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Liposomal Amphotericin B

A Review of its Use as Empirical Therapy in Febrile Neutropenia and in the Treatment of Invasive Fungal Infections

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Data Selection

Sources: Medical literature published in any language since 1980 on 'amphotericin B liposomal', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'amphotericin B liposomal' or 'liposomal amphotericin B'. Searches were last updated 23 February 2009.

Selection: Studies in patients with febrile neutropenia or invasive fungal infections who received liposomal amphotericin B. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Liposomal amphotericin B, febrile neutropenia, invasive fungal infections, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Liposomal amphotericin B (AmBisome®) is a lipid-associated formulation of the broad-spectrum polyene antifungal agent amphotericin B. It is active against clinically relevant yeasts and moulds, including *Candida* spp., *Aspergillus* spp. and filamentous moulds such as Zygomycetes, and is approved for the treatment of invasive fungal infections in many countries worldwide. It was developed to improve the tolerability profile of amphotericin B deoxycholate, which was for many decades considered the gold standard of antifungal treatment, despite being associated with infusion-related events and nephrotoxicity.

In well controlled trials, liposomal amphotericin B had similar efficacy to amphotericin B deoxycholate and amphotericin B lipid complex as empirical therapy in adult and paediatric patients with febrile neutropenia. In addition, caspofungin was noninferior to liposomal amphotericin B as empirical therapy in adult patients with febrile neutropenia. For the treatment of confirmed invasive fungal infections, liposomal amphotericin B was more effective than amphotericin B deoxycholate treatment in patients with disseminated histoplasmosis and AIDS, and was noninferior to amphotericin B deoxycholate in patients with acute cryptococcal meningitis and AIDS. In adults, micafungin was shown to be noninferior to liposomal amphotericin B for the treatment of candidaemia and invasive candidiasis. Data from animal studies suggested that higher dosages of liposomal amphotericin B might improve efficacy; however, in the AmBiLoad trial in patients with invasive mould infection, there was no statistical difference in efficacy between the standard dosage of liposomal amphotericin B 3 mg/kg/day and a higher 10 mg/kg/day dosage, although the standard dosage was better tolerated.

Despite being associated with fewer infusion-related adverse events and less nephrotoxicity than amphotericin B deoxycholate and amphotericin B lipid complex, liposomal amphotericin B use is still limited to some extent by these adverse events. Both echinocandins were better tolerated than liposomal amphotericin B. The cost of liposomal amphotericin B therapy may also restrict its use, but further pharmacoeconomic studies are required to fully define its cost effectiveness compared with other antifungal agents. Based on comparative data from well controlled trials, extensive clinical experience and its broad spectrum of activity, liposomal amphotericin B remains a first-line option for empirical

therapy in patients with febrile neutropenia and in those with disseminated histoplasmosis, and is an option for the treatment of AIDS-associated cryptococcal meningitis, and for invasive *Candida* spp. or *Aspergillus* spp. infections.

Pharmacological Properties

Amphotericin B, a macrocyclic, polyene antifungal agent, is thought to act by binding to ergosterol, the principal sterol in fungal cell membranes and *Leishmania* cells. This results in a change in membrane permeability, causing metabolic disturbance, leakage of small molecules and, as a consequence, cell death. *In vitro* and *in vivo* studies have shown that liposomal amphotericin B remains closely associated with the liposomes in the circulation, thereby reducing the potential for nephrotoxicity and infusion-related toxicity associated with conventional amphotericin B. Amphotericin B shows very good *in vitro* activity against a broad spectrum of clinically relevant fungal isolates, including most strains of *Candida* spp. and *Aspergillus* spp., and other filamentous fungi such as Zygomycetes. Liposomal amphotericin B has proven effective in various animal models of fungal infections, including those for candidiasis, aspergillosis, fusariosis and zygomycosis. Liposomal amphotericin B also shows immunomodulatory effects, although the mechanisms involved are not fully understood, and differ from those of amphotericin B deoxycholate and amphotericin B colloidal dispersion.

In adult patients with febrile neutropenia, intravenous liposomal amphotericin B has nonlinear pharmacokinetics, with higher than dose-proportional increases in exposure being consistent with reticuloendothelial saturation and redistribution of amphotericin B in the plasma compartment. Liposomal amphotericin B is rapidly and extensively distributed after single and multiple doses, with steady-state concentrations of amphotericin B attained within 4 days and no clinically relevant accumulation of the drug following multiple doses of 1–7.5 mg/kg/day. In autopsy tissue, the highest concentrations of the drug were found in the liver and spleen, followed by the kidney, lung, myocardium and brain tissue. Elimination of liposomal amphotericin B, like that of amphotericin B deoxycholate, is poorly understood; its route of metabolism is not known and its excretion has not been studied. The terminal elimination half-life is about 7 hours. No dosage adjustment is required based on age or renal impairment.

Clinical Efficacy

In several randomized, double-blind trials (n = 73–1095) in adult and/or paediatric patients, liposomal amphotericin B was effective as empirical therapy or as treatment for confirmed invasive fungal infections, including invasive candidiasis, candidaemia, invasive mould infection (mainly aspergillosis), histoplasmosis and cryptococcal meningitis. All agents were administered as an intravenous infusion; the typical dosage for liposomal amphotericin B was 3 mg/kg/day. Treatment was generally given for 1–2 weeks.

Participants in trials evaluating empirical therapy had neutropenia and a persistent fever despite antibacterial treatment and had received chemotherapy or undergone haematopoietic stem cell transplantation. As empirical therapy in adult and paediatric patients, liposomal amphotericin B appeared to be as effective as amphotericin B deoxycholate (approximately 50% of patients in each group achieved treatment success) or amphotericin B lipid complex (approximately 40% of liposomal amphotericin B recipients experienced treatment success). Of note, in the first trial, results of the statistical test to determine equivalence between treatments were not reported. In the second trial, efficacy was assessed as an 'other' endpoint. In another trial, caspofungin was shown to be noninferior to liposomal amphotericin B, with approximately one-third of patients in each group experiencing treatment success.

Liposomal amphotericin B was significantly more effective than amphotericin B deoxycholate for the treatment of moderate to severe disseminated histoplasmosis in patients with AIDS, with 88% and 64% of patients, respectively, having a successful response. Liposomal amphotericin B was noninferior to amphotericin B deoxycholate for the treatment of cryptococcal meningitis in terms of mycological success. Micafungin therapy was shown to be noninferior to liposomal amphotericin B for the treatment of adult patients with candidaemia or invasive candidiasis. In a substudy in paediatric patients, which was not powered to determine noninferiority, liposomal amphotericin B was as effective as micafungin for the treatment of candidaemia or invasive candidiasis. In this patient population, within each trial, 90% of adult patients and approximately three-quarters of paediatric patients in both treatment groups experienced a successful response. In patients with invasive mould infection (mainly aspergillosis), there was no difference in efficacy between a higher dosage of liposomal amphotericin B (10 mg/kg/day) and the standard dosage (3 mg/kg/day), with 46% and 50% of patients experiencing a favourable overall response.

Tolerability

In well designed clinical trials, liposomal amphotericin B was generally at least as well tolerated as other lipid-associated formulations of amphotericin B and better tolerated than amphotericin B deoxycholate in adult and paediatric patients. Compared with other amphotericin B formulations, liposomal amphotericin B treatment was associated with a lower incidence of infusion-related adverse events and nephrotoxicity. A higher than recommended dosage of liposomal amphotericin B (10 mg/kg/day) was associated with an increased incidence of nephrotoxicity compared with the standard dosage (3 mg/kg/day), although the incidence of infusion-related reactions did not differ between treatment groups.

In general, liposomal amphotericin B treatment was not as well tolerated as echinocandin therapy in well designed clinical trials. As empirical therapy or for the treatment of confirmed invasive fungal infections in adult patients, liposomal amphotericin B recipients experienced more infusion-related events and nephrotoxicity than caspofungin or micafungin recipients. There was no difference in the incidence of these adverse events between the liposomal amphotericin B and micafungin groups in a study in paediatric patients.

1. Introduction

Invasive fungal infections cause significant morbidity and mortality, particularly in immunocompromised patients who are at high risk for these infections.[1] Patients at risk include those receiving cancer chemotherapy, patients with HIV infection, and patients with acute leukaemia or haematopoietic stem cell transplant recipients who experience prolonged neutropenia.[1,2] More aggressive treatment strategies, together with improvements in medical care that extend survival of critically ill patients, mean the number of immunosuppressed patients has increased. As a consequence, the incidence of invasive fungal infections has also increased.[1]

In the past, invasive fungal infections were mainly caused by *Candida* species, notably *Candida albicans*, but the epidemiology of invasive fungal infections has changed, and mould infections (mainly invasive aspergillosis) and non-albicans *Candida* infections have become more common (reviewed by Cornely[1]).

Amphotericin B deoxycholate (i.e. conventional amphotericin B) is a broad-spectrum polyene antifungal agent that has been available for several decades.[1] The broad spectrum of activity (see section 2) contributed to it being considered the gold standard of antifungal therapy for many years, despite being associated with high incidences of infusion-related adverse events and nephrotoxicity.[1] Although amphotericin B

deoxycholate still has a place in antifungal therapy, newer drugs such as lipid-associated formulations of amphotericin B, and other classes of antifungal agents such as the azoles (e.g. voriconazole) and echinocandins (e.g. caspofungin and micafungin), have challenged, and in some cases replaced it as first-line treatment choices.

There are three widely available lipid-associated formulations of amphotericin B, which were developed to minimize the toxicity associated with conventional amphotericin B: liposomal amphotericin B (AmBisome®) [the focus of this review]; amphotericin B lipid complex; and amphotericin B colloidal dispersion. Other liposomal amphotericin B formulations (that are not approved or not widely approved) have different properties to AmBisome®;[3,4] data presented in this review pertain only to the AmBisome® formulation of liposomal amphotericin B.

Liposomal amphotericin B is approved for the treatment of invasive fungal infections in many countries worldwide, although specific indications and approved dosages vary between countries. It has also been investigated (but is not approved) for prophylaxis of fungal infections. This review focuses on several of the approved indications in Ireland (the reference label for the EU), namely the treatment of confirmed invasive fungal infections and empirical treatment for presumed fungal infection in patients with neutropenia and fever of unknown origin who have not responded to antibacterial therapy.[5] Liposomal amphotericin B is also approved for the treatment of visceral leishmaniasis, which has been reviewed previously[6] and is beyond the scope of this review.

2. Pharmacodynamic Properties

2.1 Mechanism of Action

The pharmacodynamic properties of liposomal amphotericin B have been reviewed previously in *Drugs*[6] and elsewhere.[7,8]

Amphotericin B is a macrocyclic, polyene antifungal agent produced by *Streptomyces nodosus*, which is thought to act by binding to ergosterol, the principal sterol in fungal cell membranes and *Leishmania* cells.[5,6] This binding results in a change in membrane permeability, causing metabolic disturbance, leakage of small molecules and, as a consequence, cell death.[5,6] Amphotericin B is fungicidal *in vitro*[9] and may be fungicidal or fungistatic *in vivo* depending on the concentration of the drug attained in body fluids and the susceptibility of the fungus.[5]

Liposomal amphotericin B is a lyophilized formulation that consists of amphotericin B incorporated into the lipid bilayer of small unilamellar liposomes (mean diameter <100 nm), which are composed of hydrogenated soy phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol.[6] This association of amphotericin B with liposomes does not appear to affect the *in vitro* antifungal activity of amphotericin B, but does reduce the nephrotoxicity and infusion-related toxicity of the drug (also see section 5) and alters its pharmacokinetic properties (section 3).[7,8,10]

In vitro and *in vivo* studies have shown that liposomal amphotericin B accumulates at sites of fungal infection, where it binds to fungal cell membranes and causes cell death.[6,8] In addition, liposomal amphotericin B remains closely associated with the liposomes in the circulation, thereby reducing the potential for nephrotoxicity and infusion-related toxicity associated with conventional amphotericin B.[6,8,10] Preclinical studies suggest that amphotericin B-induced nephrotoxicity may be the result of an interaction between renal cells and amphotericin B that is prevented by encapsulation of the drug in liposomes (reviewed by Sabra et al.[11]). For instance, administration of amphotericin B deoxycholate significantly reduces the glomerular filtration rate (GFR) by 44% and renal blood flow by up to 65% in rats versus no change with liposomal amphotericin B administration.[11] In addition, preclinical evidence suggests that indirect effects mediated by humoral mediators may be involved.[11]

2.2 Antifungal Activity

Most *in vitro* studies have used amphotericin B in the deoxycholate form (i.e. conventional

amphotericin B); liposomal amphotericin B *in vitro* data are discussed where available. Amphotericin B shows very good activity against a broad spectrum of clinically relevant fungal isolates, including most strains of *Candida* spp. and *Aspergillus* spp., *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Rhodotorula* spp., *Cryptococcus neoformans* and *Sporothrix schenkii*.[5] Furthermore, amphotericin also shows very good activity against *Saccharomyces cerevisiae*,[12] *Fusarium* spp.,[13,14] *Cladosporium* spp.,[15] *Scytalidium* spp.,[16] *Scedosporium* spp.[14] and Zygomycetes.[17-19] Amphotericin B shows no or minimal activity against bacteria and viruses.[5]

As reviewed by Coukell and Brogden,[6] there was no difference in antifungal activity between the liposomal and conventional formulations of amphotericin B in terms of *in vitro* activity against clinically relevant fungal isolates. The minimum inhibitory concentrations (MICs) required to inhibit 90% of isolates (MIC_{90}) with liposomal or conventional amphotericin B were: *Candida* spp. 0.62 and 1.25 μg/mL (n = 72 isolates); *Aspergillus* spp. 1.25 and 2.5 μg/mL (n = 13); *C. neoformans* 0.62 and 1.25 μg/mL (n = 32); and *Fusarium* spp. 2.5 and 2.5 μg/mL (n = 8).

2.2.1 *In vitro* Activity

The US Clinical and Laboratory Standards Institute (CLSI) has developed a standardized method for broth microdilution testing of antifungal agents against yeasts.[20,21] No specific interpretative MIC breakpoints using these methods have been established for amphotericin B.[21] Discussion of *in vitro* activity focuses on data from studies published since 2003. Unless stated otherwise, MIC values were determined using broth microdilution assays described by the CLSI (or its predecessor the National Committee for Clinical Laboratory Standards). Of note, the clinical relevance of *in vitro* activity of antifungal agents remains to be fully determined.

Candida spp.

Amphotericin B showed very good *in vitro* activity against 331 clinical isolates of *Candida* spp. (year of collection not stated), as determined in broth microdilution assays (table I).[22] Overall, the geometric mean MIC against these *Candida* spp. isolates was 0.15 μg/mL for amphotericin B, 0.16 μg/mL for posaconazole (not tabulated) and 0.91 μg/mL for fluconazole.[22] In another study of 293 *Candida* spp. isolates collected in Spain from 1997 to 1999, MIC_{90} values for amphotericin B against *C. albicans* (n = 127), *C. parapsilosis* (n = 86) and *C. tropicalis* (n = 30) were all 1 μg/mL, and those for *C. glabrata* (n = 25) and *C. krusei* (n = 10) were both 2 μg/mL.[23] Overall, 91% of these *Candida* spp. isolates were considered susceptible to amphotericin B (i.e. MIC ≤1 μg/mL) compared with 87% of isolates for fluconazole (i.e. MIC ≤8 μg/mL) and 92% for voriconazole (i.e. MIC ≤1 μg/mL).[23]

These data were supported by another study that evaluated 572 *Candida* spp. clinical isolates, collected between 2001 and 2003 in Taiwan, using an Etest assay;[24] MIC_{90} values against *C. albicans* (n = 290 isolates), *C. tropicalis* (n = 137), *C. parapsilosis* (n = 75), *C. glabrata* (n = 54), *C. krusei* (n = 11) and *C. guilliermondii* (n = 5) were 0.19, 0.25, 0.125, 0.38, 0.38 and 0.032 μg/mL,

Table I. Comparative *in vitro* activity of amphotericin B against clinical isolates of *Candida* spp. using broth microdilution assays[22]

Clinical isolate	No. of isolates	MIC_{90} (μg/mL) [MIC range]	
		amphotericin B	fluconazole
Candida albicans	191	0.5 [0.01–1]	32 [0.06 to >256]
C. tropicalis	42	0.5 [0.01–1]	1 [0.125–4]
C. lusitaniae	30	0.5 [0.125–1]	1 [0.06–0.125]
C. glabrata	32	0.5 [0.01–1]	64 [0.125–128]
C. parapsilosis	20	0.25 [0.01–0.5]	1 [0.125–64]
C. famata	16	1 [0.125–1]	16 [2–32]

MIC = minimum inhibitory concentration; **MIC_{90}** = minimum inhibitory concentration required to inhibit 90% of isolates.

Table II. Comparative *in vitro* activity of amphotericin B against clinical isolates of filamentous fungi collected in North America between January 2000 and December 2001[25] or internationally[26] (mainly from patients in the US, Germany and France) up until 2004

Clinical isolate	Diekema et al.[25]			Espinel-Ingroff et al.[26]		
	no. of isolates	amphotericin B MIC_{90} (μg/mL) [% S][a]	Voriconazole MIC_{90} (μg/mL) [% S][a]	no. of isolates	amphotericin B MIC_{90} (μg/mL)	Voriconazole MIC_{90} (μg/mL)
***Aspergillus* spp.**	372	1 [91]	1 [95]			
A. fumigatus	256	1 [96]	0.5 [99]	292	2	0.5
A. flavus	30	2 [70]	1 [100]	36	2	0.5
A. niger	29	1 [100]	2 [66]	21	1	0.5
A. versicolor	20	2 [80]	1 [95]			
A. terreus	16	2 [38]	1 [100]	43	2	0.5
***Fusarium* spp.**	11	2 [82]	>8 [18]	21	0.5–4[b]	1–16[b]
***Paecilomyces* spp.**	6	0.06 to >8[b] [67]	0.03–2[b] [83]			
P. lilacinus				5	16–16[b]	0.06–0.125[b]
Paracoccidioides brasiliensis				10	0.5	0.035
***Penicillium* spp.**	35	2 [86]	2 [80]			
P. marneffei				34	1	0.003
Zygomycetes				9[c]	0.25–2[b]	8–16[b]
Mucor spp.	3	0.5–1[b] [100]	1 to >8[b] [33]			
Rhizopus spp.	5	0.5–1[b] [100]	1 to >8[b] [40]			

a MIC ≤1 μg/mL.

b MIC range.

c Included *Absidia corymbifera, Cunninghamella bertholletiae, Mucor racemosus, Rhizomucor pusillus, Rhizopus arrhizus and R. microsporus.*

MIC = minimum inhibitory concentration; **MIC_{90}** = MIC required to inhibit 90% of isolates; **S** = susceptible.

respectively, with an overall MIC value against all *Candida* spp. isolates of 0.19 μg/mL. Of these isolates, only one isolate was considered resistant to amphotericin B (i.e. had an MIC of ≥1 μg/mL).

Aspergillus spp. and Other Filamentous Fungi

In two recent studies, amphotericin B showed very good *in vitro* activity against filamentous fungi collected in North America[25] or internationally,[26] including *Aspergillus* spp., *Fusarium* spp. and Zygomycetes (table II). Where evaluated,[25] the susceptibility rate (i.e. percentage with an MIC ≤1 μg/mL) for amphotericin B against these filamentous fungi was 89%, compared with 90% for voriconazole, 95% for posaconazole, 91% for ravuconazole and 93% for caspofungin.

Of interest, several studies have shown that amphotericin B has excellent activity against Zygomycetes,[17-19,25,26] with data from two[25,26] of these studies shown in table II. In the largest study,[17] the MIC_{90} value for amphotericin B was 2 μg/mL compared with >16, >16, 1 and >256 μg/mL, respectively, for itraconazole, voriconazole, posaconazole and caspofungin against 45 clinical Zygomycetes isolates.

Other *In vitro* Effects

Amphotericin B demonstrated a post-antifungal effect (PAFE) against most clinical isolates of Zygomycetes, including *Rhizopus* and *Mucor* spp., but not against *Rhizomucor* spp.[27] For example, at 1 × MIC of amphotericin B, the mean PAFEs against *Absidia corymbifera*, *Rhizopus oryzae*, *R. microsporus* and *Mucor* spp. were 4.2, 5.2, 3 and 3.5 hours, respectively; corresponding values for nystatin at 1 × MIC were 0.8, 3.3, 1.7 and 5.8 hours. Overall, against all 30 clinical isolates, amphotericin B demonstrated a significantly longer PAFE at higher MIC concentrations (i.e. 4 × MIC against *A. corymbifera* or 1 × MIC for all other strains) than nystatin (4.6 vs 2.9 hours; $p < 0.05$).

Amphotericin B showed a significant PAFE against clinical isolates of *C. guilliermondii*, *C. kefyr* and *C. lusitaniae*, whereas no PAFE was observed with fluconazole or voriconazole, and the PAFE for caspofungin was measurable only for *C. lusitaniae*.[28] The PAFE at 1×MIC of amphotericin B ranged from 9.2 to 14.9 hours (mean 11.2 hours) against the six isolates tested.[28] Moreover, amphotericin B and caspofungin demonstrated concentration-dependent fungicidal activity, whereas the triazoles showed fungistatic activity, regardless of the concentration of drug.

When combined with anidulafungin[29] or caspofungin[30] in *in vitro* studies, amphotericin B showed synergy or indifference against most *Aspergillus* spp. and *Fusarium* spp. test isolates. Against *Aspergillus* spp., amphotericin B plus anidulafungin showed synergy for 5 of 26 isolates, antagonism for 5 of 26 isolates and indifference for 16 of 26 isolates, whereas indifference was observed against all seven *Fusarium* spp. isolates tested for this combination.[29] In the other study, amphotericin B plus caspofungin showed synergistic or additive effects against more than half of the 14 *Aspergillus* spp. and 6 *Fusarium* spp. tested, and no antagonism.[30] Both studies evaluated synergy using checkerboard broth microdilution assays and classified interactions based on the fractional inhibitory concentration index.[29,30]

Liposomal amphotericin B has shown good *in vitro* activity against biofilm-associated *C. albicans* and *C. parapsilosis* isolates.[31] Although the clinical relevance of this finding remains to be fully determined, these biofilms often develop on medically implanted devices (e.g. on indwelling catheters and parenteral feeding lines) and are associated with the development of invasive candidiasis. Moreover, these biofilm infections often show resistance to antifungal agents.[31]

2.2.2 In vivo Activity

Liposomal amphotericin B has proven effective in various animal models of fungal infections, including those for candidiasis,[32,33] aspergillosis,[3,34-42] fusariosis[43] and zygomycosis.[44] In *in vivo* models of fungal infections in the brain, lung and kidneys, liposomal amphotericin B appeared to be localized at these sites (as reviewed by Adler-Moore and Proffitt[7]). Discussion here focuses on studies that evaluated the comparative efficacy of the various formulations of amphotericin B in animal models of aspergillosis.

In several animal models of aspergillosis, including models of pulmonary,[36,37] disseminated,[42] CNS[34,35] and renal[35] aspergillosis, liposomal amphotericin B was generally as effective as amphotericin B lipid complex and amphotericin B colloidal dispersion, and at least as effective as conventional amphotericin B in significantly prolonging survival and reducing fungal burden in tissues compared with control animals. Furthermore, liposomal amphotericin B was associated with less nephrotoxicity than treatment with amphotericin B lipid complex.[37]

Data from studies in steroid-immunosuppressed rats have suggested that high doses of liposomal amphotericin B may be more effective than standard dosages in treating invasive pulmonary aspergillosis.[40,41] There were significantly greater reductions in colony forming units per gram of lung ($p = 0.012$), lung weight ($p = 0.002$) and fungal biomass (as measured by quantification of chitin, a fungal cell wall component) [$p = 0.001$] in rats given liposomal amphotericin B 10 mg/kg/day than in those given 3 mg/kg/day, although survival did not differ significantly between the two groups.[41] Another study in rats reported a significant increase in survival for rats given liposomal amphotericin B 10 mg/kg/day for 4 days followed by 3 mg/kg/day until the end of the study (total 7 days) compared with those given amphotericin B deoxycholate 1 mg/kg/day for 7 days ($p < 0.009$), but there was no significant improvement versus amphotericin B deoxycholate 1 mg/kg/day for those given liposomal amphotericin B 5 mg/kg/day, those given 10 mg/kg/day for 3 days followed by no treatment, or those given 10 mg/kg/day for 3 days followed by 3 mg/kg/day.[40]

Although MIC values are one way to predict antifungal activity, they do not necessarily reflect *in vivo* activity and thus, the inter-relationships between pharmacodynamic and pharmacokinetic parameters have been evaluated in animal studies

as a way of predicting antifungal activity.[9,45,46] For example, in a rabbit model of haematogenous *C. albicans* meningoencephalitis using standard dosages, concentrations of, and exposure to, liposomal amphotericin B was significantly ($p < 0.05$) higher than corresponding values with amphotericin B deoxycholate, amphotericin B colloidal dispersion or amphotericin B lipid complex (maximum plasma concentration [C_{max}] 62.02, 3.87, 1.79, 0.99 μg/mL, respectively; area under the plasma concentration-time curve [AUC] from 0 to 24 hours [AUC_{24}] 1141, 14.44, 11.21 and 10.03 μg • h/mL).[46] In addition, exposure to amphotericin B deoxycholate was significantly ($p < 0.05$) higher than that to amphotericin B lipid complex or amphotericin B colloidal dispersion. Furthermore, rabbits treated with liposomal amphotericin B or amphotericin B deoxycholate showed complete clearance of *C. albicans* infection from brain tissue. As a result, when an MIC of 1 μg/mL was used, a strong inverse correlation was observed for C_{max} : MIC, AUC_{24} : MIC, the drug concentration in the tissue and MIC ratio, and the time during the dosing interval during which plasma concentrations were greater than the MIC. However, these correlations were weak if the MICs of the individual formulations were used.[46]

2.2.3 Resistance

The development of resistance to amphotericin B in *Candida* spp. is difficult to determine because of the very narrow range of MICs obtained and the lack of a clear interpretive MIC breakpoint.[47] However, an MIC of >1 μg/mL for amphotericin B against a *Candida* spp. isolate is unusual and possibly means a resistant strain or one that necessitates treatment with high doses of amphotericin B. Of note, the susceptibility of *Candida* spp. to amphotericin B appears to show very little temporal or geographical variation.[47]

Although resistance to amphotericin B is rare in *C. albicans* isolates, *C. glabrata* and *C. krusei* isolates appear to be less susceptible to amphotericin B than *C. albicans*, and treatment of *C. glabrata* and *C. krusei* infections may require higher dosages of amphotericin B than other species of *Candida*.[47] Despite initial susceptibility to amphotericin B, *C. lusitaniae* can develop resistance to amphotericin B during treatment.[47]

Several genes involved in ergosterol biosynthesis have been shown to be potentially involved in the acquisition of experimentally induced amphotericin B resistance to a laboratory strain of *C. albicans* (namely SC5314).[48] After serial passages of this laboratory strain in the presence of increasing concentrations of amphotericin B, 134 genes were shown to be up- or downregulated by ≥50% using a DNA microarray analysis. The upregulation of *ERG5*, *ERG6* and *ERG25* genes was considered particularly important because these genes are pivotal to sterol biosynthesis at points in the pathway where sterol biosynthesis may take an alternative route, potentially leading to sterols other than ergosterol being the main sterol in the fungal cell wall thereby reducing susceptibility to amphotericin B. In addition, several histone, protein synthesis and energy generation genes were also shown to be downregulated.[48]

Aspergillus terreus is intrinsically resistant to amphotericin B *in vitro* and *in vivo*.[49] In 16 *A. terreus* isolates collected in North America in 2000–1, the MIC_{90} for amphotericin B was 2 μg/mL and only 37.5% of isolates were inhibited at an MIC ≤1 μg/mL.[25] In contrast, 100% of *A. terreus* isolates were susceptible (at MIC ≤1 μg/mL) to caspofungin, itraconazole, posaconazole, ravuconazole and voriconazole.[25] The mechanism for resistance to amphotericin B in *A. terreus* is not known, but increased catalase production may be involved.[49]

2.3 Immunomodulatory Effects

Invasive fungal infections generally occur in severely immunocompromised patients and thus, enhancement of the immune response may play a pivotal role in the success of treatment (reviewed by Ben-Ami et al.[50]).

The various formulations of amphotericin B have been shown to have differential effects on immune functions, most of which were evaluated in *in vitro* and *in vivo* studies.[50] The

pro-inflammatory effects of amphotericin B deoxycholate and amphotericin B colloidal dispersion are associated with acute infusion-related toxicity and dose-dependent nephrotoxicity that correlates with increased blood levels of inflammatory cytokines.[50,51] In contrast, liposomal amphotericin B and amphotericin B lipid complex are associated with a downregulation of pro-inflammatory cytokines and are associated with less severe infusion-related toxicity and a reduced potential to cause nephrotoxicity (see section 5).[50,51]

Although the mechanisms of these inflammatory effects are not fully understood, *in vitro* studies have suggested the upregulation of gene expression and production of inflammatory cytokines is mediated via interaction of amphotericin B deoxycholate with Toll-like receptor (TLR)-2 and CD14.[50] Liposomal amphotericin B may lessen the inflammatory effects by diverting signalling from TLR-2 to TLR-4.[52] Furthermore, the liposomes are known to have anti-inflammatory properties themselves, and may reduce neutrophil leakage into inflammation sites.[50]

Preclinical and clinical data have shown that amphotericin B acts synergistically with heat shock protein 90 antibodies to improve humoral immunity and clinical response rates.[50,53] *In vitro* evidence also suggests that liposomal amphotericin B, like amphotericin B deoxycholate and amphotericin B lipid complex, acts synergistically with polymorphonuclear leukocytes[54,55] and monocytes[54,56] to damage hyphae of *A. fumigatus*[54-56] and *F. solani*[54] isolates.

3. Pharmacokinetic Properties

The pharmacokinetic parameters of intravenous liposomal amphotericin B, based upon plasma concentrations of amphotericin B, have been evaluated in adult patients with febrile neutropenia;[57] distribution data are based on autopsy material from patients who had been treated with liposomal amphotericin B or amphotericin B colloidal dispersion for proven or suspected invasive mycoses[58] and animal studies.[59,60] These data are supplemented with information from the manufacturer's prescribing information.[5] The pharmacokinetic properties of liposomal amphotericin B have been extensively reviewed in *Drugs*[6] and elsewhere,[61] and are briefly reviewed here. Wherever available, discussion focuses on data for recommended dosages of liposomal amphotericin B. Mean pharmacokinetic parameters for recommended dosages of liposomal amphotericin B are summarized in table III.

Liposomal amphotericin B has nonlinear pharmacokinetics over a dosage range of 1–7.5 mg/kg/day, with higher than dose proportional increases in exposure being consistent with reticuloendothelial saturation and redistribution of amphotericin B in the plasma compartment.[57]

Liposomal amphotericin B is rapidly and extensively distributed after single and multiple intravenous doses and has a significantly different pharmacokinetic profile than amphotericin B deoxycholate (reviewed by Coukell and Brogden[6]).[5] C_{max} values and exposure to amphotericin B were higher after administration of the liposomal formulation than after amphotericin B deoxycholate.[5,6] Steady-state concentrations of amphotericin B are attained within 4 days, with no clinically relevant accumulation of the drug following multiple doses of 1–7.5 mg/kg/day.[5]

Liposomal amphotericin B is extensively distributed throughout the body, which is reflected in the high volume of distribution on day 1 and on the last day (table III).[57] Amphotericin B in the deoxycholate form is highly protein bound (>95% bound), with *in vitro* studies showing that human serum albumin and α_1-acid glycoprotein contribute to this binding.[62] In autopsy tissue from 20 patients who had received treatment with liposomal amphotericin B or amphotericin B colloidal dispersion, the highest concentrations of amphotericin B were found in tissues from the liver (mean 103 vs 94 μg/mL in amphotericin B colloidal dispersion group) and spleen (60 vs 81 μg/mL), followed by kidney (12 vs 37 μg/mL), lung (12 vs 32 μg/mL), myocardium (3 vs 6 μg/mL) and brain tissues (1 vs 1 μg/mL).[58] Unlike amphotericin B deoxycholate, liposomal amphotericin B and other lipid formulations of amphotericin B showed very good penetration

Table III. Mean pharmacokinetic properties of intravenous liposomal amphotericin B after single and multiple infusions of recommended doses in febrile neutropenic adult patients. In this prospective, nonblind, sequential-dose-escalation study, 36[a] patients received empirical treatment for 3–20 days[57]

Parameter	Dosage			
	1 mg/kg/d		2.5 mg/kg/d	
	day 1	last day	day 1	last day
AUC_{∞} (μg • h/mL)	32	66	71	213
Vd (L/kg)	0.58	0.16	0.69	0.18
Vd_{ss} (L/kg)	0.44	0.14	0.40	0.16
$t_{1/2\beta}$ (h)	10.7	7.0	8.1	6.3
CL (mL/h/kg)	39	17	51	22

a Total number of patients (n = 8 in each of the 1 and 2.5 mg/kg/d groups). Data for other two groups (5.0 and 7.5 mg/kg/day) [n = 12 and 8] are not shown as these dosages are not recommended in the EU.

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; **CL** = clearance; **$t_{1/2\beta}$** = terminal elimination half-life; **Vd** = volume of distribution; **Vd_{ss}** = Vd at steady state.

into bone marrow in noninfected rabbits, with the concentration of amphotericin B in bone marrow after administration of lipid formulations being at least 4-fold higher ($p < 0.05$) than after treatment with amphotericin B deoxycholate.[59] These data are supported by other animal studies (reviewed by Adler-Moore and Proffitt[60]).

The route of metabolism of amphotericin B remains unknown and its excretion has not been studied.[5] After multiple doses of liposomal amphotericin B, the terminal elimination half-life of amphotericin B was approximately 7 hours in febrile neutropenic adult patients (table III).[5,57] There is no glomerular filtration of liposomal amphotericin B because of the size of the liposomes; hence, there is no interaction between amphotericin B and the cells of the distal tubuli after liposomal amphotericin B administration and the potential for nephrotoxicity is reduced compared with amphotericin B deoxycholate (section 5).[5]

There have been no specific drug interaction studies conducted using liposomal amphotericin B, although based on studies using amphotericin B, the same potential interactions may enhance drug-related toxicity such as nephrotoxicty and hypokalaemia (see also section 5); see section 6 for discussion of these potential interactions.[5]

No dosage adjustment is required based on age or renal impairment.[5] The effect of renal impairment on the pharmacokinetic profile of liposomal amphotericin B has not been formally evaluated; however, patients in clinical trials who had pre-existing renal impairment did not require dosage adjustment.[5] Evidence suggest that no dosage adjustment is required in patients undergoing haemodialysis or filtration procedures; however, administration of liposomal amphotericin B should be avoided during these procedures (section 6).[5]

4. Clinical Efficacy

Liposomal amphotericin B has been investigated for use as empirical therapy in patients with febrile neutropenia and for the treatment of invasive fungal infections in numerous prospective and retrospective clinical studies. This section discusses randomized, double-blind, multicentre trials of liposomal amphotericin B (focusing on approved dosages) versus comparators approved in the EU for the indication being evaluated.

In light of this, a large (n = 837), randomized, nonblind, multicentre, noninferiority trial, in which voriconazole failed to meet the criteria for noninferiority to liposomal amphotericin B for empirical therapy in patients with neutropenia and persistent fever, is not discussed further because voriconazole is not approved for this indication (see section 7).[63]

The large AmBiLoad trial,[64] which compared a higher than recommended dosage of liposomal

Table IV. Comparative efficacy of liposomal amphotericin B (L-AMB) in randomized, double-blind, multicentre trials of empirical therapy in patients (pts) with neutropenia and persistent fever. All analyses were based on the modified intent-to-treat population. The studies were an equivalence study,[65] a safety study[66] (primarily) and a noninferiority study[67]

Study	Treatment regimen[a]	No. of pts (mean age [range]; y)	Mean duration of treatment (d)	Treatment success rate[b] (% of pts) [95% CI]
Versus other amphotericin B formulations				
Walsh et al.[65]	L-AMB 3 mg/kg/d	343 (41 [2–79])	10.8	50.1[c] [45, 56]
	AMBD 0.6 mg/kg/d	344 (42 [2–80])	10.3	49.4 [44, 55]
Wingard et al.[66][d]	L-AMB 3 mg/kg/d	85 (41.4 [3–74])	8.6	40.0
	ABLC 5 mg/kg/d	78 (42.8 [2–76])	7.5	33.3
Versus caspofungin (CAS)				
Walsh et al.[67]	L-AMB 3 mg/kg/d	539 (49[e] [16–83])	12.5	33.7[f]
	CAS 70 mg [1d], then 50 mg/d	556 (51[e] [17–83])	13.0	33.9[f] [–5.6, 6.0][g]

a Dosage could be adjusted based on efficacy and/or tolerability.[65,67]

b Primary[65,67] or other[66] endpoint, termed treatment success,[65] successful response[66] or favourable overall response.[67] Defined as a composite of five[65,67] or six[66] criteria: successful treatment of any baseline fungal infection;[65-67] no breakthrough fungal infection during treatment[66] or within 7 days after completion of treatment;[65,67] survival for 7 days after the completion[66,67] or initiation[65] of treatment; no premature discontinuation of study drug due to toxicity[65-67] or lack of efficacy;[65,67] resolution of fever during the period of neutropenia;[65-67] and no alternative systemic antifungal treatment for a probable or proven fungal infection.[66]

c The results of the prespecified analysis for equivalence were not reported (i.e. the between-group difference and the 95% CI for the difference).

d Data for the L-AMB 5 mg/kg/day treatment group (n = 81) are not shown as this dosage is not approved in the EU.

e Median age.

f Adjusted for stratification according to risk (allogeneic HSCT pts or those with relapsed acute leukaemia were considered high risk and all others were low risk) and whether or not pts had received systemic antifungal prophylaxis.

g 95.2% CI for between-group difference. CAS was noninferior to L-AMB if the 95.2% CI for the difference in treatment success (adjusted for stratification) between CAS and L-AMB recipients included 0 and the lower limit was not less than −10%.[67]

ABLC = amphotericin B lipid complex; **AMBD** = amphotericin B deoxycholate; **HSCT** = haematopoietic stem cell transplantation.

amphotericin B with the standard dosage for the treatment of invasive mould infections, is discussed.

4.1 Empirical Therapy in Patients with Febrile Neutropenia

Three randomized, double-blind, multicentre trials in patients with persistent fever and neutropenia who had not responded to antibacterial therapy compared the efficacy of liposomal amphotericin B with that of amphotericin B deoxycholate (n = 687),[65] amphotericin B lipid complex (n = 244)[66] or caspofungin (n = 1095)[67] [see table IV for study details]. One study (vs caspofungin)[67] included only adult patients (≥16 years of age); the other two trials, which evaluated different amphotericin B formulations, included paediatric (aged ≥2 years) and adult patients.[65,66]

Before randomization to treatment groups, patients were stratified according to whether or not they had received nephrotoxic immunosuppressants (ciclosporin or tacrolimus),[66] or by prior use of systemic antifungal prophylaxis and by risk (patients who had undergone allogeneic haematopoietic stem cell transplantation [HSCT] or who had relapsed acute leukaemia were considered high risk).[67]

Eligibility criteria were generally similar across the trials. Eligible patients had received chemotherapy for cancer or had undergone HSCT; were neutropenic (absolute neutrophil count $<500/mm^3$); had a fever (>38°C); and had received antibacterial therapy for 3,[66] 4[67] or 5[65] days.

Patients were excluded from the trials if they had a confirmed invasive fungal infection[65-67] or an uncontrolled bacterial infection at the time of randomization,[65-67] or a Karnofsky score <30

(scale 0–100).[67] Exclusion criteria also included raised baseline serum levels of AST (>5[67] or >10[65,66] ×upper limit of normal [ULN]), ALT (>5[67] or >10[65,66] ×ULN), alkaline phosphatase (>3,[67] >5[66] or >10[65] ×ULN), bilirubin (>3[67] or >5[66] ×ULN, or >3 or >5 mg/dL if transaminase levels were ≥2× or <2×ULN[65]) or serum creatinine (>2×ULN[65] or >3 mg/dL[66]).

Liposomal amphotericin B was administered by intravenous infusion at a dosage of 3 mg/kg/day in all studies.[65-67] One study[66] also included a treatment arm of liposomal amphotericin B 5 mg/kg/day (dosage not approved in the EU for this indication), which is not discussed further or tabulated. All agents were given intravenously (see table IV for specific dosage details). The duration of the infusions was only specified in one study; this study used a 120-minute infusion for both study drugs.[66]

In all three studies, premedication to minimize infusion-site reactions was not permitted prior to the first dose, but was permitted for subsequent infusions if there was an infusion reaction to the first dose.[65-67] Two of the studies allowed for alterations to study drug dosages.[65,67] Study drugs were administered until the patient recovered from neutropenia (i.e. when the absolute neutrophil count was ≥500 cells/mm^3)[65] or for up to 3 days after recovery from neutropenia[66,67] up to a maximum of 42 days.[66]

One of these trials evaluated whether liposomal amphotericin B was equivalent to amphotericin B deoxycholate treatment,[65] another whether there were differences between amphotericin B lipid complex and liposomal amphotericin B in terms of safety[66] and the third whether caspofungin was noninferior to liposomal amphotericin B for empirical treatment of febrile neutropenia.[67]

The primary endpoint was treatment success[65] or favourable overall response,[67] which was defined as a composite of five criteria (see table IV for details). The third study reported rates of successful response,[66] which included an additional component in the composite endpoint (see table IV for details). The composite endpoint was not the primary endpoint in this study,[66] as it was designed to evaluate the safety of liposomal amphotericin B versus amphotericin B lipid complex (see section 5.1.1).[66] All analyses were based on the modified intent-to-treat (mITT) population, which included all patients who received at least one dose of study drug.[65-67]

Equivalence of liposomal amphotericin B to amphotericin B deoxycholate was demonstrated if the 95% CI for the difference in success rates between the treatment groups was between –0.10 and 0.10.[65] Noninferiority of caspofungin to liposomal amphotericin B was demonstrated if the 95.2% CI for the difference in treatment success (adjusted for stratification) between caspofungin and liposomal amphotericin B recipients included 0 and the lower limit was not less than –10%.[67]

Baseline characteristics were similar across treatment groups in each trial.[65-67] Approximately half of the patients in the trials involving different formulations of amphotericin B had undergone HSCT (45–51%).[65,66] Of the patients in the amphotericin B lipid complex trial who had not undergone HSCT, 33.2% had acute leukaemia.[66] In the trial comparing caspofungin with liposomal amphotericin B, over 62% of patients had acute myelogenous leukaemia.[67]

4.1.1 Versus Other Amphotericin B Formulations

As empirical therapy in patients with persistent fever and neutropenia, treatment was successful in 50.1% of liposomal amphotericin B recipients and 49.4% of amphotericin B deoxycholate recipients in the equivalence trial (table IV).[65] Of note, the results of the prespecified analysis for equivalence (i.e. the between-group difference and 95% CI values) were not reported.[65] Approximately 58% of patients in both treatment groups experienced a resolution of fever during the period of neutropenia, and most liposomal amphotericin B or amphotericin B deoxycholate recipients had successful treatment of any baseline fungal infection (81.8% vs 72.7%), no breakthrough fungal infections (90.1% vs 89.2%), no premature discontinuation of study drug (85.7% vs 81.4%) and were alive 7 days after initiation of treatment (92.7% vs 89.5%).[65]

There were no significant differences in treatment success between liposomal amphotericin B and amphotericin B lipid complex (table IV).[66]

4.1.2 Versus Caspofungin

Caspofungin was no less effective than liposomal amphotericin B as empirical therapy in patients with persistent fever and neutropenia based on the composite primary endpoint of treatment success (table IV).[67] Thirty-four percent of patients in both treatment groups experienced treatment success, with the between group difference (adjusted for strata) of 0.2% (95.2% CI −5.6, 6.0) satisfying the criteria for noninferiority.[67]

When each component of the composite primary endpoint was assessed separately, and based on a significance level of $p \leq 0.05$ (defined in the study), liposomal amphotericin B was less effective than caspofungin for three of the components (secondary endpoint). Significantly more caspofungin than liposomal amphotericin B recipients experienced successful treatment of baseline fungal infection (51.9% vs 25.9%; between-group difference 25.9%; 95% CI 0.9, 51.0; $p = 0.04$), no premature discontinuation of study drug (89.7% vs 85.5%; between-group difference 4.2%; 95% CI 0.3, 8.1; $p = 0.03$) and survival for at least 7 days following completion of treatment (92.6% vs 89.2%; between-group difference 3.4%; 95% CI 0.0, 6.8; $p = 0.05$).[67]

However, the between-group differences for the other two components of the composite primary endpoint were not statistically significant. There was an absence of breakthrough fungal infections in 94.8% and 95.5% of caspofungin or liposomal amphotericin B recipients (between-group difference −0.8%; 95% CI −3.3, 1.8) and 41.2% and 41.4% of caspofungin or liposomal amphotericin B recipients experienced resolution of fever during the period of neutropenia (between-group difference −0.2%; 95% CI −6.0, 5.6).[67]

The overall mortality rates during the study were 13.7% in the liposomal amphotericin B group and 10.8% in the caspofungin group.[67] A Kaplan-Meier analysis of survival favoured caspofungin ($p = 0.04$).[67]

4.2 In Patients with Confirmed Invasive Fungal Infections

The efficacy of liposomal amphotericin B for the treatment of confirmed invasive fungal infections has been investigated in five randomized, double-blind, multicentre trials (n = 73–392; see table V for dosage and design details, including definitions of the primary efficacy populations).[64,68-71] One of the studies has not been fully published and is available as an abstract;[71] additional study data have been obtained from a US FDA medical review.[72]

4.2.1 In Patients with Invasive Mould Infection

The AmBiLoad trial compared the efficacy of a higher dosage of liposomal amphotericin B (10 mg/kg/day) with that of the standard 3 mg/kg/day dosage for the treatment of invasive mould infections (mainly aspergillosis).[64] Results from animal studies (section 2.2.2) suggested that using a higher dosage of liposomal amphotericin B might improve efficacy. Study treatment was blinded for 14 days, then all patients received liposomal amphotericin B 3 mg/kg/day until the end of treatment, as determined by a study investigator.[64]

In the AmBiLoad trial, patients had a proven or probable invasive mould infection; those with a possible mould infection were also enrolled in the study, but were disqualified from analysis if the infection was not identified as being proven or probable within 4 working days of enrolment.[64] The randomization process included stratification by age, type of infection, allogeneic HSCT status and duration of neutropenia at baseline.[64]

Baseline characteristics in the treatment groups were similar.[64] Most patients (93% of both treatment groups) had haematological malignancies and 96% and 97% of liposomal amphotericin B 3 or 10 mg/kg/day recipients had proven or probable *Aspergillus* spp. infections, and the most common site of infection was the lungs (92% and 89%).[64]

Patients were excluded from the trial if they had received other systemic antifungal therapy for ≥4 days for the currently diagnosed fungal infection or ≥4 days of systemic polyene treatment within the previous 2 weeks, had a serum creatinine level >2 × ULN, or transaminase, bilirubin, or alkaline phosphatase levels >5 × ULN.[64]

Table V. Comparative efficacy of liposomal amphotericin B (L-AMB) in the treatment of confirmed invasive fungal infections in randomized, double-blind, multicentre trials. All study drugs were administered by intravenous infusion and the planned duration of study treatment was 14 days, unless otherwise stated

Study	Treatment regimen	No. of evaluable pts[a] (median age [range]; y)	Median[64,69,70] or mean[72] duration of treatment (d)	Treatment success[b] (% of pts) [95% CI][c]
In pts with invasive mould infection				
Cornely et al.[64]	L-AMB 3 mg/kg/d[d]	107 (50.9 [15–76])[e]	15	50 [–10, 18]
(AmBiLoad)	L-AMB 10 mg/kg/d [14 d], then 3 mg/kg/d[d]	94 (50.4 [2–78])[e]	14	46
In pts with candidaemia or invasive candidiasis				
Kuse et al.[69]	L-AMB 3 mg/kg/d[f]	190 (56.0 [16–97])	15	89.5
	MFG 100 mg/d[f]	202 (54.5 [18–89])	15	89.6 [–5.9, 6.2][g]
Queiroz-Telles et al.[70]	L-AMB 3 mg/kg/d[f]	50 (<1 [<1–15])	14.5	76.0
	MFG 2 mg/kg/d[f]	48 (1.0 [<1–15])	15	72.9 [–20.1, 15.3]
In pts with histoplasmosis associated with AIDS				
Johnson et al.[68]	L-AMB 3 mg/kg/d	51 (33 [16–68])[h]		88* [1, 52]
	AMBD 0.7 mg/kg/d	22		64
In pts with cryptococcal meningitis associated with AIDS				
Hamill et al.[71,72][i]	L-AMB 3 mg/kg/d	60 (37 [22–61])[j]	13.5	58.3 [–6.9, 28.5][k]
	AMBD 0.7 mg/kg/d	61 (39 [10–59])[j]	13.3	47.5

a Where specified, pt numbers are for the primary efficacy population (i.e. the mITT,[64,68] PP[69] or mycologically evaluable[72] population). The mITT population consisted of all pts who received at least one dose of study drug[64,68] and had a protocol-defined diagnosis of proven or probable invasive mould infection within 4 working days[64] or had confirmed disseminated histoplasmosis.[68] The PP population was defined as pts who had a confirmed *Candida* spp. infection at baseline and an investigator's assessment of response at therapy end, had received at least five doses of study drug and who had not taken any prohibited medication.[69] In the paediatric study,[70] the primary efficacy population was not specified; data for the mITT population are tabulated (i.e. all pts who received at least one dose of study drug and had a confirmed *Candida* spp. infection at baseline). In the study in pts with cryptococcal meningitis,[72] the mycologically evaluable population consisted of all pts who received at least one dose of study drug, had a confirmed cryptococcal meningitis culture at baseline and had at least one follow-up culture.

b Primary endpoint. Termed clinical[68] or treatment[69,70] success (i.e. clinical and mycological success); mycological success (i.e. negative cerebrospinal fluid culture result);[72] or favourable overall response (partial or complete clinical, radiological and, where available, microbiological response).[64]

c For difference between treatment groups.

d Treatment was double-blind for the first 14 d, then all pts received nonblind treatment with L-AMB 3 mg/kg/d.

e Mean age.

f Dosages were adjusted based on efficacy (and toxicity for L-AMB); the MFG dosage was also adjusted based on bodyweight.

g MFG was noninferior to L-AMB; the lower bound of the two-sided 95% CI for the between-group difference, after adjustment for baseline neutropenic status, was above −15%.

h For all pts. Age not reported for each treatment group.

i Data for the L-AMB 6 mg/kg/d treatment group (n = 75 mycologically evaluable) are not tabulated as this dosage is not approved in the EU. Available as an abstract,[71] supplemented by data from a US FDA medical review.[72]

j Age of pts in mITT population: all pts who received at least one dose of study drug (n = 86 for L-AMB 3 mg/kg/d and n = 87 for AMBD 0.7 mg/kg/d). Only one paediatric patient (aged 10 years) participated in the study.

k L-AMB 3 mg/kg/d was noninferior to AMBD; the lower bound of the two-sided 95% CI for the between-group difference was above −20%.

AMBD = amphotericin B deoxycholate; **MFG** = micafungin; **mITT** = modified intent-to-treat; **PP** = per protocol; **pt** = patient. * p = 0.014 vs AMBD.

The AmBiLoad trial based the primary overall response assessment on clinical, radiological and microbiological (when available) findings, and included complete and partial responses as successful outcomes, with analyses conducted in the mITT population (see table V for definition and study design).[64] Statistical analyses were adjusted for duration of neutropenia and transplantation

status at baseline. Survival up to 12 weeks was a secondary endpoint of the study.

There was no significant difference in efficacy between liposomal amphotericin B 3 and 10 mg/kg/day in terms of the primary endpoint of a successful response (i.e. a complete or partial response) [table V]; the higher dosage was as effective as the standard dosage for treatment of invasive mould infections.[64] In the low-dose groups, 1% of patients experienced a complete response and 49% a partial response, whereas in the high-dose group, complete and partial responses were achieved by 2% and 44% of recipients.

The survival rate was not significantly different between liposomal amphotericin B 3 and 10 mg/kg/day recipients at the end of study treatment (93% vs 88%) or at 12 weeks after study entry (72% vs 59%).[64]

4.2.2 In Patients with Candidaemia or Invasive Candidiasis

The comparative efficacy of liposomal amphotericin B has been evaluated in well designed trials in adult (aged ≥16 years)[69] or paediatric (aged <16 years)[70] patients with candidaemia or invasive candidiasis (see table V for dosage and design details). Participants had clinical signs of systemic *Candida* spp. infection and at least one positive *Candida* spp. culture from blood or another sterile site within the previous 4 days. Treatment was planned to last a minimum of 14 days and a maximum of 4 weeks, or 8 weeks for patients with chronic disseminated candidiasis, *Candida* spp. osteomyelitis or endocarditis.[69,70]

In both studies, patient baseline characteristics and demographics were similar between treatment groups.[69,70] In the adults who received liposomal amphotericin B or micafungin, the most common underlying conditions were haematological disorders (13% and 19%), solid organ tumours (20% and 14%) and diabetes mellitus (12% and 12%).[69] In the paediatric study, the most common underlying conditions were haematological malignancies (22.2% and 28.8%; acute leukaemia was the most common [16.7% and 19.2%]), gastrointestinal disorders (14.8% and 19.2%) and premature birth (20.4% and 19.2%).[70] The incidence of neutropenia at baseline in liposomal amphotericin B and micafungin recipients was 10% and 13% in the study in adults[69] and 24.1% and 13.5% in the paediatric study.[70]

Patients who had received other systemic antifungal treatment for ≥3 days in the previous week (except neutropenic patients who could receive antifungal prophylaxis), or had transaminase levels ≥10× ULN or bilirubin levels ≥5× ULN were excluded.[69,70]

The primary endpoint was overall treatment success, which required a clinical and mycological response at the end of treatment.[69,70] The definition of clinical response was a complete or partial resolution of symptoms, and mycological response was defined as eradication or presumed eradication (i.e. when a patient had a complete clinical response but a biopsy for culture was contraindicated).[69,70] Secondary endpoints were not specified.[69,70]

Primary efficacy outcomes in the study in adults were assessed in the per-protocol (PP) population (see table V for definition).[69] Primary diagnosis and efficacy data were reviewed by a blinded independent data review board.[69] The trial was a noninferiority trial designed to determine if micafungin was noninferior to liposomal amphotericin B.[69] Noninferiority was demonstrated if the lower bound of the two-sided 95% CI for the between-group difference for micafungin versus liposomal amphotericin B, after adjustment for baseline neutropenic status, was above −15%.[69] The demonstration of noninferiority in the intent-to-treat (ITT) [those who received at least one dose of study drug] and mITT (those in the ITT population who had a confirmed *Candida* spp. infection at baseline) populations, in addition to the PP analysis, were deemed essential to conclude noninferiority.[69]

The trial in paediatric patients was part of the larger trial[69] and was intended to allow descriptive assessment of the comparative efficacy of micafungin and liposomal amphotericin B, but was not powered to determine noninferiority.[70] Outcomes were reported for the ITT, mITT and PP populations, with a focus on the mITT population (table V).[70]

In Adult Patients

Micafungin was noninferior to liposomal amphotericin B for the treatment of adults with candidaemia or invasive candidiasis, based on the primary efficacy population (i.e. PP population) [table V].[69] In the PP population, the between-group difference was 0.1% (95% CI −5.9, 6.2); the difference between groups after adjustment for neutropenic status at baseline was 0.7% (95% CI −5.3, 6.7). Analyses of differences between micafungin and liposomal amphotericin B recipients in the mITT (74.1% vs 69.6%; between-group difference after adjustment for baseline neutropenic status 4.9%; 95% CI −3.0, 12.8) and ITT (71.6% vs 68.2%; between-group difference after adjustment for baseline neutropenic status 3.9%; 95% CI −3.9, 11.6) populations also satisfied the criteria for noninferiority, as did the independent data review board analysis of the PP population (81.4% vs 80.4%; between-group difference after adjustment for baseline neutropenic status 1.8%; 95% CI −6.1, 9.6).[69]

Overall mycological persistence of *Candida* species was not significantly different between micafungin and liposomal amphotericin B recipients at the end of therapy in the PP population (9% vs 9%), and species specificity for mycological persistence appeared to be similar between treatment groups (statistical analysis not reported).[69] Seven micafungin and six liposomal amphotericin B recipients had recurrent *Candida* spp. infections during the 12 weeks following treatment. Mortality rates for micafungin or liposomal amphotericin B recipients in the ITT population were 18% and 17% during the treatment phase of the study, with 40% of patients in each group dying during the treatment phase and 12-week follow-up period. The fungal infections were thought to have contributed to death in 13% and 9% of micafungin or liposomal amphotericin B recipients (no significant difference between groups).[69]

In Paediatric Patients

There was no significant difference between liposomal amphotericin B and micafungin as first-line treatment of candidaemia or invasive candidiasis infections in paediatric patients, with over 70% of patients in the mITT population successfully treated (table V).[70] The difference in overall treatment success between micafungin and liposomal amphotericin B, adjusted for neutropenic status, was −2.4% (95% CI −20.1, 15.3).[70]

In both the liposomal amphotericin B and micafungin treatment groups in the mITT population, 15.6% (7 of 45 patients) of patients experienced mycologic persistence at the end of therapy.[70] Recurrence of fungal infection (same species and site as baseline) during the 12-week post-treatment follow-up occurred in three micafungin and no liposomal amphotericin B recipients. Mortality rates in the ITT population were 1.9% (1 of 52 patients) and 11.1% (6 of 54) during treatment with micafungin or liposomal amphotericin B, respectively, and 25.0% (13 of 52) and 24.1% (13 of 54) when the 12-week follow-up period was included. Fungal infections were considered to have contributed to death in 7.7% (4 of 52 patients) of micafungin recipients and 5.6% (3 of 54) of liposomal amphotericin B recipients.[70]

4.2.3 In Patients with Histoplasmosis and AIDS

Patients with AIDS who had moderate to severe disseminated histoplasmosis received a 2-hour intravenous infusion of liposomal amphotericin B or amphotericin B deoxycholate as therapy for histoplasmosis (table V).[68] Following successful induction therapy (primary endpoint) for up to 14 days, itraconazole was administered for 10 weeks as consolidation therapy. Patients with serum creatinine levels >2× ULN and ≥3 days prior treatment with ketoconazole, itraconazole, fluconazole or amphotericin B were excluded.

Clinical response was defined as a maximum daily temperature <37.8°C for 72 hours, no increase in severity of histoplasmosis symptoms and the resolution of at least one histoplasmosis symptom that qualified the patient for the study.[68] Survival rates were also assessed. Outcomes for successful induction therapy were assessed in the mITT population (see table V). Baseline characteristics did not differ significantly between treatment groups.[68]

In patients with AIDS, liposomal amphotericin B was significantly more effective than amphotericin B deoxycholate for induction treatment of moderate to severe disseminated histoplasmosis (table V).[68] The between-group difference in clinical success rates was 24% (95% CI 1, 52). During induction therapy, 2% (1 of 53) of liposomal amphotericin B recipients and 13% (3 of 24) of amphotericin B deoxycholate recipients died (p = 0.04).[68] The death in the liposomal amphotericin B group was due to bacteraemia, whereas the deaths in the conventional amphotericin group were due to progression of disseminated histoplasmosis.[68]

There were no significant differences between liposomal amphotericin B and amphotericin B deoxycholate recipients for secondary endpoints, including time to defervescence, rate of blood culture conversion (mycological efficacy), and change in urine and serum *H. capsulatum* antigen levels.[68]

4.2.4 In Patients with Cryptococcal Meningitis and AIDS

Patients with AIDS and confirmed acute cryptococcal meningitis received liposomal amphotericin B 3 or 6 mg/kg/day (6 mg/kg/day dosage not approved in the EU for this indication and not discussed further or tabulated) or amphotericin B deoxycholate 0.7 mg/kg/day as induction therapy for cryptococcal meningitis (table V).[71,72] Patients who had already received other antifungal treatment for the present meningitis infection were eligible for the study provided specified antifungal agents had been used and if treatment had been started ≤72 hours prior to study entry.

Study drugs were administered via intravenous infusion over 2–4 hours once daily for a planned duration of 14 days of uninterrupted therapy; the induction treatment phase was followed by consolidation therapy with fluconazole 400 mg/day (oral or intravenous) to complete an overall treatment period of 10 weeks.[72] Patients with systemic fungal infections other than cryptococcal meningitis, serum creatinine levels >2× ULN, or AST or ALT levels >10× ULN were excluded from the study.

The primary efficacy endpoint was the incidence of mycological success, which was defined as cerebrospinal fluid (CSF) culture conversion (negative for *C. neoformans*) in the mycologically evaluable population (see table V) at week 2.[72] Baseline characteristics did not differ significantly between treatment groups.

In patients with AIDS, liposomal amphotericin B was noninferior to amphotericin B deoxycholate for induction treatment of acute cryptococcal meningitis in terms of culture conversion at week 2 (table V).[72] The difference in mycological success rates between the liposomal amphotericin B 3 mg/kg/day and amphotericin B deoxycholate 0.7 mg/kg/day groups was 10.8% (95% CI −6.9, 28.5), which met the prespecified criteria for noninferiority (lower bound of 95% CI for between-group difference above −20%).

There was no significant difference between liposomal amphotericin B 3 mg/kg/day (86%) and amphotericin B deoxycholate (88%) recipients for the secondary endpoint of survival at week 10 (ITT population).[72] For the secondary endpoint of therapeutic success (clinical and mycological success) at week 10, liposomal amphotericin B 3 mg/kg/day did not meet the criteria for noninferiority to amphotericin B deoxycholate 0.7 mg/kg/day in either the therapeutically evaluable population (67.5% vs 75.5%; 95% CI for between-group difference −26.5, 10.5) or the mITT (as defined by the FDA) population (37% vs 53%; 95% CI for between-group difference −32.8, 1.5).[72] The therapeutically evaluable population consisted of mycologically evaluable patients who completed treatment or died during weeks 2–10 (n = 40 and 53) of the trial, the FDA mITT population was defined as those with a positive baseline CSF culture who received at least one dose of study drug (n = 73 and 76).[72]

5. Tolerability

This section focuses on the tolerability profile of liposomal amphotericin B at a dosage of 3 mg/kg/day versus amphotericin B deoxycholate, amphotericin B lipid complex, micafungin or caspofungin in the double-blind, multicentre trials discussed in section 4. One study in patients

with febrile neutropenia was specifically designed to assess safety; the primary endpoint was the incidence of infusion-related chills/rigors on day 1.[66] Survival was a secondary endpoint in some trials and is discussed in section 4.

Liposomal amphotericin B was generally at least as well tolerated as other lipid formulations of amphotericin B and better tolerated than amphotericin B deoxycholate. However, in adult patients, liposomal amphotericin B treatment was not as well tolerated as therapy with caspofungin or micafungin. On the other hand, in paediatric patients, liposomal amphotericin B treatment appeared to be as well tolerated as micafungin therapy.

As might be expected, higher than recommended dosages of liposomal amphotericin B are not as well tolerated as recommended dosages of liposomal amphotericin B. In the AmBiLoad trial, significantly more patients with invasive mould infections in the liposomal amphotericin B 10 mg/kg/day than in the 3 mg/kg/day group discontinued treatment due to adverse events (32% vs 20%; $p = 0.035$) or experienced nephrotoxicity (31% vs 14%; $p < 0.01$) or grade 3 hypokalaemia (blood potassium <3.0 mmol/L) [30% vs 16%; $p = 0.015$], although the incidence of infusion-related events (such as nausea, vomiting, fever, chills or hypersensitivity) did not differ significantly between treatment groups (overall incidence not reported).[64]

Treatment was discontinued due to adverse events by 5–20% of liposomal amphotericin B 3 mg/kg/day recipients in double-blind trials.[66-70,72] Discontinuation rates were not reported in two studies.[65,68] Significantly fewer liposomal amphotericin B (3 or 5 mg/kg/day) than amphotericin B lipid complex recipients discontinued treatment because of adverse events (12.7% vs 32.1%; $p = 0.001$).[66]

The percentage of patients who discontinued treatment due to drug-related adverse events was significantly higher in the liposomal amphotericin B group than in the caspofungin group (8.0% vs 5.0%; $p = 0.04$).[67] Discontinuation rates due to adverse events did not significantly differ between liposomal amphotericin B and micafungin groups in adult (9.0% vs 4.9%)[69] or paediatric (16.7% vs 3.8%)[70] patients with candidaemia or invasive candidiasis.

There were generally no significant between-group differences in the percentage of patients experiencing elevations from baseline in liver enzyme levels, including levels of transaminases, in clinical trials discussed in section 4.[65-67,69,70] However, significantly fewer caspofungin than liposomal amphotericin B recipients had an increase in serum alkaline phosphatase (7.0% vs 12.0%; between-group difference −5.1; 95% CI −8.5, −1.6) or serum creatinine (1.2% vs 5.5%; between-group difference −4.3; 95% CI −6.4%, −2.1%) levels or a decrease in potassium levels (7.3% vs 11.8%; between-group difference −4.5; 95% CI −7.9, −1.0).[67]

5.1 Infusion-Related Events

The most common adverse events reported with liposomal amphotericin B in the trials discussed in section 4 were infusion-related reactions or events, which were predominantly fever and chills or rigors, but also included nausea, vomiting and other events such as dyspnoea, hypotension, hypertension, tachycardia and flushing.[65-70,72] Premedication may reduce infusion-related reactions (section 6). Some studies did not allow premedication to prevent infusion-related events on day 1 of treatment, but premedication was allowed if required for subsequent infusions;[65-68] one study allowed medication for prophylaxis or treatment of infusion-related reactions,[72] and others did not state whether premedication was permitted or used.[69,70] Two studies reported infusion-related events on day 1 separately.[65,66]

5.1.1 Versus Other Amphotericin B Formulations

Liposomal amphotericin B treatment was associated with significantly fewer infusion-related adverse events than amphotericin B deoxycholate in patients with febrile neutropenia,[65] disseminated histoplasmosis (25% vs 63%; $p = 0.002$)[68] or cryptococcal meningitis (31.4% for liposomal amphotericin B 3 mg/kg/day vs 66.7% for amphotericin B 0.7 mg/kg/day; $p < 0.001$).[72] On day 1 of the study in patients with febrile neutropenia,

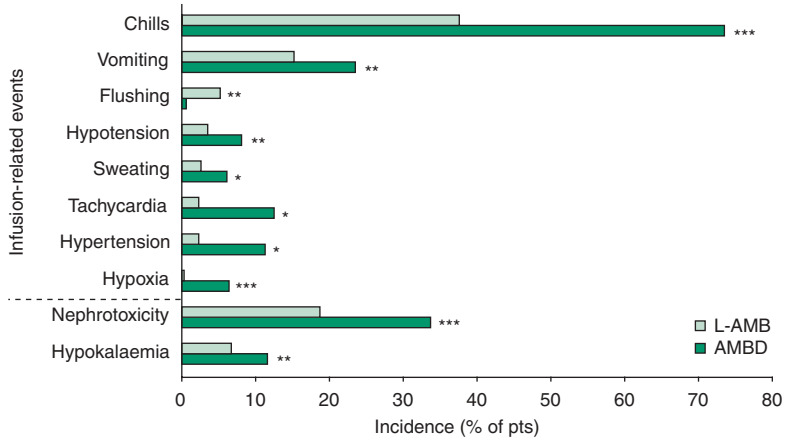

Fig. 1. Tolerability profile of liposomal amphotericin B (L-AMB) vs amphotericin B deoxycholate (AMBD) in patients (pts) with neutropenia and persistent fever. In this double-blind trial, patients were randomized to receive intravenous L-AMB 3 mg/kg/day (n = 343) or AMBD 0.6 mg/kg/day (n = 344) until recovery from neutropenia (mean 10.8 and 10.3 days, respectively).[65] Incidences during the entire treatment period of infusion-related events that occurred in >5% of pts in either treatment group and with a significant between-group difference, and of nephrotoxicity (defined as >2 × increase in serum creatinine level from baseline) and hypokalaemia (serum potassium ≤2.5 mmol/L). * $p \leq 0.05$, ** $p \leq 0.02$, *** $p \leq 0.001$ vs comparator.

significantly fewer liposomal amphotericin B than amphotericin B deoxycholate recipients experienced fever (increase ≥1.0°C) following infusion (16.9% vs 43.6% of infusions; $p \leq 0.001$), chills or rigors (18.4% vs 54.4%; $p \leq 0.001$) and other events (including dyspnoea, hypotension, hypertension, tachycardia, diaphoresis and flushing) [16.6% vs 23.8%; $p \leq 0.05$].[65]

Over the duration of treatment, the most common infusion-related reactions in the liposomal amphotericin B and amphotericin B deoxycholate groups were chills, nausea and vomiting.[65] Infusion-related reactions that occurred in >5% of patients in either treatment group and with a significant between-group difference are shown in figure 1.[65] As a consequence of the higher frequency of infusion-related reactions in the amphotericin B deoxycholate group, there was a significantly higher use of premedications (paracetamol [acetaminophen], diphenhydramine, pethidine, lorazepam or hydrocortisone) to prevent infusion-related reactions after day 1 in this group.[65] Grade 3 (severe) or 4 (life-threatening) toxic reactions (Southwestern Oncology Group Scale) that occurred in significantly fewer patients in the liposomal amphotericin B than the amphotericin B deoxycholate group were fever (7% vs 20.3%; $p < 0.001$), chills (10.2% vs 42.7%; $p < 0.001$), dyspnoea (5.8% vs 10.8%; $p < 0.05$), nausea (3.5% vs 7.3%; $p < 0.05$) and vomiting (1.2% vs 5.5%; $p < 0.01$).[65]

In patients with neutropenia and persistent fever, significantly fewer liposomal amphotericin B 3 mg/kg/day recipients than amphotericin B lipid complex recipients experienced chills/rigors (primary endpoint; 18.8% vs 79.5%; $p \leq 0.001$) or fever (23.5% vs 57.7%; $p \leq 0.001$) on day 1 of treatment, with the between-group difference in the incidence of these adverse events also being significant ($p \leq 0.001$) on days 2–5.[66] Furthermore, the overall incidence of infusion-related reactions was also significantly lower in liposomal amphotericin B 3 mg/kg/day recipients than in amphotericin B lipid complex recipients on day 1 (51.8% vs 88.5%; $p \leq 0.001$). Significantly fewer patients receiving liposomal amphotericin B 3 mg/kg/day than amphotericin B lipid complex required medications (paracetamol, pethidine, diphenhydramine and hydrocortisone) to treat infusion-related reactions (43.5% vs 73.1%; $p < 0.001$).[66]

5.1.2 Versus Echinocandins

Liposomal amphotericin B treatment was associated with significantly ($p < 0.001$) more infusion-related events than caspofungin in patients with

neutropenia and persistent fever (51.6% vs 35.1%).[67] In addition, significantly ($p < 0.05$) more liposomal amphotericin B than caspofungin recipients experienced chills (24.7% vs 13.8%), nausea (11.3% vs 3.5%), vomiting (8.6% vs 3.5%), dyspnoea (4.2% vs 2.0%) and flushing (4.2% vs 1.8%), although there was no significant between-group difference in the incidence of drug-related fever (19.4% vs 17.0%).[67]

In terms of infusion-related adverse events, liposomal amphotericin B treatment was as well tolerated as micafungin in paediatric patients with candidaemia or invasive candidiasis (18.5% vs 13.5%),[70] but not as well tolerated in another trial in adult patients with this type of infection (28.8% vs 17.0%; $p = 0.001$).[69] In adult patients, rigors (6.4% vs 0.8% in the micafungin group; $p = 0.0006$) and back pain (4.5% vs 0.4%; $p = 0.003$) also occurred with a higher frequency in the liposomal amphotericin B group.[69] Treatment was discontinued because of infusion-related events in one micafungin recipient and nine liposomal amphotericin B recipients.[69]

5.2 Nephrotoxicity and Hypokalaemia

The most serious adverse event associated with the use of all amphotericin B formulations, including liposomal amphotericin B, is nephrotoxicity.[73] Nephrotoxicity may be severe, and may lead to death or permanent renal damage and the need for renal dialysis.[73,74]

In studies discussed in section 4, nephrotoxicity was assessed by measurement of serum creatinine levels, and was generally defined as a greater than 2-fold increase in serum creatinine level from baseline.[65-67] Hypokalaemia was defined as a serum potassium level of <3 mmol/L,[66] ≤2.5 mmol/L[65] or was not defined.[67-70]

5.2.1 Versus Other Amphotericin B Formulations

The incidence of nephrotoxicity was significantly lower with liposomal amphotericin B than with other formulations of amphotericin B.[65,66,68,72] Nephrotoxicity occurred in significantly fewer patients with persistent fever and neutropenia who received liposomal amphotericin B than recipients of amphotericin B deoxycholate (figure 1)[65] or amphotericin B lipid complex (14.1% [3 mg/kg/day] and 14.8% [5 mg/kg/day] vs 42.3%; $p \leq 0.001$).[66] The incidence of nephrotoxicity was also significantly ($p = 0.003$) lower in patients with AIDS and disseminated histoplasmosis receiving liposomal amphotericin B (9%; 5 of 53) than in those receiving amphotericin B deoxycholate (38%; 9 of 24).[68] In patients with AIDS and cryptococcal meningitis, the incidence of nephrotoxicity (defined as serum creatinine >1.2 mg/dL and >2-fold increase from baseline) was significantly lower in liposomal amphotericin B 3 mg/kg/day than amphotericin B deoxycholate 0.7 mg/kg/day recipients (14.0% vs 33.3%; $p = 0.004$).[72]

Hypokalaemia was significantly less common in liposomal amphotericin B than in amphotericin B deoxycholate recipients with neutropenia and persistent fever (figure 1),[65] but the incidence was not significantly different between liposomal amphotericin B and amphotericin B lipid complex recipients in another trial (22.4% vs 37.2%).[66]

5.2.2 Versus Echinocandins

Liposomal amphotericin B treatment was associated with a significantly higher incidence of renal adverse events than caspofungin[67] or micafungin[69] in adult patients, although there was no significant difference observed in the incidence of these adverse events between the liposomal amphotericin B and micafungin groups in paediatric patients.[70] In one study in patients with neutropenia and persistent fever, nephrotoxicity was only evaluated in patients with a creatinine clearance of >30 mL/min (>1.8 L/h).[67] In this study, significantly more liposomal amphotericin B than caspofungin recipients experienced nephrotoxicity (11.5% vs 2.6%; $p < 0.001$).[67] In adult patients with candidaemia or invasive candidiasis, significantly ($p < 0.0001$) more liposomal amphotericin B (29.9%) than micafungin (10.3%) recipients experienced a change in serum creatinine from normal at baseline to high (>ULN) during study treatment, although there was no significant between-group difference in the percentage of patients whose serum creatinine

levels changed from normal at baseline to >2× ULN after treatment (3.7% vs 2.1%).[69] Furthermore, there was a significantly greater decrease in the mean peak estimated GFR in liposomal amphotericin B than in micafungin recipients (least squares mean difference between groups −17.6 mL/min/1.73 m^2; 95% CI −24.1, −11.1; $p < 0.0001$).[69] In paediatric patients with candidaemia or invasive candidiasis,[70] there were no significant between-group differences in terms of changes in serum creatinine levels from baseline or in the mean peak decrease in estimated GFR (−17.9 vs −2.6 mL/min/1.73 m^2; $n = 15$ liposomal amphotericin B and 21 micafungin recipients).

There were no significant differences in the incidence of hypokalaemia between liposomal amphotericin B and caspofungin (4.2% vs 3.7%) in adult patients,[67] or liposomal amphotericin B and micafungin in adult (12.0% vs 6.8%)[69] or paediatric (11.1% vs 5.8%)[70] patients.

6. Dosage and Administration

Intravenous liposomal amphotericin B is approved in many countries worldwide for the treatment of invasive fungal infections. Approved indications differ between countries and local prescribing information should be referred to for specific indications and dosage and administration details. As the drug was approved in many European countries based on a mutual recognition process, this section is based on the prescribing information of Ireland[5] (the reference label for the EU).

Because the various amphotericin B formulations (conventional amphotericin B and the lipid-associated formulations) have different requirements for reconstitution and dose administration, it is recommended that generic and tradenames are used when prescribing to ensure correct dosages and formulations are used.[75]

In the Irish product information, liposomal amphotericin B is indicated for the treatment of systemic mycotic infections that are susceptible to liposomal amphotericin B, which include cryptococcosis, North American blastomycosis, disseminated candidiasis, coccidioidomycosis, aspergillosis, histoplasmosis, zygomycosis and some cases of American mucocutaneous leishmaniasis; for the treatment of fever of unknown origin in patients with neutropenia; and as primary therapy for visceral leishmaniasis in immunocompetent or immunocompromised patients (indication not discussed in this review).[5]

Because of reports of anaphylaxis and anaphylactoid reactions with liposomal amphotericin B infusions, the Irish product information recommends administering an initial 1 mg test dose of liposomal amphotericin B by slow intravenous infusion (up to 10 minutes) and monitoring the patient for 30 minutes afterwards.[5]

In patients with systemic mycotic infections or neutropenia and fever of unknown origin, liposomal amphotericin B should be administered by intravenous infusion (over 30–60 minutes) at a starting dosage of 1 mg/kg/day.[5] The dosage may be increased stepwise to a maximum of 3 mg/kg/day as required. There is no recommended duration of treatment, but a cumulative dose of 1–3 g over 3–4 weeks is typical. Liposomal amphotericin B has been administered for up to 5 months (cumulative dose 30 g) with no significant toxicity.[5]

Liposomal amphotericin B may be administered to paediatric patients (>1 month old) at the same dosage based on bodyweight as that used in adults, and no changes to dosage are required in elderly patients or patients with renal impairment; administration of liposomal amphotericin B to renal dialysis patients should be avoided during the dialysis procedure.[5] Liposomal amphotericin B may be used in patients with diabetes, although it has a high sugar content (≈900 mg sucrose/vial).[5]

Infusion-related reactions may occur with liposomal amphotericin B treatment (section 5.1), but may be prevented by using slower infusion rates (2-hour infusion) or by the preadministration of other drugs such as diphenhydramine, paracetamol, pethidine and/or hydrocortisone.[5]

Nephrotoxicity may occur with liposomal amphotericin B treatment (section 5.2) and routine laboratory assessment of serum electrolytes and markers of renal, hepatic and haematopoietic function is recommended, particularly in patients

also receiving other nephrotoxic drugs (e.g. ciclosporin, aminoglycosides or pentamidine).[5] Reductions in dosage, or treatment interruption or discontinuation should be considered for patients who experience a decline in renal function or other parameters.[5] Concurrent administration of liposomal amphotericin B with nephrotoxic agents (e.g. ciclosporin, pentamidine, antineoplastic agents and aminoglycosides) may potentiate drug-induced nephrotoxicity.[5] Hypokalaemia associated with liposomal and other formulations of amphotericin B may be potentiated by concomitant use of corticosteroids, corticotropin and loop or thiazide diuretics.[5] In addition, coadministration with flucytosine may enhance flucytosine-related toxicity by potentially increasing the cellular uptake of flucytosine and/or impairing its renal excretion.[5]

Local prescribing information should be consulted for specific indications and dosage recommendations, reconstitution instructions, other contraindications, warnings and precautions, specific dosage recommendations in specific patient populations and drug interactions.

7. Place of Liposomal Amphotericin B as Empirical Therapy in Febrile Neutropenia and in the Treatment of Invasive Fungal Infections

Systemic treatment options for invasive fungal infections include the polyenes (amphotericin B deoxycholate and its lipid-associated formulations, including liposomal amphotericin B), the triazoles (voriconazole, itraconazole, fluconazole and posaconazole) and the echinocandins (caspofungin, micafungin and anidulafungin). Flucytosine is a nucleoside analogue that is used infrequently, usually in combination with amphotericin B for severe *Candida* spp. infections[76,77] or AIDS-associated cryptococcal meningitis.[78]

The choice of antifungal treatment will depend on the clinical status of the patient (e.g. the presence of underlying conditions such as haematological malignancies or neutropenia), concomitant therapy, prior antifungal use and, importantly, species identification.[76,79] Fungal pathogens should be identified to the species level, as initial treatment choice may need to be modified. Susceptibility testing is recommended for *Candida* spp. isolates, but not for *Aspergillus* spp. isolates.[79] Other factors to consider are tolerability, ease of administration and cost.

Patients with prolonged neutropenia due to chemotherapy or HSCT are at high risk of invasive fungal infections.[2,80] Early treatment of invasive fungal infections improves the likelihood of treatment success, but there may be few clinical signs of fungal infection other than a persistent fever despite broad-spectrum antibacterial treatment.[76] The practice of empirically treating patients with neutropenia who have had a persistently high temperature for several days, despite antibacterial therapy, for a presumed fungal infection has generally become accepted, although the evidence for benefits of empirical treatment is limited.[81]

In addition to empirical therapy or treatment for proven invasive fungal infections, other treatment strategies are antifungal prophylaxis in high-risk patients or pre-emptive treatment based on positive radiographic or laboratory tests indicative of an invasive fungal infection but without histopathological or culture identification of the pathogen.[82,83] Optimal treatment strategies for prevention and/or treatment of invasive fungal infections have not been established, although recommendations based on evidence from well controlled trials have been published recently.[82,83]

European guidelines for treatment of fungal infections include the recent update from the 2007 European Conference on Infections in Leukemia (ECIL)[2,79] and 2008 guidelines from the British Committee for Standards in Haematology (BCSH).[81] The guidelines from the Infectious Diseases Society of America (IDSA) are also discussed here; the aspergillosis treatment guidelines[84] were updated in 2008 and the candidiasis treatment guidelines[76] were updated in 2009. The major guidelines focus on *Candida* spp. or *Aspergillus* spp. infections, as these are the most common types of fungal infection. US guidelines for histoplasmosis[85] or cryptococcal meningitis[78] treatment are also available.

Liposomal amphotericin B and caspofungin are strongly recommended as empirical therapy for presumed fungal infections in patients with febrile neutropenia in the ECIL guidelines.[79] The BCSH guidelines also recommend liposomal amphotericin B or caspofungin if empirical antifungal treatment is given, but discourage empirical antifungal therapy generally, stating insufficient evidence of efficacy.[81] Other generally recommended options (with strong or moderate evidence for efficacy) for empirical antifungal therapy in the ECIL guidelines[79] are amphotericin B deoxycholate (in patients with no risk factors for nephrotoxicity), amphotericin B lipid complex and voriconazole, although voriconazole is not approved for this indication in the EU or the US.

In randomized, double-blind trials, intravenous liposomal amphotericin B provided effective empirical therapy in adult and paediatric patients with febrile neutropenia (section 4.1). Furthermore, it was as effective as amphotericin B lipid complex and appeared to be as effective as amphotericin B deoxycholate, although for the latter comparative trial the results of the statistical comparison for equivalence were not reported (section 4.1.1). In addition, empirical therapy with caspofungin was shown to be noninferior to liposomal amphotericin B therapy (section 4.1.2); liposomal amphotericin B was considered the appropriate comparator because it had been shown to be better tolerated than amphotericin B deoxycholate.[67]

Of note, in a randomized, nonblind, noninferiority trial, empirical treatment with voriconazole failed to meet the prespecified criteria to demonstrate its noninferiority to liposomal amphotericin B therapy in patients with neutropenia and persistent fever, and was therefore not approved for this indication.[63] There was some controversy regarding the way the outcomes of this trial[63] were reported (i.e. the emphasis placed on secondary outcomes) and the conclusions that were drawn by the authors (i.e. that voriconazole is an appropriate alternative to liposomal amphotericin B for empirical therapy).[80,86-91] This trial highlighted concerns regarding the use of the five-component composite endpoint as an indication of efficacy in empirical therapy trials because the resolution of fever component has a substantial impact on the overall outcome and may not be related to antifungal treatment.[80,92,93] It has been suggested that future trials should use prevention of breakthrough fungal infections, patient survival and treatment of baseline fungal infections to assess efficacy.[94] The arbitrary use between individual studies of different timepoints to distinguish baseline from breakthrough fungal infections has also been questioned.[86,92] Although it is not approved specifically for empirical therapy in patients with febrile neutropenia, voriconazole is still recommended as an empirical therapy option in European treatment guidelines, based on the decrease in breakthrough fungal infections seen in the voriconazole versus liposomal amphotericin B trial and because it is the recommended treatment option for invasive aspergillosis.[2]

For the treatment of candidaemia or invasive candidiasis, ECIL[79] and IDSA[76] guidelines recommend fluconazole, an echinocandin (caspofungin, anidulafungin or micafungin), amphotericin B deoxycholate, lipid-associated amphotericin B formulations or voriconazole as first- or second-line therapy. The IDSA guidelines recommend lipid-associated amphotericin B formulations as an option for primary therapy in neutropenic patients with candidaemia or suspected candidiasis, and as alternative therapy in nonneutropenic patients.[76] The ECIL guidelines recommend lipid-associated amphotericin B formulations, caspofungin or voriconazole over fluconazole and amphotericin B deoxycholate in patients with haematological malignancies and neutropenia.[79]

Voriconazole is strongly recommended as first-line treatment for invasive aspergillosis infections in the ECIL[79] and IDSA[84] guidelines. IDSA guidelines[84] recommend liposomal amphotericin B as an alternative primary treatment option in some patients. The ECIL guidelines[79] generally recommend (classification B) liposomal amphotericin B or amphotericin B lipid complex as an alternative option for primary therapy of invasive aspergillosis when voriconazole is

contraindicated. ECIL[79] and IDSA[84] guidelines include a general recommendation for liposomal amphotericin B as an option for salvage therapy of invasive aspergillosis, along with voriconazole (if not used first-line), amphotericin B lipid complex, caspofungin and posaconazole.

In adult and paediatric patients with invasive *Candida* spp. infections or AIDS-associated histoplasmosis or cryptococcal meningitis, recommended dosages of intravenous liposomal amphotericin B provided effective treatment, with 58–90% of patients experiencing a successful response in randomized double-blind trials (section 4.2). Moreover, in studies evaluating micafungin in patients with candidaemia or invasive candidiasis, micafungin was shown to be noninferior to liposomal amphotericin B treatment in adults; a smaller study in paediatric patients was not powered to determine noninferiority between these two agents (section 4.2.2); liposomal amphotericin B was chosen as the reference drug because of similar efficacy and improved tolerability compared with amphotericin B deoxycholate.[95] As induction therapy for moderate to severe disseminated histoplasmosis in patients with AIDS, liposomal amphotericin B treatment was more effective than amphotericin B deoxycholate (section 4.2.3), and liposomal amphotericin B was noninferior to amphotericin B deoxycholate for induction therapy of cryptococcal meningitis in patients with AIDS (section 4.2.4).

Because amphotericin B deoxycholate was the standard antifungal treatment for several decades, most trials in patients with invasive *Candida* spp. or *Aspergillus* spp. infections have compared newer antifungal agents with amphotericin B deoxycholate.[79] Hence, liposomal amphotericin B has not been directly compared with voriconazole in a well controlled trial for the treatment of aspergillosis. The positioning of voriconazole as first-line treatment for invasive aspergillosis in current treatment guidelines[79,84] was based on a nonblind trial that demonstrated the superiority of voriconazole to amphotericin B deoxycholate for the primary treatment of invasive aspergillosis.[96] This study has been criticized for its design,[86,97,98] notably the choice of amphotericin B deoxycholate as comparator instead of liposomal amphotericin B; however, liposomal amphotericin B was not licensed for primary therapy of aspergillosis when the study was planned.[99] Concerns were also raised over the large difference in treatment durations (10 days for amphotericin B deoxycholate vs 77 days for voriconazole), and the absence of premedications to minimize infusion-related events and fluid and electrolyte supplementation to reduce toxicity in amphotericin B deoxycholate recipients.[86,100]

It is not possible to draw conclusions from historical comparisons between different trials. Nonetheless, the treatment success and 12-week survival rates for liposomal amphotericin B 3 mg/kg/day (50% and 72%, respectively) in the AmBiLoad trial (section 4.2.1) appeared similar to those observed in the voriconazole group (52.8% and 70.8%) in the voriconazole versus amphotericin B deoxycholate study,[96] and this was considered evidence for the efficacy of liposomal amphotericin B in the treatment of invasive mould infection.[64] This claim has subsequently been questioned;[101] however, based on the results of the AmBiLoad trial, the ECIL and IDSA have recommended liposomal amphotericin B as alternative primary therapy for invasive aspergillosis when voriconazole is contraindicated.[79,84]

One of the major drawbacks to liposomal amphotericin B use is the potential for nephrotoxicity, which is reduced, but not eliminated, with liposomal amphotericin B compared with amphotericin B deoxycholate (section 5.2.1). The potential for nephrotoxicity must be considered, particularly when liposomal amphotericin B is coadministered with other potentially nephrotoxic agents (section 6). Fluid and electrolyte supplementation may reduce nephrotoxicity and infusion-related adverse events can be minimized or prevented by using premedication or by slowing the rate of infusion (section 6).

In double-blind trials, treatment with liposomal amphotericin B was associated with significantly fewer infusion-related events (section 5.1.1) and less nephrotoxicity (section 5.2.1) than amphotericin B deoxycholate or amphotericin B lipid

complex. In adult patients, significantly fewer caspofungin and micafungin recipients experienced infusion-related events (section 5.1.2) or nephrotoxicity (section 5.2.2) than liposomal amphotericin B recipients, although in paediatric patients there was no significant difference in the incidence of these adverse events between the liposomal amphotericin B and micafungin groups (sections 5.1.2 and 5.2.2).

There are few well controlled trials of amphotericin B deoxycholate versus the lipid-associated amphotericin B formulations, or directly comparing the lipid-associated formulations of amphotericin B, and much of the clinical data on these formulations are from nonblind studies, observational studies and retrospective reviews. IDSA[76,84] and ECIL[79] guidelines do not always distinguish between the lipid-associated amphotericin B formulations in their recommendations. However, preclinical data (section 2.2.2) and limited clinical data (sections 4.1.1, 4.2.3 and 4.2.4) suggest than liposomal amphotericin B is generally at least as effective as other lipid-associated formulations and amphotericin B deoxycholate, while being associated with a lower incidence of adverse events (sections 5.1.1 and 5.2.1). Although amphotericin B colloidal dispersion has not been compared directly with liposomal amphotericin B, amphotericin B colloidal dispersion was associated with a greater incidence of infusion-related adverse events than amphotericin B deoxycholate in clinical trials,[102,103] and is generally not recommended in treatment guidelines.[2,79,84]

The pharmacological properties of individual antifungal agents are important aspects to consider when deciding on the treatment to use. Amphotericin B has a broad spectrum of activity against most clinically relevant fungal isolates, including *Candida* spp., *Aspergillus* spp. and other filamentous fungi such as Zygomycetes (section 2.2.1). To date, the development of resistance to amphotericin B in *C. albicans* appears to be relatively uncommon. However, amphotericin B is less active against some fungal pathogens, notably *C. krusei* and *C. glabrata*, and some pathogens may be resistant (e.g. *A. terreus*) or may develop resistance to amphotericin B during treatment (e.g. *C. lusitaniae*) [section 2.2.3]. For some antifungal agents, the development of resistance is more of a concern; for example; with fluconazole many *C. krusei* and *C. glabrata* isolates are inherently resistant.[1] Voriconazole is active against *C. krusei*, *C. glabrata* and *A. terreus*, but is not active against Zygomycetes.[1]

Liposomal amphotericin B is the antifungal agent of choice for zygomycosis, based on *in vitro* and *in vivo* data, clinical experience and its improved tolerability compared with amphotericin B deoxycholate.[104] The rarity of zygomycosis infections mean that large clinical trials have not been possible. Of note, the echinocandins and most triazoles (apart from posaconazole) have no activity against Zygomycetes, with breakthrough infections being a problem.[105-107] Following historical use of amphotericin B deoxycholate at higher than normal dosages, higher than recommended dosages (10–15 mg/kg/day) of liposomal amphotericin B have been used to treat zygomycosis, although the optimal dosage of liposomal amphotericin B for the treatment of zygomycosis has not been established.[104]

The optimal dosage of liposomal amphotericin B for other types of fungal infections is also not known and recommended dosages vary between countries; for example, in the EU the approved dosage is 1–3 mg/kg/day (see section 6) whereas in the US approved dosages range between 3 and 6 mg/kg/day,[108] depending on the type of fungal infection. In contrast to data from animal studies which suggested higher liposomal amphotericin B dosages might improve efficacy, the AmBiLoad trial (section 4.2.1) found there was no difference in efficacy between a higher dosage of 10 mg/kg/day and the approved 3 mg/kg/day dosage for the treatment of invasive mould infections (mainly pulmonary aspergillosis), but the higher dosage was associated with more adverse events (section 5).[64]

Like the echinocandins, amphotericin B formulations must be administered intravenously, whereas most triazoles have the advantage of being available as an oral or intravenous formulation. With liposomal amphotericin B, a test dose should be given to check for anaphylactic

reactions and consideration should be given to the sugar content of the formulation in diabetic patients (section 6). It is important to ensure the correct amphotericin B formulation is given at the correct dosage, as all formulations have different requirements for reconstitution and dosing (section 6).

Amphotericin B formulations are approved for use in paediatric patients,[5,109-111] although, as might be expected, there is a lack of well controlled studies of liposomal amphotericin B in neonates.[112,113] Amphotericin B deoxycholate is the most commonly used antifungal drug in neonates with invasive fungal infections,[114] and liposomal amphotericin B has the potential to reduce nephrotoxicity or infusion-related adverse events in neonates compared with amphotericin B deoxycholate, although this has not been conclusively shown.[112]

Although the acquisition cost of liposomal amphotericin B and other newer antifungal agents (such as the echinocandins) is relatively high, consideration of acquisition cost alone (along with the clinical profile) is a superficial approach to evaluating the costs and benefits of therapy and greater insight may be provided by formal pharmacoeconomic analyses. Of the pharmacoeconomic analyses of liposomal amphotericin B available in the literature, only three fully published analyses were identified that incorporated approved European indications for the antifungal agents, appropriate comparative clinical data and recent European cost values (i.e. year 2005 or later).[115-117] These modelled studies were from a healthcare payer perspective (i.e. included only direct medical costs). Relative to the use of liposomal amphotericin B in the treatment of suspected systemic fungal infection in patients with febrile neutropenia, the use of caspofungin was predicted to be at least cost neutral in a German cost-comparison study[115] and cost effective in terms of the cost per quality-adjusted life year (QALY) gained in a UK cost-utility study.[116] Although the two drugs were considered to have similar efficacy in this indication, based on the noninferiority study by Walsh et al.[67] (section 4.1.2), liposomal amphotericin B was associated with a greater risk of nephrotoxicity (section 5.2.2), which increased medical costs[115,116] and reduced the number of QALYs gained[116] relative to caspofungin. In a German cost-effectiveness analysis of liposomal amphotericin B versus micafungin in the treatment of systemic candidiasis,[117] the between-treatment differences were not considered significant based on probabilistic sensitivity analyses. Modelled pharmacoeconomic analyses are subject to a number of inherent limitations, as they rely on a number of assumptions and results may not be applicable to other geographical regions. Nevertheless, the relative place of liposomal amphotericin B in each of its approved indications would be clarified by further well designed modelled and prospective pharmacoeconomic analyses.

In conclusion, liposomal amphotericin B is a broad-spectrum antifungal agent with activity against clinically relevant yeasts and moulds, including *Candida* spp., *Aspergillus* spp. and filamentous moulds such as Zygomycetes. In well controlled trials, liposomal amphotericin B had similar efficacy to amphotericin B deoxycholate and amphotericin B lipid complex as empirical therapy in adult and paediatric patients with febrile neutropenia. In addition, caspofungin was noninferior to liposomal amphotericin B as empirical therapy in adult patients with febrile neutropenia. For the treatment of confirmed invasive fungal infections, liposomal amphotericin B was more effective than amphotericin B deoxycholate treatment in patients with disseminated histoplasmosis and AIDS, and was noninferior to amphotericin B deoxycholate in patients with acute cryptococcal meningitis and AIDS. In adults, micafungin was shown to be noninferior to liposomal amphotericin B for the treatment of candidaemia and invasive candidiasis. Data from animal studies suggested that higher dosages of liposomal amphotericin B might improve efficacy; however, in the AmBiLoad trial in patients with invasive mould infection, there was no statistical difference in efficacy between the standard dosage of liposomal amphotericin B 3 mg/kg/day and a higher 10 mg/kg/day dosage, although the standard dosage was better tolerated.

Despite being associated with fewer infusion-related adverse events and less nephrotoxicity

than amphotericin B deoxycholate and amphotericin B lipid complex, liposomal amphotericin B use is still limited to some extent by these adverse events. Both echinocandins were better tolerated than liposomal amphotericin B. The cost of liposomal amphotericin B therapy may also restrict its use, but further pharmacoeconomic studies are required to fully define its cost effectiveness compared with other antifungal agents. Based on comparative data from well controlled trials, extensive clinical experience and its broad spectrum of activity, liposomal amphotericin B remains a first-line option for empirical therapy in patients with febrile neutropenia and in those with disseminated histoplasmosis, and is an option for the treatment of AIDS-associated cryptococcal meningitis, and for invasive *Candida* spp. or *Aspergillus* spp. infections.

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