin B (AmBisome), granulocyte colony-stimulating factor, and surgery: report of five cases. Pediatr Hematol Oncol 1995 Nov-Dec; 12: 577-86
58. Pasic S, Flannagan L, Cant AJ. Liposomal amphotericin (AmBisome) is safe in bone marrow transplantation for primary immunodeficiency. Bone Marrow Transplant 1997; 19: 1229-32
59. Evdoridou J, Roilides E, Bibashi E, et al. Multifocal osteoarthritis due to *Candida albicans* in a neonate: serum level monitoring of liposomal amphotericin B and literature review. Infection 1997; 25 (2): 44-8
60. Lazar JT, Ksionski GE. Efficacy of safety of AmBisome (liposomal amphotericin B) in primary episodes of cryptococcosis in patients with HIV infection [abstract no. W.B.2177]. 7th International Conference on AIDS: 1991 Jun 16-21; N
61. Mota-Miranda A, Gomes H, Marques R, et al. Liposomal amphotericin B in the treatment of opportunistic fungal infections. Rev Esp Quimioter 1994 Jun; 7: 146-9
62. Coker RJ, Viviani M, Gazzard BG, et al. Treatment of cryptococcosis with liposomal amphotericin B (AmBisome) in 23 patients with AIDS. AIDS 1993 Jun; 7: 829-35
63. Codeluppi M, Mussini C, Borghi V, et al. Liposomal amphotericin B in therapy in patients with AIDS [abstract no. P34]. Glasgow AIDS Meeting 1992 Nov
64. Leenders ACAP, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meniingitis. AIDS 1997; 11: 1463-71
65. Leggiadro RJ, Kline MW, Hughes WT. Extrapulmonary cryptococcosis in children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1991; 10: 658-62
66. Manfredi R, Coronado OV, Mastroianni A, et al. Liposomal amphotericin B and recombinant human granulocyte-macrophage colony stimulating factor (rHuGM-CSF) in the treatment of paediatric AIDS-related cryptococcosis. Int J STD AIDS 1997; 8: 406-8
67. Fisher NC, Mutimer DJ. Targeted and empirical liposomal amphotericin B therapy in liver transplantation: a 2-year review [abstract no. 1537]. Hepatology 1996; 24 (4, Pt. 2) Program Suppl.: 511A
68. Ng TTC, Denning DW. Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections: evaluation of United Kingdom compassionate use data. Arch Intern Med 1995 May 22; 155: 1093-8
69. Munckhof W, Jones R, Tosolini FA, et al. Cure of Rhizopus sinusitis in a liver transplant recipient with liposomal amphotericin B [letter]. Clin Infect Dis 1993 Jan; 16: 183
70. Cofrancesco E, Boschetti C, Viviani MA, et al. Efficacy of liposomal amphotericin-B (AmBisome) in the eradication of *Fusarium* infection in a leukaemic patient. Haematologica 1992 May-Jun; 77: 280-3
71. Ellis ME, Clink H, Younge D, et al. Successful combined surgical and medical treatment of fusarium infection after bone marrow transplantation. Scand J Infect Dis 1994; 26: 225-8
72. Harten P, Baron Y, Euler HH. Liposomal amphotericin B therapy in disseminated histoplasmosis [letter]. Arch Intern Med 1995 Jul 24; 155: 1556
73. Berlanga JJ, Querol S, Gallardo D, et al. Successful treatment of *Curvularia* sp infection in a patient with primarily resistant acute promyelocytic leukemia. Bone Marrow Transplant 1995 Oct; 16: 617-9
74. Davidson RN, di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. Q J Med 1994 Feb; 87: 75-81
75. Davidson RN, di Martino L, Gradoni L, et al. Short-course treatment of visceral leishmaniasis with liposomal amphotericin B (AmBisome). Clin Infect Dis 1996 Jun; 22: 938-43
76. di Martino L, Davidson RN, Giacchino R, et al. Treatment of visceral leishmaniasis in children with liposomal amphotericin B. J Pediatr 1997; 131: 271-7
77. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). J Infect 1996 Mar; 32: 133-7
78. Seaman J, Boer C, Wilkinson R, et al. Liposomal amphotericin B (AmBisome) in the treatment of complicated kala-azar under field conditions. Clin Infect Dis 1995 Jul; 21: 188-93
79. Thakur CP, Pandey AK, Sinha GP, et al. Comparison of three treatment regimens with liposomal amphotericin B (AmBisome Rm) for visceral leishmaniasis in India: a randomized dose-finding study. Trans R Soc Trop Med Hyg 1996 May-Jun; 90: 319-22
80. Ringdén O, Andström 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: S10-14
81. Perfect JR, Lindsay MH, Drew RH. Adverse drug reactions to systemic antifungals: prevention and management. Drug Saf 1992 Sep-Oct; 7: 323-63
82. Meunier F, Prentice HG, Ringdén O. Liposomal amphotericin B (AmBisome): safety data from a phase II/III clinical trial. J Antimicrob Chemother 1991 Oct; 28 Suppl. B: 83-91
83. Bates CM, Carey PB, Hind CRK. Anaphylaxis due to liposomal amphotericin (AmBisome) [letter]. Genitourin Med 1995 Dec; 71: 414
84. Laing RBS, Milne LJR, Leen LJR, et al. Anaphylactic reactions to liposomal amphotericin [letter]. Lancet 1994 Sep 3; 344: 682
85. 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 Jan; 14: 41-3
86. Ringdén O, Andström E, Remberger M, et al. Allergic reactions and other rare side-effects of liposomal amphotericin [letter]. Lancet 1994 Oct 22; 344: 1156-7
87. Torre I, López-Herce J, Vázquez P. Anaphylactic reaction to liposomal amphotericin B in children. Ann Pharmacother 1996 Sep; 30: 1036-7
88. Aguado JM, Hidalgo M, Moya I, et al. Ventricular arrhythmias with conventional and liposomal amphotericin [letter]. Lancet 1993 Nov 13; 342: 1239
89. Goodwin SD, Cleary JD, Walawander CA, et al. Pretreatment regimens for adverse events related to infusion of amphotericin B. Clin Infect Dis 1995 Apr; 20: 755-61
90. Hoeprich PD. Clinical use of amphotericin B and derivatives: lore, mystique, and fact. Clin Infect Dis 1992 Mar; 14 Suppl. 1: S114-9
91. NeXstar Pharmaceuticals Limited. AmBisome: summary of product characteristics. Cambridge, England. 1996 Feb 07
92. NeXstar Pharmaceuticals Inc. Ambisome(R) (liposomal amphotericin B.P.): product monograph. Boulder, Colorado, USA, 1995

© Adis International Limited. All rights reserved.

93. Pereira da Silva L, Videira Amaral JM, Cordeiro Ferreira N. Which is the most appropriate dosage of liposomal Amphotericin-B (AmBisome) for the treatment of fungal infections in infants of very low birth weight? [letter; comment]. Pediatrics 1993 Jun; 91: 1217-8
94. Lackner H, Schwinger W, Urban C, et al. Liposomal amphotericin-B (AmBisome) for treatment of disseminated fungal infections in two infants of very low birth weight. Pediatrics 1992 Jun; 89 (Pt 2): 1259-61
95. Leibovitz E, Juster A, Amitay A, et al. Liposomal amphotericin B (AmBisome) in the treatment of disseminated fungal infections in very low birth weight (VLBW) infants [abstract no. 4112]. 20th International Congress of Chemotherapy: 1997 Jun 29-Jul 3; Sydney, 128
96. Drugs used in the treatment of infection. British National Formulary. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1997 Sep: 230-292
97. Tollemar J, Ringdén O. Lipid formulations of amphotericin B: less toxicity but at what economic cost? Drug Saf 1995 Oct; 13: 207-18
98. Persson U, Tennvall GR, Andersson S, et al. Cost-effectiveness analysis of treatment with liposomal amphotericin B versus conventional amphotericin B in organ or bone marrow transplant recipients with systemic mycoses. Pharmacoeconomics 1992 Dec; 2: 500-8
99. Boogaerts M, Tormans G, Maes E, et al. Cost-effectiveness analysis of Ambisome (AMB) vs amphotericin B (AMPHOB) in the empiric treatment of febrile neutropenia in adults and children [abstract no. 55-IV]. Blood 1996 Nov 15; 88 Suppl. 1: 501a
100. Stewart A, Powles R, Hewetson M, et al. Costs of antifungal prophylaxis after bone marrow transplantation: a model comparing oral fluconazole, liposomal amphotericin and oral polyenes as prophylaxis against oropharyngeal infections. Pharmacoeconomics 1995 Oct; 8: 350-61
101. Richardson MD. Systemic fungal infections [68572]. Care Critically Ill 1994; 10: 258-61
102. Denning DW. Epidemiology and pathogenesis of systemic fungal infections in the immunocompromised host. J Antimicrob Chemother 1991; 28 Suppl. B: 1-16
103. Herbrecht R. The changing epidemiology of fungal infections: are the lipid-based forms of amphotericin B an advance? Eur J Haematol 1996; 56 Suppl. 57: 12-7
104. Uzun O, Anaissie EJ. Problems and controversies in the management of hematogenous candidiasis. Clin Infect Dis 1996; 22 Suppl. 2: S95-S101
105. Swerdloff JN, Filler SG, Edwards Jr. JE. Severe candidal infections in neutropenic patients. Clin Infect Dis 1993; 17 Suppl. 2: S456-67
106. Beyer J, Schwartz S, Heinemann V, et al. Strategies in prevention of invasive pulmonary aspergillosis in immunosuppressed or neutropenic patients. Antimicrob Agents Chemother 1994 May; 38: 911-7
107. Mahgoub ES. Agents of mycetoma. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious disease. 4th ed. ed. Vol. 2. New York: Churchill Livingstone, 1995: 2327-40
108. Powderly WG. Recent advances in the management of cryptococcal meningitis in patients with AIDS. Clin Infect Dis 1996; 22 Suppl. 2: S119-23
109. Abu-Salah KM. Amphotericin B: an update. Br J Biomed Sci 1996 Jun; 53: 122-33
110. British Society for Antimicrobial Chemotherapy Working Party. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. Lancet 1992; 340: 648-51
111. Gallis HA. Amphotericin B: a commentary on its role as an antifungal agent and as a comparative agent in clinical trials. Clin Infect Dis 1996 May; 22 Suppl. 2: S145-7
112. Gøtzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. BMJ 1997; 314: 1238-44
113. Pearson RD, de Queiroz Sousa A. Leishmania species: visceral (kala-azar), cutaneous, and mucosal leishmaniasis. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious disease. 4th ed. ed. Vol. 2. New York: Churchill Livingstone, 1995: 2428-42
114. Gradoni L, Bryceson A, Desjeux P. Treatment of Mediterranean visceral leishmaniasis. Bull World Health Organ 1995; 73 (2): 191-7
115. Ashford RW, Desjeux P, deRaadt P. Estimation of population at risk of infection and number of cases of leishmaniasis. Parasitol Today 1992; 8 (3): 104-5

Correspondence: *Allan Coukell*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz

© Adis International Limited. All rights reserved.