

# Safety and efficacy of liposomal amphotericin B for the empirical therapy of invasive fungal infections in immunocompromised patients

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**Abstract:** Liposomal amphotericin B is a “true” liposomal formulation of amphotericin B with greatly reduced nephrotoxicity and minimal infusion-related toxicity. This broad spectrum polyene is well tolerated and effective against most invasive fungal infections. In view of the current limitations on diagnostic capability of invasive fungal infections, most clinicians are often compelled to use antifungal drugs in an empiric manner; liposomal amphotericin B continues to play an important role in the empiric management of invasive fungal infections, despite the recent availability of several other drugs in the azole and echinocandin classes.

**Keywords:** invasive fungal infections, immunocompromised hosts, empiric therapy, polyenes, efficacy and safety

## Introduction

Invasive fungal infections (IFIs) have become a leading cause of morbidity and mortality among immunocompromised patients.<sup>1</sup> The incidence of IFIs in these patient populations has increased dramatically over the past three decades. The most common fungal pathogens include *Candida albicans* and *Aspergillus fumigatus* and cryptococcus. However, uncommon pathogens such as non-*albicans* *Candida* spp, opportunistic yeast-like fungi (eg, *Trichosporon* and *Rhodotorula* spp), non-*fumigatus* *Aspergillus* spp, Mucorales and hyaline molds (eg, *Fusarium* and *Scedosporium* spp) are now emerging as not-so-uncommon opportunistic pathogens.<sup>2,3</sup> Etiologic identification of fungal pathogens is frequently difficult, particularly in compromised hosts, since reliable, noninvasive diagnostic tests are presently not available; such situations often compel the clinician to use drugs in an empiric fashion. However, the suspected fungal pathogens are often less susceptible to many antifungal agents including the “broadly-active” amphotericin B (AmB).<sup>4–8</sup> Thus, the choice of appropriate agents for empirical antifungal therapy has become a challenge; in the context of recently available, non-invasive diagnostic tests and newer antifungal drugs, the role of amphotericin B as a drug for empiric therapy has become less clear. This review will provide an overview of liposomal amphotericin B (L-AmB) and focus on efficacy studies as well as the safety and tolerability of this drug for the empiric treatment of IFIs.

## Management of IFIs in the immunocompromised host

Multiple factors have contributed to the new epidemiologic trends of IFIs, notably a growing number of immunocompromised states (ie, cancer, hematologic stem cell

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and solid organ transplantation, major surgeries, acquired immune deficiency syndrome, the elderly, etc), the advent of potent immunosuppressant drugs and their widespread use, and the use of antifungal prophylaxis.<sup>9–12</sup>

In contrast to most bacterial infections, the diagnosis of IFIs is challenging. Delay in diagnosis leads to delayed initiation of appropriate antifungal therapy and, hence, increased mortality. In this setting, early and definitive diagnosis is critical in the management of IFIs. However, clinical presentation of IFIs is often nonspecific; moreover, signs and symptoms could be absent in the early stages of the disease. Fever without signs of localized infection is the most common clinical presentation.<sup>13</sup> Fever is of particular concern in severely immunosuppressed patients such as those with profound and prolonged neutropenia following chemotherapy for cancer. Radiographic signs and laboratory tests such as galactomannan and 1,3-beta-D-glucan are used as surrogate markers for the diagnosis and management of IFIs.<sup>14,15</sup>

Prompt initiation of appropriate antifungal therapy of IFIs is crucial for optimal outcome. Current strategies for the management of IFIs include prophylactic, empiric, pre-emptive, and targeted therapy<sup>15,16</sup> (Figure 1). Prophylactic strategy includes administration of a narrow- or broad-spectrum antifungal drug (active against yeasts or yeasts and molds) to high-risk patient population before the onset of signs/symptoms of infection. Empirical antifungal therapy is often initiated when a microbiological diagnosis of IFI is

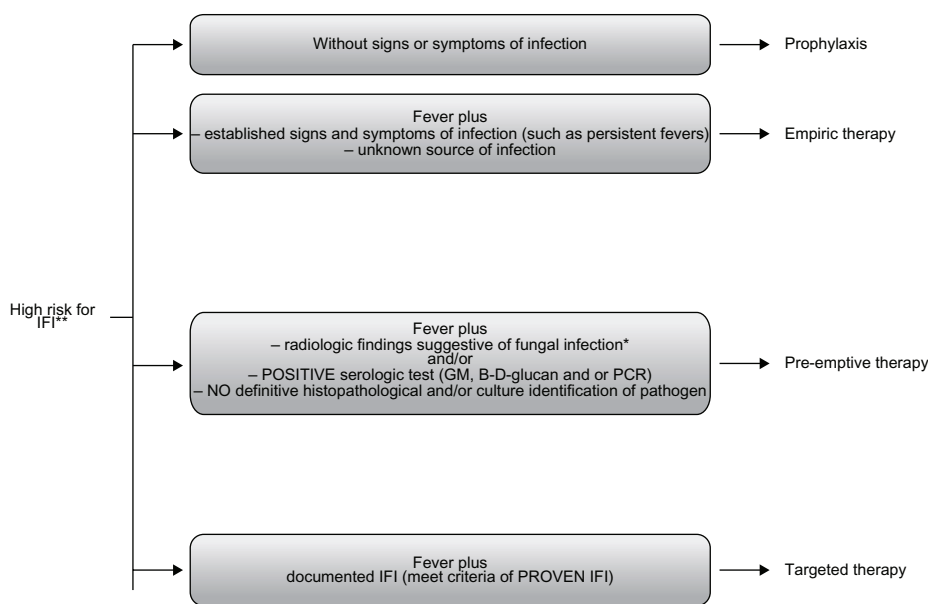
unavailable in high-risk presently neutropenic patients presenting with persistent or recurring fevers despite 4–7 days of appropriate antibiotic therapy (duration of neutropenia expected to be more than 7 days).

Pre-emptive therapy is initiated when suggestive but nonspecific radiographic signs are present and/or laboratory tests are suggestive of IFIs, without microbiological or histopathological confirmation of IFI. Targeted therapy is initiated when there is microbiologically and/or histologically proven IFI.<sup>15,16</sup>

## Antifungal drugs

There are three main classes of systemic antifungal drugs available for the treatment of IFIs: polyenes, azoles, and echinocandins. Azoles deplete ergosterol and compromise fungal cell-wall integrity by dose-dependent inhibition of cytochrome-P450-dependent 14 $\alpha$ -demethylase.<sup>17</sup> Currently available systemic azoles include fluconazole, itraconazole, voriconazole, and posaconazole. Echinocandins are compounds that disrupt cell-wall synthesis by inhibiting the synthesis of 1,3-beta-D-glucan, which is a critical component of most fungal cell walls.<sup>18</sup> Echinocandins include caspofungin, anidulafungin, and micafungin. Azoles and echinocandins are relatively safe and well tolerated.<sup>18,19</sup>

The polyenes include conventional amphotericin B (AmB-D) and lipid formulations of amphotericin B (amphotericin B lipid complex [ABLC], L-AmB, and amphotericin B collo-



**Figure 1** Current strategies for the management of IFI in high-risk patients.

**Notes:** \*High-resolution computed tomography scan of the lungs showing new  $\geq 1$  cm single or multiple nodules with or without halo sign, lobar consolidation, wedge-shaped consolidative infarct; \*\*classic example: patients with prolonged and profound neutropenia after intense chemotherapy for hematologic malignancy.

**Abbreviations:** GM, serum Galactomannan; IFI, invasive fungal infection; PCR, polymerase chain reaction.

dal dispersion [ABCD] formulations).<sup>20</sup> AmB-D binds with sterols, principally ergosterol in the fungal cell membrane. This binding is followed by increased leakage of intracellular ions out of the fungal cells resulting in osmotic disruption with increased membrane permeability and, ultimately, cell death. Polyenes also interfere with membrane-associated oxidative enzyme function, which is also lethal for the cell.<sup>20</sup>

Lipid formulations of amphotericin B were developed to decrease toxicity and improve the tolerability profile of AmB-D. Lipid formulations of amphotericin B have different structures. ABLC has a ribbon-like structure, ABCD is composed of disc-like structures, and L-AmB forms small uniform spherical lipid vesicles or liposomes containing amphotericin B.<sup>21</sup> The three formulations produce tissue amphotericin B concentrations ranging from 90% lower than, to 500% higher than the serum levels seen with AmB-D. Most consistently, reduced concentrations are seen in the kidney, thus accounting for the markedly lower nephrotoxicity. The doses of lipid forms of amphotericin B are higher than that of amphotericin B deoxycholate; such high but equipotent doses are better tolerated and there is also a clear reduction in the frequency and severity of nephrotoxicity.

### Spectrum of activity: amphotericin B

Despite the differences in the structures of lipid formulations and AmB-D, their spectrum of activity is comparable.<sup>22</sup> Amphotericin B is active against clinically relevant yeasts such as most *Candida* spp and *Cryptococcus neoformans* and molds, including most *Aspergillus* spp and Mucorales. AmB is also active against *Histoplasma* spp, *Paracoccidioides* spp, *Blastomyces* spp, and *Coccidioides* spp.<sup>20</sup>

Several *Candida* species such as *Candida lusitanae*, *Candida guilliermondii*, and *Candida rugosa* may be resistant to AmB.<sup>23–25</sup> Also, *Trichosporon* spp, an infrequent cause of catheter-related fungemia, are resistant to AmB.<sup>26,27</sup>

Non-*fumigatus* *Aspergillus* spp, in particular *Aspergillus terreus*, *Aspergillus flavus* and *Aspergillus nidulans*, have demonstrated clinical resistance to AmB.<sup>28–30</sup> Similarly, *Aspergillus ustus* is an uncommon clinical species that may have decreased susceptibility to AmB.<sup>31–33</sup> However, *Aspergillus lentulus*, a recently described *Aspergillus* species, has demonstrated variable in vitro susceptibility to AmB.<sup>34,35</sup> AmB has limited activity against *Fusarium* spp (especially *Fusarium solani*), although it has better activity as compared with other agents such as the older azoles (eg, Itraconazole) and echinocandins.<sup>8,36,37</sup> Mucorales are susceptible to AmB – the drug has been the drug of choice for the treatment of mucormycosis; however, clinical response

has been variable and the overall mortality of patients with mucormycosis has remained high, particularly in patients with persistent immunosuppression or poor source control. A newer azole, posaconazole is active against most Mucorales and appears to be promising for the treatment of this disease.<sup>8,38</sup> Isavuconazole, a more recent broad-spectrum azole, available in oral and parenteral forms, is under clinical investigation. *Scedosporium* spp are intrinsically resistant to AmB. While *Scedosporium apiospermum* is susceptible to itraconazole, voriconazole, and posaconazole, *Scedosporium prolificans* is considered resistant to all available antifungal agents.<sup>39,40</sup> Limited data are available to support the optimal antifungal therapy against *Acremonium* spp. Clinically relevant species of *Acremonium*, *Alternaria*, *Cladosporium* and *Exophiala* have demonstrated high minimal inhibitory concentrations for AmB.<sup>41</sup>

### Safety and tolerance: L-AmB

Conventional amphotericin B (AmB-deoxycholate [AmB-D]) was considered the gold standard of antifungal treatment for many decades. Infusion-related reactions and dose-dependent nephrotoxicity are major limitations of this drug.<sup>21</sup> Indeed, these side effects are associated with increased morbidity in immunocompromised patients.<sup>42</sup> Other toxicities reported with the use of AmB-D include local thrombophlebitis, nausea and vomiting, and anemia. Less frequently, hepatotoxicity (ie, transient elevation of transaminase levels and acute liver failure) has been associated with the use of AmB-D.<sup>42</sup>

In general, all lipid formulations of AmB have been associated with reduced nephrotoxicity compared with AmB-D.<sup>21,43,44</sup> White et al reported a randomized, double-blind multicenter superiority trial in which ABCD (4 mg/kg/d) was compared with AmB-D (0.8 mg/kg/d) for the empiric management of febrile neutropenia.<sup>43</sup> Therapeutic response was similar (43%–50%), but renal dysfunction was less likely to develop and occurred later in ABCD recipients ( $P < 0.001$  for both parameters). Infusion-related hypoxia and chills were more common in ABCD recipients than AmB-D recipients ( $P = 0.013$  and  $P = 0.018$ , respectively). In clinical practice, in view of its frequent infusion-related intolerability, ABCD is not favored.

In a randomized, double-blind comparative study, Wingard et al evaluated the safety of L-AmB versus ABLC in the empirical treatment of febrile neutropenia.<sup>45</sup> In this study, L-AmB at a dose of 3 or 5 mg/kg/d was associated with significantly fewer infusion-related reactions and other toxicities (ie, nausea, vomiting) when compared to ABLC at a dose of 5 mg/kg/d. There was nonsignificant difference in

the rates of hepatotoxicity, hypokalemia, and anemia between patients receiving either ABLC or L-AmB. Since the publication of Wingard et al's study, it has been widely believed that L-AmB is less nephrotoxic than ABLC. However, in a recently published study, Safdar et al conducted a meta-analysis to evaluate nephrotoxicity associated with ABLC and L-AmB.<sup>46</sup> After adjusting for heterogeneity across the studies included in the meta-analysis, the authors found that the nephrotoxicity was similar for ABLC and L-AmB in patients receiving either drug as antifungal therapy or prophylaxis.

While all three lipid formulations of AmB exhibit reduced nephrotoxicity compared with AmB-D, L-AmB appears to be the safest in terms of infusion-related reactions. Table 1 summarizes the current US Food and Drug Administration (FDA)-approved indications for the use of L-AmB and all available antifungal agents.

## Empirical therapy: liposomal amphotericin B (L-AmB)

The strategy of empirical antifungal therapy has been systematically evaluated only in the setting of antibiotic-refractory fever in patients with chemotherapy-induced neutropenia. Table 2 summarizes the clinical trials of L-AmB in the empiric management of fever in neutropenic patients.

In a randomized trial by Walsh et al, L-AmB was as effective as AmB-D for the empirical therapy of fever in adult and pediatric neutropenic patients.<sup>47</sup> In this study, 687 patients were randomized to empirical treatment with L-AmB at a dose

of 3.0 mg/kg/d or AmB-D at 0.6 mg/kg/d.<sup>47</sup> Rates of successful treatment were similar (50.1% for patients receiving L-AmB and 49.4% for those receiving AmB-D.) Rates of survival were also similar (93% for L-AmB and 90% for AmB-D). Significantly, the use of L-AmB was associated with fewer proven breakthrough IFIs (11 patients [3.2%]) compared to patients receiving AmB-D (27 patients [7.8%],  $P = 0.009$ ).

As previously discussed, Wingard et al conducted a randomized, double-blind comparative study of L-AmB (3–5 mg/kg/d) versus ABLC (5 mg/kg/d) in the empirical treatment of febrile neutropenia.<sup>45</sup> Among 244 patients included, actual response rates were 40% (3 mg/kg/d) and 42% (5 mg/kg/d) for L-AmB, and 33% for ABLC. While the primary endpoint in this study was the incidence of infusion-related reactions, the authors found no significant differences in successful response and survival in both adult and pediatric patients.<sup>45</sup>

With the introduction of new classes of antifungal agents, the efficacy of L-AmB for empirical therapy has been compared with that of caspofungin<sup>48–50</sup> and voriconazole.<sup>51</sup> Many prospective, randomized, multicenter comparative trials evaluating echinocandins have been published<sup>48,49,51</sup> (Table 2). In these studies, efficacy assessment was based on a composite endpoint consisting of five criteria: (1) successful treatment of any baseline fungal infection, (2) absence of any breakthrough fungal infection during therapy or within 7 days after the completion of therapy, (3) survival for 7 days after the completion of therapy, (4) no premature discontinuation of study therapy because of drug-related toxicity or lack of efficacy,

**Table 1** US Food and Drug Administration-approved indication of antifungal agents for the management of IFIs

| Indication                                      | Echinocandins |                  |      | Newer azoles |      | Polyenes         |                   |                  |                  |
|---|---------------|------------------|------|--------------|------|------------------|-------------------|------------------|------------------|
|   | CAS           | MICA             | ANID | VOR          | POS  | AmB-D            | ABLC              | ABCD             | L-AmB            |
| Empiric treatment of invasive fungal infections | YES           |                  |      |              |      |                  |                   |                  | YES              |
| Prophylaxis of <i>Candida</i> infections        |               | YES <sup>§</sup> |      |              | YES* |                  |                   |                  |                  |
| Prophylaxis of invasive aspergillosis           |               |                  |      |              | YES* |                  |                   |                  |                  |
| Target therapy of invasive aspergillosis        | YES           |                  |      | YES          |      | YES <sup>†</sup> | YES <sup>++</sup> | YES <sup>‡</sup> | YES <sup>°</sup> |
| Target therapy of mucormycosis                  |               |                  |      |              |      | YES <sup>†</sup> | YES <sup>++</sup> |                  |                  |
| Salvage treatment of IFIs                       |               |                  |      | YES•         |      |                  | YES <sup>++</sup> |                  |                  |
| Oropharyngeal candidiasis                       | YES           | YES              | YES  | YES          |      |                  | YES <sup>++</sup> |                  | YES <sup>°</sup> |
| Invasive candidiasis                            | YES           | YES              | YES  | YES••        |      | YES <sup>†</sup> | YES <sup>++</sup> |                  | YES <sup>°</sup> |

**Notes:** \*In patients aged  $\geq 13$  years, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem-cell transplant recipients with graft versus host disease or those with hematologic malignancies with prolonged neutropenia from chemotherapy; <sup>§</sup>in patients undergoing allogeneic hematopoietic stem-cell transplant; <sup>†</sup>infections with *Scedosporium* spp and *Fusarium* spp in patients refractory to or intolerant of other agents. <sup>°</sup>in nonneutropenic patients. <sup>†</sup>AmB-D is approved for the treatment of potentially life-threatening fungal infections: aspergillosis; cryptococcosis (torulosis); North American blastomycosis; systemic candidiasis; coccidioidomycosis; histoplasmosis; and zgomycosis including mucormycosis due to susceptible species of the genera *Absidia*, *Mucor*, and *Rhizopus* and infections due to related susceptible species of *Conidiobolus* and *Basidiobolus*, and sporotrichosis; <sup>††</sup>ABLC approved for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B; <sup>‡</sup>ABCD is approved for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of conventional amphotericin B; <sup>°</sup>L-AmB (AmBisome) is approved for the treatment of patients with *Aspergillus* spp, *Candida* spp, and/or infections due to *Cryptococcus* spp refractory to conventional AmB or in patients with marked renal impairment or when severe toxicity precludes the use of conventional AmB; also approved for the treatment of cryptococcal meningitis in human immunodeficiency virus–infected patients and visceral leishmaniasis.

**Abbreviations:** ABCD, amphotericin B colloidal dispersion; AmB-D, amphotericin B deoxycolate; ABLC, amphotericin B lipid complex; ANID, anidulafungin; CAS, caspofungin; IFIs, invasive fungal infections; L-AmB, liposomal amphotericin B; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

**Table 2** Summary of clinical trials comparing efficacy and safety of liposomal amphotericin B with other antifungal agents for empirical antifungal therapy in patients with neutropenia and persistent fevers

| Reference/<br>type of study  | Treatment regimen<br>(dose)  | Number<br>of patients | Mean age<br>(range)   | Patient<br>population<br>(% of patients)  | Mean<br>duration of<br>treatment     | Renal toxicity <sup>‡</sup><br>(% of patients)   | Infusion related<br>reactions <sup>†</sup><br>(% of patients)                         | Treatment<br>success rate*<br>(% of patients)        | Comments   |
|--|--|-----------------------|---|---|--------------------------------------|--|---|--|--|
| Walsh <sup>47</sup><br>Randomized,<br>double blind,<br>multicenter<br>clinical trial   | L-AmB<br>(3 mg/kg/d)<br>Amb-D<br>(0.6 mg/kg/d)   | 343                   | 41<br>(2-79)<br>42<br>(2-80)  | HSCt: 45%<br>Non-HSCt: 55%<br>HSCt: 47%<br>Non-HSCt: 53%  | 10.8 days<br>10.3 days               | 19%<br>34%<br>( <i>P</i> < 0.001)  | 17% <sup>§</sup><br>44% <sup>§</sup><br>( <i>P</i> < 0.001)                           | 50.1%<br>[95% CI: 45-56]<br>49.4%<br>[95% CI: 44-55] | L-AMB was associated<br>with significant reduction<br>of breakthrough infections<br>(mostly non- <i>albicans</i><br><i>Candida</i> infections)<br>Study designed to<br>detect differences<br>in toxicity, not efficacy.<br>Breakthrough infection<br>rates were similar in<br>three groups.<br>Breakthrough IFI<br>occurred in 8 patients<br>on voriconazole and<br>21 patients on L-AmB<br>( <i>P</i> = 0.02).<br>Hepatotoxicity was<br>similar in both groups. |
| Wingard <sup>45</sup><br>Randomized,<br>double blind,<br>multicenter<br>clinical trial | L-AmB<br>(3 mg/kg/d)<br>L-AmB<br>(5 mg/kg/d)<br>ABLC<br>(5 mg/kg/d)  | 85<br>81<br>78        | 41.4<br>(3-74)<br>42<br>(2-84)<br>42.8<br>(2-76)<br>46.3<br>(12-82) | HSCt: 46%<br>Non-HSCt: 54%<br>HSCt: 49%<br>Non-HSCt: 51%<br>BMT: 51%<br>Non-BMT: 49%<br>HSCt: 47.7% | 8 days<br>8 days<br>8 days<br>7 days | 14.1%<br>14.8%<br>42.3%<br>( <i>P</i> ≤ 0.01)  | 51.8% <sup>†</sup><br>48.1% <sup>†</sup><br>88.5% <sup>†</sup><br>( <i>P</i> ≤ 0.001) | 40%<br>42%<br>33.3%<br>26%                           | Abnormal vision<br>22%<br>Flushing 3.4%<br>Chills 13.7%  |
| Walsh <sup>51</sup><br>Randomized,<br>open labeled,<br>multicenter<br>clinical trial   | Voriconazole<br>6 mg/kg IV Q12 h<br>on day 1,<br>then 3 mg/kg IV Q12 h<br>or 200 mg PO after<br>at least 3 days of<br>IV therapy | 415                   | 45<br>(12-80)   | HSCt: 51.4%   | 7 days                               | With concomitant<br>Nephrotoxic drugs <sup>‡</sup> :<br>0-1 drugs: 11.3%<br>≥2 drugs: 14.3%<br>≥3 drugs: 50% | Abnormal vision<br>22%<br>Flushing 10.9%<br>Chills 29.9%<br>( <i>P</i> < 0.001)       | 30.6%  | With concomitant<br>Nephrotoxic drugs <sup>‡</sup> :<br>0-1 drugs: 9.7%<br>≥2 drugs: 39%<br>≥3 drugs: 60%<br>( <i>P</i> < 0.001)   |
| Walsh <sup>48</sup><br>Randomized,<br>double blind,<br>multicenter<br>clinical trial   | Caspofungin<br>(70 mg in day 1 and<br>then 50 mg/d)<br>L-AmB<br>(3 mg/kg/d)  | 556<br>539            | 51<br>(17-83)<br>49<br>(16-83)                                      | Acute leukemia:<br>75.8%<br>(Allo-HSCT: 6.5%)<br>Acute leukemia:<br>72.2%<br>(Allo-HSCT: 7.2%)      | 13 days<br>12.5 days                 | 2.6%<br>11.5%<br>( <i>P</i> < 0.001)   | 47%<br>59%<br>( <i>P</i> < 0.001)   | 33.9%<br>33.7%                                       | Most patients included<br>in the study had acute<br>leukemia.<br>Breakthrough<br>infections were similar<br>in both groups.  |

(Continued)

Table 2 (Continued)

| Reference/<br>type of study                                   | Treatment regimen<br>(dose)  | Number<br>of patients | Mean age<br>(range) | Patient<br>population<br>(% of patients)                             | Mean<br>duration of<br>treatment | Renal toxicity <sup>‡</sup><br>(% of patients) | Infusion related<br>reactions <sup>†</sup><br>(% of patients) | Treatment<br>success rate*<br>(% of patients) | Comments   |
|---|--|-----------------------|---------------------|--|----------------------------------|--|---|---|--|
| Maertens <sup>49</sup>  | Caspofungin  | 56                    | 6<br>(2–16)         | Acute leukemia:<br>60.7%   | 11.6 days                        | 5.5%   | 48.2%   | 46.6%   | Study conducted<br>exclusively in pediatric<br>population.                                   |
| Randomized,<br>double blind,<br>multicenter<br>clinical trial | (70 mg/m <sup>2</sup> on day 1,<br>then 50 mg/m <sup>2</sup> daily)<br>L-AmB (3 mg/kg/d) | 26                    | 5.5 (2–16)          | (Allo-HSCT: 10.7%)<br>Acute leukemia:<br>65.4%<br>(Allo-HSCT: 65.4%) | 11.4 days                        | 8%   | [95% CI:<br>34.7–62.0]<br>46.2%                               | [95% CI:<br>33.5–59.6]<br>32.2%               | Limitation: small sample.<br>Only 1 patient in L-AmB<br>group had breakthrough<br>infection. |

**Notes:** <sup>†</sup>Infusion related reactions include fevers, chills, hypotension, chest pain, tachycardia, etc; <sup>‡</sup>nephrotoxic effect was defined by an elevation in the serum creatinine level to more than 1.5 times the base-line value; <sup>\*</sup>treatment success rate was determined by a composite outcome score consisting of five criteria: (1) successful treatment of any baseline fungal infection, (2) absence of any breakthrough fungal infection during therapy or within seven days after the completion of therapy, (3) survival for 7 days after the completion of therapy, (4) no premature discontinuation of study therapy because of drug related toxicity or lack of efficacy, and (5) resolution of fever during neutropenia. Treatment was considered successful if all five criteria were met. <sup>†</sup>Infusion-related reactions on day 1 study drug infusion; <sup>‡</sup>fevers within 1 hour of drug infusion (increase of  $\geq 1.0^{\circ}\text{C}$ ); overall rate of infusion-related reactions was not provided; <sup>†</sup>nephrotoxic drugs were aminoglycosides, cyclosporine, and foscarnet.

**Abbreviations:** ABLC, amphotericin B lipid complex; AmB-D, amphotericin B deoxycolate; CI, confidence interval; L-AmB, liposomal amphotericin B; BMT, bone marrow transplant; Allo, allogeneic; HSCT, hematological stem cell transplant.

and (5) resolution of fever during neutropenia. Treatment was considered successful if all five criteria were met.<sup>47</sup>

In a randomized, double-blind multicenter trial of 1095 patients with persistent fever and neutropenia, Walsh et al showed that caspofungin was as effective as L-AmB.<sup>48</sup> The overall success rates were 33.9% for caspofungin and 33.7% for L-AmB (95.2% confidence interval: -5.6 to 6.0) caspofungin improved survival (92.6% and 89.2% for caspofungin and L-AmB, respectively;  $P = 0.05$ ) and response rates in patients with IFIs (51.9% vs 25.9%;  $P = 0.04$ ). Breakthrough fungal infections were similar in the two groups. Also resolution of fever during the period of neutropenia was comparable. Fewer patients in the caspofungin group encountered nephrotoxicity and there were fewer infusion-related events or premature discontinuations of therapy. The authors concluded caspofungin to be as effective as L-AmB.

More recently, Maertens et al reported the results of a randomized, double-blind multicenter trial comparing empirical therapy with caspofungin versus L-AmB in pediatric patients.<sup>49</sup> In this study, patients were randomized to receive caspofungin (70 mg loading dose on day 1 followed by 50 mg/d) or L-AmB (3 mg/kg/d). Although the main endpoint of this study was safety, clinical efficacy was also evaluated. Overall success rates were similar across treatment groups (46.4% and 32% for caspofungin and L-AmB, respectively).

Walsh et al conducted a randomized, nonblinded multicenter trial among febrile neutropenic patients comparing empirical antifungal therapy with L-AmB versus voriconazole.<sup>51</sup> In this study, voriconazole failed to meet the prespecified criteria for noninferiority to L-AmB. A total of 837 patients (415 assigned to voriconazole and 422 to L-AmB) were evaluated for success of treatment. Based upon prespecified criteria, voriconazole was inferior to L-AmB with overall success rates of 26% with voriconazole and 30.6% with L-AmB (95% confidence interval: -10.6 to 1.6). Importantly, however, documented breakthrough IFIs occurred less frequently among voriconazole recipients – eight patients (1.9%) in the voriconazole group versus 21 patients (5%) in the L-AmB group ( $P = 0.02$ ). After stratifying for risk, overall success rates were 32% and 30% for high-risk patients receiving voriconazole and L-AmB, respectively. The authors concluded that voriconazole is a suitable alternative to L-AmB for empiric antifungal therapy in patients with neutropenia and persistent fever.

Because of its broad spectrum of activity, rarely documented resistance, and long track record of clinical efficacy, AmB-D has been the standard choice for the empirical treatment in patients with persistent fever and

neutropenia for many decades. However, antifungal agents that have become available over the past 15 years are less toxic and are as effective as AmB-D in the empiric treatment of IFIs.<sup>45,47–51</sup> Indeed, based on the data discussed, L-AmB and caspofungin have now been approved by the FDA for the empiric antifungal therapy in febrile neutropenic patients.<sup>52,53</sup>

All echinocandins are safe, well tolerated, and have a similar spectrum of antifungal activity. However, FDA-approved indications of these drugs differ.<sup>52,53</sup> Caspofungin is approved for empirical therapy of febrile neutropenia and for the treatment of invasive aspergillosis in patients refractory to or intolerant to other approved drugs.<sup>53</sup> Micafungin, however, has been approved for antifungal prophylaxis in stem-cell transplantation. Limited data suggest that the safety and efficacy of caspofungin and micafungin are comparable in the empiric treatment of invasive aspergillosis, but micafungin has not been licensed for this use.<sup>54</sup> Similarly, despite the widespread use of voriconazole as empiric therapy and prophylaxis of IFIs, voriconazole is not FDA approved for these indications.<sup>55</sup> Posaconazole, based on available data, has been approved for the prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk, severely immunocompromised adult patients.<sup>55</sup>

In summary, the three lipid formulations of AmB have demonstrated similar efficacy and fewer adverse events compared with conventional amphotericin B deoxycholate. Amphotericin B colloidal dispersion, in view of its unacceptably high frequency of infusion-related toxicities similar to amphotericin B deoxycholate, is no longer favored. L-AmB has fewer infusion-related adverse reactions as compared with ABLC. Both L-AmB and ABLC appear to have similar nephrotoxic potential.

L-AmB has been rigorously evaluated in the empiric treatment of patients with neutropenia and antibiotic-refractory fever. The drug appears safe as well as effective. Besides neutropenic fever, empiric therapy may be required in some nonneutropenic situations as well. For example, allogeneic stem-cell recipients with graft versus host disease may require empiric antifungal therapy in the setting of undiagnosed, nodular pulmonary infiltrates. Although not clinically proven, L-AmB may be an appropriate empiric choice in such situations, particularly in the background of prophylactic use of broad-spectrum azoles. During the last decade, many thought that amphotericin B-deoxycholate and its lipid forms would become obsolete in view of the recently released, less-toxic azoles and echinocandins. That has not turned out to be so. Despite the fact that amphotericin B is an “old” drug, L-AmB plays and will continue to play an important role in

the empiric antifungal management of patients at high risk for invasive fungal infections.

## Disclosure

The authors report no conflicts of interest in this work.

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