Lipid Formulations of Amphotericin B: Clinical Efficacy and Toxicities

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Commercially available lipid formulations of amphotericin B (Abelcet, Amphotec, and AmBisome) represent a significant advance in drug delivery technology. Differences in biochemical, pharmacokinetic, and pharmacodynamic properties among the lipid products have been shown in vitro and in vivo models. Clinical experience with these products has been primarily in patients either refractory to or intolerant of conventional amphotericin B deoxycholate (AmBd). None of the lipid-based products demonstrates superior efficacy when prospectively compared with AmBd in the treatment of documented infections. When used for the empirical treatment of febrile neutropenia, AmBisome significantly reduced the incidence of proven emergent fungal infections but did not improve short-term survival rates, in comparison with AmBd. Acute infusion-related adverse events vary, whereas nephrotoxicity is reduced with all three lipid formulations. Until superior efficacy is clearly shown (for documented infections) or pharmacoeconomic analyses document the value of these drugs, use of such expensive agents should be highly restricted to those who are intolerant of or refractory to AmBd.

Despite the availability of newer, less toxic azoles, amphotericin B (AmB) remains the agent of choice for treatment of many serious systemic fungal infections. The recent development of resistance to azoles and the increased prevalence of fungal infections have reemphasized the value of AmB. However, the usefulness of the conventional AmB deoxycholate (AmBd) formulation is limited by its well-known dose-limiting nephrotoxicity.

For the past decade, investigators have evaluated the use of phospholipid vesicles known as liposomes as a target drug delivery system for AmB, in an attempt to attenuate its nephrotoxicity and increase its therapeutic potential. Lopez-Berestein et al. created the first liposomal formulation of AmB experienced with in humans [1]. Their experience led to further development of the lipid formulations of AmB by the pharmaceutical industry. In December 1995, amphotericin B lipid complex, or ABLC (Abelcet; The Liposome Co., Princeton, NJ), became the first lipid-formulated AmB product to receive approval by the U.S. Food and Drug Administration (FDA) for use in the United States. Subsequently, another lipid-formulated AmB product, amphotericin B colloidal dispersion, or ABCD (Amphotec; Sequus Pharmaceuticals, Menlo Park, CA), received FDA approval in December 1996. More recently, a third product, AmBisome (L-AmB; NeXstar Pharmaceuticals/ Fujisawa, San Dimas, CA), long commercially available outside of the United States, received FDA approval in August 1997.

This article will provide a basic understanding of the use of phospholipid vesicles as a drug delivery system. In addition, the biochemical, pharmacokinetic, and pharmacodynamic differences among the lipid-formulated AmB products also will be discussed. Finally, a critical evaluation of the clinical efficacy and toxicity of these products, based on the English-language literature (including abstracts), will be performed to clarify the potential role of each product.

Liposomes as Drug Delivery Systems

Liposomes are biodegradable vesicles that consist of an aqueous environment surrounded by phospholipid bilayers. The first description of liposomes was made over 30 years ago by Alec Bangham in Cambridge, England, who noted the spontaneous formation of microscopic closed vesicles when high concentrations of phospholipids were dispersed in water [2]. In the ensuing years, researchers using various methods were able to produce liposomes with different biochemical properties by altering characteristics such as size, electrical charge, permeability, and lipid composition of the vesicles.

For the past 20 years, the practical application of liposomes as delivery systems has been investigated [3, 4]. Water-soluble and fat-soluble substances, including drugs, enzymes, and genes, have been successfully entrapped in the aqueous phase of the bilayer or incorporated into the lipid bilayer itself. AmB is a polyene antibiotic with an optimal molecular structure...
Table 1. Comparison of the biochemical and pharmacokinetic properties of the lipid-formulated amphotericin B (AmB) products.

<table>
<thead>
<tr>
<th>Property</th>
<th>AmBd*</th>
<th>ABLC²</th>
<th>ABCD</th>
<th>L-AmBi³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid composition (molar ratio)</td>
<td>...</td>
<td>DMPC/DMPG (7:3)</td>
<td>Cholesteryl sulfate (2:1:0.8)</td>
<td>HPC/Chol/DSPG (2:1)</td>
</tr>
<tr>
<td>AmB content (mol %)</td>
<td>...</td>
<td>33%</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Human tissue distribution: µg per g of tissue (% of total dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>93.2 (26.2)</td>
<td>196.0</td>
<td>175.7 (18.3)</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>59.3 (1.0)</td>
<td>290.0</td>
<td>201.5 (3)</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>12.9 (3.1)</td>
<td>222.0</td>
<td>16.8 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>18.9 (0.8)</td>
<td>6.9</td>
<td>22.8 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Not studied</td>
<td>1.6</td>
<td>0.56 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>3.7 (0.13)</td>
<td>5.0</td>
<td>4.3 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex; AmBd = amphotericin B deoxycholate; CHOL = cholesterol; DMPC = dimyristoylphosphatidylcholine; DMPG = dimyristoylphosphatidylglycerol; DSPG = distearoylphosphatidylglycerol; HPC = hydrogenated phosphatidylcholine; L-AmB = AmBisome.

* Average concentrations of AmB in tissue obtained at autopsy from six patients who received cumulative AmB doses ranging from 206 mg to 2,688 mg.

² Tissue concentrations at autopsy in one heart transplant patient who received three doses of ABLC (5.3 mg/[kg \cdot d]).

³ Average tissue concentrations at autopsy in three patients who received cumulative doses ranging from 820 mg to 3,428 mg of AmBisome.

§ Figures are available only for AmBd and L-AmB and were calculated on the basis of total drug per organ (mg), divided by total dose received (mg).

for liposomal incorporation. Theoretically, entrapment of AmB into liposomes would increase its therapeutic index through selective transfer of AmB to the target fungal cell, with reduced uptake into human cells.

The first liposomal AmB formulation evaluated in humans consisted of multilamellar vesicles made up of a mixture of two phospholipids, dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG), in a 7:3 molar ratio containing 5%–10% molar ratio of amphotericin to lipid. The initial clinical experience with liposomal AmB involved neutropenic cancer patients with progressive fungal infections refractory to treatment with AmBd [5, 6]. Although uncontrolled, treatment results suggested that invasive refractory fungal disease may respond to liposomal AmB. In addition, liposomal AmB appeared to be less nephrotoxic than AmBd.

This initial clinical experience led to the development of similar products over the past 10 years. Of the three lipid-formulated AmB products that are commercially produced today, ABLC is most closely related to the original formulation. ABLC consists primarily of the nonliposomal structures of the lipid bilayers, called ribbons, which were responsible for the observed reduction in toxicity [7, 8]. The concentration of AmB in ABLC is 33 mol%, vs. 2%–7% by weight for the original formulation. The other two commercial lipid-based products differ from ABLC, not only in vesicular structure but also in phospholipid composition and AmB content (table 1). ABCD is another lipid complex containing cholesteryl sulfate and AmB in a 1:1 molar ratio with a disklike morphology. AmBosome is the only commercially produced lipid formulation that contains liposomal structures.

In Vivo Disposition

The pharmacokinetics and tissue distribution of the drug-laden liposomes are strongly affected by their physicochemical properties, such as vesicle size, bilayer rigidity, and surface electrical charge [9, 10]. Larger liposome vesicles clear more rapidly from the bloodstream than smaller ones, while positively charged and neutral liposomes circulate longer than those of a similar size that are negatively charged. The surface electrical charge differs by the type of phospholipid (i.e., phosphatidylcholine vs. phosphatidylglycerol). Moreover, the addition of cholesterol to the phospholipid bilayers enhances liposomal stability, resulting in a decreased rate of vesicle clearance from circulation and a longer biological half-life.

Although plasma levels achieved with all three products differ from one another, the clinical significance of such a difference is unknown [10, 11]; the extent of tissue distribution may be an important determinant of treatment outcome. On the basis of autopsy data obtained from eight patients who received the conventional AmBd formulation, tissue drug concentrations were found to be highest in the liver and spleen, followed by the kidneys and lungs [12] (table 1). With the lipid-based products, it is likely that the extent of tissue distribution depends on the size of lipid vesicles, as demonstrated by the
different tissue concentrations of AmB measured in human autopsy studies.

Both ABLC and L-AmB distribute minimally to the kidneys, heart, and lungs and concentrate primarily in the spleen and liver, where the reticuloendothelial system phagocytic cells reside [13, 14]. The low concentrations of drug found in kidneys correlate with the clinical observation of reduced nephrotoxicity of ABLC and L-AmB. No data detailing the distribution pattern of ABCD in humans are available at present. One factor complicating interpretation of data concerning serum and tissue concentrations is the inability to differentiate between lipid-bound and free amphotericin; the bioavailability of AmB may be highly variable among the three preparations, owing to their biochemical differences [10]. Future studies are needed to evaluate the relationship between serum or tissue concentrations of AmB in lipid-formulated products and treatment outcomes.

Following intravenous administration, uptake by the reticuloendothelial system accounts for the major disposition of liposomes [15, 16]. In addition, liposomes may be distributed to various tissues by association with circulating lipoproteins in the bloodstream such as high- and low-density lipoproteins [16]. It is hypothesized that monocytes/macrophages in peripheral blood take up the drug-laden liposomes and transport them to the site of inflammation or infection [17, 18]. In the setting of neutropenia, plasma lipoproteins may assume a major role in the transport mechanism [16]. Once the drug-laden liposomes or lipid complexes reach the site of action, it is speculated that free active drug is released through the action of phospholipases [7, 16, 19].

Some fungi produce extracellular phospholipases, as do activated mammalian cells, including phagocytic cells, vascular smooth-muscle cells, and capillary endothelial cells. These cells exist in a wide variety of tissues, including liver, spleen, lung, and vascular smooth muscle under inflammatory conditions. It is possible that the amounts of AmB that are bioavailable depend upon the infecting fungal organism, the presence of neutropenia, or extent of inflammation, potentially influencing the treatment dose required for optimal response.

Pharmacodynamic Comparison

Both the phospholipid:AmB ratio and the type of phospholipid appear to be important determinants of fungicidal activity and toxicity [20]. Differential activity has been documented between conventional AmBd and individual lipid-formulated product on a milligram-per-milligram basis in various animal models of fungal infection. ABLC was determined to be less active than AmBd in a murine model of invasive aspergillosis in immunocompromised animals; up to five times as much ABLC was required to achieve similar survival rates [21]. However, ABLC was effective in controlling infection, while AmBd was ineffective at the maximum tolerated dose in cases of candidiasis and cryptococcosis [8, 21].

Similarly, ABCD was found to be less effective than AmBd in tissue clearance of invasive aspergillosis [22, 23] and coccidioidomycosis [24]. However, ABCD was equally effective and less toxic than conventional AmBd for cryptococcosis [25]. On the other hand, L-AmB treatment resulted in longer survival when given at doses equal to those of AmBd for invasive aspergillosis, but the greatest rate of reduction of pulmonary hemorrhage was at a dosage of 5 mg/(kg · d) [26].

Only data from one study has presented a direct comparison of the in vivo activities of all three lipid-based products against one another and against AmBd in a murine model of cryptococcosis [27]. Treatment groups of 10 mice each received 1, 5, 10, and 1 mg/kg of ABCD, ABLC, L-AmB, and AmBd, respectively. When treatment groups were compared at the 1-mg/kg dosage levels, survival rates were better with all lipid-based products than with AmBd, in the following order: ABCD > L-AmB > ABLC > AmBd. Even though the authors noted that ABCD was equivalent to L-AmB and that both were superior to ABLC in reducing fungal burden in the brain, none of the mice survived free of infection at the site. In summary, animal data suggest that the optimal AmB preparation and treatment dose depend on the specific pathogen.

Clinical Experience

To date, clinical experience with these products has primarily been in compassionate-use studies and small series of cases. All English-language studies published (excluding case reports and abstracts) are summarized in table 2. Only patients with documented systemic fungal infections are included. As yet, no comparative studies between lipid-bound AmB products have been performed. Efficacy data available on the new products have concerned a wide range of systemic mycoses: candidiasis, aspergillosis, cryptococcosis, fusariosis, mucormycosis, and coccidioidomycosis.

Because candidiasis and aspergillosis have been the most frequently treated infections, relative efficacy will be reviewed for these indications. A comparison of the toxicity profiles for each product will emphasize acute infusion-related adverse events (IRAEs) and nephrotoxicity. Other toxicities such as hypokalemia and anemia will not be discussed here, as they were inconsistently reported in the available literature.

Amphotericin B Lipid Complex

ABLC was the first lipid-based formulation to receive FDA approval in United States. The original approved indication was limited to the treatment of aspergillosis in patients refractory to or intolerant of conventional AmBd. The indication has now expanded to include all fungal infections.

Clinical experience with ABLC primarily has been compassionate treatment of confirmed or presumed fungal infections in patients refractory to or intolerant of conventional AmBd therapy. Most of the available information is derived from abstracts presented at professional meetings. Published data on
Table 2. Published data on efficacy of lipid-based amphotericin B (AmB) products.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>AmB lipid-based product studied (no. of patients)</th>
<th>Underlying condition</th>
<th>Documented systemic infection(s) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[28]</td>
<td>Open-label, compassionate use</td>
<td>ABLC (20)</td>
<td>HM</td>
<td>Candidiasis (7), aspergillosis (2)</td>
</tr>
<tr>
<td>[29]</td>
<td>Open-label, randomized,</td>
<td>ABLC (38)</td>
<td>AIDS</td>
<td>Cryptococcal meningitis (55)</td>
</tr>
<tr>
<td></td>
<td>comparative</td>
<td>Cohort I (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort II (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort III (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AmBd (17)</td>
<td>AIDS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort IV (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[30]</td>
<td>Open-label</td>
<td>ABLC (42)</td>
<td>HM</td>
<td>Aspergillosis (9; 7 pneumonia and 2 sinusitis); candidiasis (4; 3 candidemia and 1 hepatosplenic disease); cryptococcal meningitis (1)</td>
</tr>
<tr>
<td>[31]</td>
<td>Open-label, compassionate use</td>
<td>ABCD (168)</td>
<td>HM</td>
<td>Among 97 evaluable: candidiasis (33), aspergillosis (32), cryptococcosis (11), mucormycosis (4), fusariosis (4), other (7), multiple (6)</td>
</tr>
<tr>
<td>[32]</td>
<td>Phase I dose-escalation</td>
<td>ABCD (75)</td>
<td>BMT</td>
<td>Candidiasis (40), aspergillosis (28), other (7)</td>
</tr>
<tr>
<td>[33]</td>
<td>Retrospective, concurrent</td>
<td>ABCD (82)</td>
<td>HM, BMT</td>
<td>Aspergillosis (probable or proven)</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>AmBd (261)</td>
<td>HM, BMT</td>
<td>Same</td>
</tr>
<tr>
<td>[14]</td>
<td>Open-label, compassionate use</td>
<td>L-AmB (126)</td>
<td>HM</td>
<td>Among 64 proven: aspergillosis (29), candidiasis (25), cryptococcosis (7), other (3)</td>
</tr>
<tr>
<td>[34]</td>
<td>Open-label, compassionate use</td>
<td>L-AmB (58)</td>
<td>HM</td>
<td>Among 27 proven: aspergillosis (17), candidiasis (6), mucormycosis (3), cryptococcosis (1)</td>
</tr>
<tr>
<td>[35]</td>
<td>Open-label, compassionate use</td>
<td>L-AmB (40)</td>
<td>HM</td>
<td>Among 9 proven: pulmonary aspergillosis (6), candidal esophagitis (3)</td>
</tr>
<tr>
<td>[36]</td>
<td>Open-label, compassionate use</td>
<td>L-AmB (116)</td>
<td>HM</td>
<td>Among 23 proven: aspergillosis (21), candidemia (2)</td>
</tr>
<tr>
<td>[37]</td>
<td>Open-label, noncomparative</td>
<td>L-AmB (23)</td>
<td>HIV+</td>
<td>Cryptococcosis (23: 19 CSF and 4 blood or urine)</td>
</tr>
<tr>
<td>[38]</td>
<td>Open-label</td>
<td>L-AmB (11)</td>
<td>Pediatric BMT</td>
<td>Candidiasis (1: urine, bone marrow)</td>
</tr>
<tr>
<td>[39]</td>
<td>Open-label</td>
<td>L-AmB (14)</td>
<td>Pediatric BMT or liver transplant</td>
<td>Among 8 proven episodes: candidiasis (5: 1 hepatosplenic, 1 hepatic, 2 pulmonary, 1 blood), pulmonary aspergillosis (3)</td>
</tr>
</tbody>
</table>

NOTE. ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex; AmBd = amphotericin B deoxycholate; BMT = bone marrow transplantation (in all or a majority of the patients); clinical response = cure and/or improvement; HM = hematologic malignancies (in all or most of the patients); L-AmB = AmBisome; NA = not applicable; NS = not stated; TIW = thrice weekly; ? = unknown.

* Overall response rates for patients who received at least 12 doses of study drug.

† Fifty-six had positive cultures for Candida (of unclear relevance to systemic disease).

the efficacy of ABLC are limited to four case reports, one open-label study, one descriptive study, and one dose-ascending comparative trial for the treatment of cryptococcal meningitis in patients with AIDS [28–30, 40–43].

**Efficacy—open-label use.** Pooled data are available from >1,500 patients who received ABLC under the compassionate-use protocol [28–30, 40–55]. In most cases, unsatisfactory clinical response was defined by receipt of a minimum dose of 500 mg of conventional AmBd, while AmB intolerance secondary to nephrotoxicity was defined as an elevation of serum creatinine level above 2.5 mg/dL. In most treated patients, hematologic malignancy was the primary underlying
<table>
<thead>
<tr>
<th>Result of prior AmBd therapy</th>
<th>AmB product dose</th>
<th>Proportion of patients with clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>?</td>
<td>Daily, mg/kg</td>
<td>Cumulative, mg (duration)</td>
</tr>
<tr>
<td>NA</td>
<td>5</td>
<td>? (1–25 d)</td>
</tr>
<tr>
<td>I: 1.2 to &gt;2.5</td>
<td>? (qd × 2 w to &gt;TIW × 4 w)</td>
<td>I: 2/6 (33)</td>
</tr>
<tr>
<td>II: 2.5 to &gt;5</td>
<td></td>
<td>II: 2/7 (29)</td>
</tr>
<tr>
<td>III: 5</td>
<td></td>
<td>III: 8/19 (42)</td>
</tr>
<tr>
<td>IV: 0.7 to &gt;1.2</td>
<td></td>
<td>IV: 7/14 (50)</td>
</tr>
<tr>
<td>?</td>
<td>5</td>
<td>(median, 10.5 d)</td>
</tr>
<tr>
<td>NA (not necessary for enrollment)</td>
<td>Initially, 0.5–4.0, up to 6</td>
<td>Median, 2,388 (median, 12.5 d)</td>
</tr>
<tr>
<td>Failure (19/82 [23%]; prior AmBd not necessary for ABCD therapy)</td>
<td>Initially 0.5, increased by 0.5 increments up to maximum tolerated dose</td>
<td>(6 w for most patients)</td>
</tr>
<tr>
<td>Overall, intolerance (67%), failure (31%); ? for those with proven disease</td>
<td>-</td>
<td>Mean, 3,500 (range, 600–16,800 [29 d; range, 8–97 d])</td>
</tr>
<tr>
<td>Intolerance/failure (19)</td>
<td>-</td>
<td>Means: 2,081 (responses), 1,207 (failures) (17 vs. 7 d)</td>
</tr>
<tr>
<td>Failure (14; median dose, 615 mg), intolerance (26; median, 365 mg)</td>
<td>-</td>
<td>Median, 730 (5–27 d)</td>
</tr>
<tr>
<td>Intolerance (60%), failure (14%); median dose, 660 mg</td>
<td>-</td>
<td>Median, 1,684; range, 180–10,440 (12 d; range, 2–96)</td>
</tr>
<tr>
<td>? (5 received)</td>
<td>-</td>
<td>Mean, 4.4 g (27 d)</td>
</tr>
<tr>
<td>Intolerance (2)</td>
<td>-</td>
<td>Median, 221</td>
</tr>
<tr>
<td>Failure (6; dose range, 107–2,800 mg), intolerance (4)</td>
<td>-</td>
<td>Mean, 1.7 g (median, 19 d)</td>
</tr>
</tbody>
</table>

Disorder. Of note, many were treated for “presumed” infections. Mean cumulative doses of up to 10,300 mg were used, with a mean daily dose of 5 mg/kg. Treatment duration ranged from 11 to 33 days.

In general, response to treatment with ABLC was greater for candidiasis than for aspergillosis. One abstract, which presented the efficacy and safety data for a total of 551 patients with documented invasive fungal infections, reported overall response rates of 70% (74 of 105) vs. 48% (82 of 170) ($P = .0004$) for yeasts and filamentous fungi, respectively [55]. The success of ABLC in patients whose AmBd therapy had previously failed was not stated. The overall mycologic eradi-
cation rate was between 52% and 75%, although analysis by organism was not possible because of inconsistent reporting.

**Efficacy—comparative trials.** Two prospective comparative trials have been performed evaluating ABLC vs. AmBd in the treatment of cryptococcal meningitis in patients with AIDS [29] and invasive candidiasis [52], respectively. Data from the latter study presently are available in abstract form.

In a randomized, open-label, ascending-dose study, ABLC and AmBd were compared in the treatment of cryptococcal meningitis [29]. The primary study objective was to evaluate the safety and tolerance of ABLC, with efficacy as a secondary evaluation. A total of 55 patients were randomized into 4 treatment groups: 3 groups received an ascending dose of ABLC at 1.2, 2.5, and 5 mg/(kg·d) for 2 weeks, followed by 2.5, 5, and 5 mg/kg thrice weekly for 4 weeks, respectively; the fourth group received AmBd at a dosage of 0.7 mg/(kg·d) for 2 weeks, followed by 1.2 mg/kg thrice weekly for 4 weeks.

Factors predictive of treatment failure and early death, such as visual abnormality, lethargy or obtundation, and a positive blood culture, were more prevalent in the ABLC groups. With respect to treatment outcomes, no significant difference in response was noted between treatment groups. Patients in the lower-dose ABLC groups (1.2 and 2.5 mg/[kg·d]) appeared to respond favorably to treatment; however, the small number of patients in each group (n = 8, n = 9) did not allow for meaningful interpretation of the efficacy data.

When results were compared between the ABLC 5 mg/(kg·d) group (n = 21) and the AmBd 0.7 mg/(kg·d) group (n = 17), comparable treatment successes were found both with intent-to-treat analysis (38% vs. 41%) and subgroup analysis among patients who had received at least 12 doses of the study drug (42% vs. 50%). Notably, a higher number of ABLC patients had persistently positive CSF cultures at the end of treatment, despite resolution of symptoms (42% vs. 14%). The disproportionate share of negative predictive outcome factors present in the ABLC groups may have influenced the above results.

A second prospective, randomized, comparative trial evaluated ABLC vs. AmBd in 231 patients for the treatment of invasive candidiasis [52]. Invasive disease was defined as candidemia, acute disseminated candidiasis, or organ infection. Patients from 27 centers were randomized to receive ABLC (5 mg/[kg·d]) or AmBd (0.6–1.0 mg/[kg·d]) in a 2:1 randomization scheme. Study groups were similar with respect to baseline characteristics, including age, underlying condition, and presence of neutropenia, as well as infection and pathogens. Hematologic malignancy and solid tumor were the major underlying disorders in both groups. Candidemia was the major indication in both groups (85%, ABLC; 83%, AmBd), and *Candida albicans* was the primary pathogen in half of the patients. The median treatment duration was 14 days in both groups.

Efficacy was evaluated only in those patients (124 ABLC and 70 AmBd recipients) who had positive baseline cultures, had received at least 4 days of treatment with the study drug, and were given fewer than 4 days of other concurrent antifungal therapy. Overall response rates were 65% with ABLC and 61% with AmBd. Comparable clinical responses were observed with subgroup analysis: underlying condition, neutrophil count, infection type, pathogen, and central venous catheter status. In general, patients with hematologic malignancy, neutropenia, candidemia, infections due to multiple *Candida* species, and central venous catheters remaining in place tended to respond less favorably to treatment by either agent. For approximately half the evaluable patients, mycologic examination was performed to document eradication (88%, ABLC; 87%, AmBd). No significant differences in relapse or survival rates were observed at the 3-month follow-up.

**Toxicity.** Both prospective comparative trials indicated that IRAEs associated with ABLC infusion occurred in one-third to one-half of the treated patients, comparable to the rate with AmBd [29, 52]. In one retrospective analysis of pediatric cancer patients, ABLC administration resulted in an incidence of IRAEs that was similar to that with AmBd, on the basis of premedication requirements (87% vs. 80%) [56]. Pooled data from emergency-use studies indicate that renal function stabilized in a majority of patients; some even experienced improvement in renal function despite continuation of therapy with ABLC [28–30, 40–56]. Significantly more patients receiving AmBd than those receiving ABLC had an elevation in the serum creatinine level from baseline at weeks 2 and 3 in the treatment of cryptococcal meningitis [29]. However, baseline serum creatinine values were not stated for those who experienced a significant change following AmBd treatment. Similarly, the number of patients with reversible nephrotoxicity was not stated.

In another comparative trial of invasive candidiasis, the incidence of nephrotoxicity was observed to be delayed and reduced in the ABLC group [52]. Doubling of baseline serum creatinine values occurred in 28% vs. 47% of patients receiving ABLC and AmBd, respectively. Study withdrawal due to nephrotoxicity occurred in 19% of AmBd vs 8% of ABLC recipients. However, criteria for withdrawal were not defined. In addition, the effect of concurrently administered nephrotoxic agents in patients who developed nephrotoxicity was not stated.

One recent retrospective analysis of patients with aspergillosis suggested that ABLC reduced the need for dialysis secondary to AmB-induced nephrotoxicity and thus improved survival rates [54]. However, the findings of this study require confirmation in a prospective comparative trial. ABLC has been well tolerated with minimal toxicity in six patients who received unusually large cumulative doses over prolonged periods of time (22.3–73.6 g over 21–121 weeks) [57].

Other notable toxic effects include elevated serum bilirubin and serum alkaline phosphatase levels. In a small retrospective analysis of pediatric patients with cancer, ABLC was withdrawn from four patients (27%) because of hyperbilirubinemia [56]. The serum bilirubin level as well as the alkaline phosphatase level were found to be significantly increased at the end of ABLC therapy in a large analysis of open-label multicenter trials of patients receiving ABLC therapy for documented inva-
sive fungal infections. The mean pretreatment and posttreatment values of total bilirubin and alkaline phosphatase were 4.66 mg/dL vs. 6.59 mg/dL and 273 IU/L vs. 320 IU/L, respectively. No significant changes in hepatic transaminases were noted. The median treatment duration and cumulative dose were 22 days and 4,856 mg in that study [55].

In addition, a recent abstract described severe hepatic cholestasis prior to death in three transplantation patients who received ABLC in combination with cyclosporine. A temporal correlation between ABLC (5 mg/[kg·d]) administration and rise in serum bilirubin was observed [58]. The severity of ABLC-associated hepatotoxicity reported here has not been corroborated by reports from other centers; however, close monitoring of patients receiving such a combination is imperative.

Summary—ABLC. ABLC appears to be as effective as AmBd in the treatment of invasive candidiasis and cryptococcal meningitis in patients with AIDS. However, further comparative studies are warranted to confirm the efficacy results and better define the optimal treatment dose. Comparative studies evaluating low-dose ABLC (2.5 mg/kg) vs. conventional AmBd for the treatment of candidemia in neutropenic patients and in liver transplant recipients are currently under way.

Pooled data from emergency-use studies suggest the primary benefit of ABLC is as salvage therapy for fungal infections refractory to conventional AmBd. While IRAEs appear to be comparable for ABLC and AmBd, the decreased nephrotoxic potential of ABLC allows it to be used in patients with nephrotoxicity secondary to AmBd treatment. Elevations in serum bilirubin and alkaline phosphatase levels are other notable laboratory abnormalities that may require close monitoring in patients receiving prolonged therapy.

Amphotericin B Colloidal Dispersion

One year following the introduction of ABLC in the United States, the FDA granted approval for the marketing of a second lipid-based formulation of AmB, amphotericin B colloidal dispersion. ABCD is approved for the treatment of invasive aspergillosis in patients who are either intolerant of or refractory to conventional AmBd. A recent supplemental new drug application for empirical therapy in febrile neutropenia, based on double-blinded comparison with AmBd, did not receive FDA approval because of insufficient efficacy data.

The majority of ABCD recipients have been either intolerant of or refractory to conventional AmBd therapy. To date, one comparative retrospective study [33], seven noncomparative open label studies, and case reports have been published in the literature [31, 32, 59–63]. In addition, one large open-label study of candidemia and one comparative trial evaluating ABCD vs. AmBd have been reported in abstract format [64, 65].

Efficacy—open-label use. Overall, data on the efficacy and safety of ABCD in >500 treated patients are available from case reports, open-label use, and randomized studies [30–32, 59–66]. Of those patients, less than half were considered to have “evaluable” systemic fungal infections (as judged by individual study investigators) that were mycologically documented. More patients received ABCD treatment for candidiasis than for aspergillosis.

A minority of the documented infections were coccidioidomycosis, cryptococcosis, mucormycosis, and fusariosis. Treatment with ABCD resulted in a response rate (including complete and partial responses) of 58% for candidiasis and 37% for aspergillosis, respectively. Mycologic eradication rates were not determined in most studies. As expected, the treatment response with use of ABCD in documented systemic infections correlated with the presence of neutropenia (<500 neutrophils/mm³); 39% of those who were neutropenic vs. 64% of nonneutropenic patients responded [31].

The daily treatment dose of ABCD was highly variable within and among studies, ranging from 0.5 mg/kg to 8 mg/kg. Although no dose-response relationship could be documented in the phase I study, it is possible that different dosages are required to achieve optimal responses, depending upon the pathogen (e.g., *Candida* vs. *Aspergillus*). Of note, the clinical response reported from one small study of low-dose ABCD therapy for nonmeningeal coccidioidomycosis was less than optimal [66]. Twenty-one patients received ABCD (1 mg/[kg·d] for 2 weeks, followed by 2 mg/kg thrice weekly for 10 weeks). The relapse or failure rate was 58% at follow-up (mean, 9 weeks).

In the treatment of candidemia, the mean daily dose employed in one open-label study was 3.9 mg/kg [64]. At present, the product packaging recommends an initial daily dose of 3.0–4.0 mg/kg, which may be increased to 6.0 mg/kg if there is no improvement or if there is evidence of progressive fungal disease. In light of the lower overall response rate with invasive aspergillosis, it may be prudent to initiate treatment with the maximum daily dose of 6.0 mg/kg for all probable or proven cases of aspergillosis, until more dose-outcome data are available.

Efficacy—comparative trials. Two studies have been performed comparing ABCD and AmBd for the treatment of invasive aspergillosis [33] and for empirical treatment of febrile neutropenia [65], respectively. However, only the latter study was prospectively designed. Results of the study are available only in abstract format [65].

The efficacy and safety of ABCD in the treatment of invasive aspergillosis were compared with those of AmBd in a retrospective, concurrent-control study [33]. All patients with proven or probable disease receiving treatment with either ABCD or AmBd were included in the study. Patients with AIDS or concomitant fungal infection were excluded. The number of evaluable patients (who received at least 7 days of therapy) in each group was 82 (ABCD) and 261 (AmBd). Treatment response, survival at 120 days, and safety were assessed. To assess the potential impact of prior AmBd therapy on the ABCD treatment group, a secondary post-hoc analysis was performed for each study endpoint by equalizing the two treatment groups for prior AmBd exposure.
Daily dosages administered were highly variable within each study group: 0.5–8.0 mg/kg (ABCD) vs. 0.1–1.4 mg/kg (AmBd). The median duration of treatment was similar between study groups (23.5 days and 22 days), with cumulative doses of 5.92 g and 1.06 g for ABCD and AmBd recipients, respectively. A comparison of the baseline patient characteristics between study groups revealed significant differences: more AmBd recipients were neutropenic (≤500/mm³) (42.5% vs. 15.9%), while more ABCD recipients had renal dysfunction (serum creatinine, ≥2 mg/dL) (40.7% vs. 8.7%). The overall clinical response rate was significantly higher for ABCD-treated patients (48.8% [40 of 82] vs. 23.4% [61 of 261]; P < .001). Notably, twice as many AmBd recipients than ABCD recipients remained persistently neutropenic (49% vs. 27%) during the study, potentially negatively affecting treatment response in the AmBd group.

In addition, because the diagnosis of aspergillosis was made postmortem for 17.2% of the AmBd recipients vs. none of the ABCD patients, treatment response may have been influenced by the AmBd dosage selected on the basis of diagnosis. Subgroup analysis of patients whose diagnoses were made before or within the first 7 days of treatment revealed similar response rates between regimens. Further subgroup analysis revealed that initial treatment with AmBd did not alter response rates between groups.

Mortality rates among patients with aspergillosis were 50% and 66.1% for ABCD and AmBd, respectively. Cause of death was not stated. More AmBd-treated patients developed renal toxicity during treatment than did ABCD recipients (43.5% vs. 8.2%). The median time to renal toxicity for AmBd recipients was estimated to be 27 days (Kaplan-Meier analysis); similar estimation was not performed for the ABCD recipients because too few had renal toxicity.

According to the authors, IRAEs could not be adequately assessed because of the retrospective design of the study. Other laboratory abnormalities included increases in alkaline phosphatase and serum bilirubin levels, without significant changes in hepatic transaminase levels. A lesser degree of change from baseline was observed for ABCD recipients than for AmBd recipients.

While the overall response rate, mortality rate, and renal safety appeared to favor ABCD, the authors cautioned that “it is not appropriate to conclude that ABCD is superior to amphotericin B as initial treatment of aspergillosis from results of a retrospective, unblinded study comparing different populations of patients.” In addition, the estimated median time to nephrotoxicity (27 days) was delayed beyond the median duration of treatment with AmBd (22 days), suggesting that most AmBd patients would have completed therapy before the development of nephrotoxicity.

Another comparative study evaluated ABCD vs. AmBd for the empirical treatment of febrile neutropenia [65]. Patients were separated into four groups, comprising adults with or without concurrent cyclosporine or tacrolimus therapy and children in similar subgroups. Patients in each group were randomized in a double-blind fashion to receive either ABCD (4 mg/kg) or AmBd (0.8 mg/kg) at least 72 hours after starting to receive empirical antibiotic therapy for neutropenic fever. A total of 101 patients received ABCD, while 93 received AmBd.

Because of the design of the study, a comparison of the relative efficacy of each formulation in treating documented infections is not possible. However, both treatments were equally successful, as defined by survival at 7 days after initiation of study drug, febrile state at end of study, evidence of fungal infection, and termination of study drug because of toxicity. In general, one-third to more than half of the patients responded sufficiently; higher response rates were observed among patients not receiving either cyclosporine or tacrolimus concurrently.

Toxicity. IRAEs, including fever, chills, and hypotension, occur commonly with ABCD. The incidence and severity of IRAEs correlate with dosage as well as infusion time. In the phase I dose-escalation study, three of five patients who received ABCD at the maximum dosage of 8 mg/(kg · d) experienced fever, chills, rigors, and hypotension requiring vasopressors [32]. Most reactions occurred with the first and second doses and usually were controlled with premedications or subsided with subsequent dosing.

Pooled data from noncomparative studies indicate that more than one-third of ABCD-treated patients reported either chills or chills and fever. Up to 86% of patients have experienced IRAEs in different studies using different dosages. Published data from comparative studies thus far have not addressed the relative occurrence of IRAEs with ABCD vs. AmBd [33, 65]. However, data presented recently to the FDA for supplemental new-drug-application consideration indicate that infusion-related toxicities (such as fever, chills, hypotension, and hypoxia) occurred more frequently in the ABCD recipients than in AmBd recipients. It is noteworthy that hypoxic events were usually associated with chills and fever; all were reversible and without sequelae.

Nephrotoxicity occurred significantly less commonly with ABCD than with AmBd in both comparative studies [33, 65]. In the double-blind randomized trial, ABCD therapy caused significantly less renal toxicity than did AmB in patients who did or did not also receive cyclosporine or tacrolimus. Renal toxicity was defined as at least a 50% decline in creatinine clearance or a doubling of or an increase of 1.0 mg/dL in the serum creatinine value. For adults not receiving concurrent nephrotoxic therapy, the incidence of nephrotoxicity with ABCD and AmB was 8.5% and 21%, respectively. In contrast, 21% vs. 67%, respectively, developed renal dysfunction when given concurrent cyclosporine or tacrolimus.

One large open-label study of 168 patients showed that 69% of patients with normal serum creatinine values at baseline still had normal values at the end of ABCD therapy [31]. The median cumulative dose and treatment duration were 2,388 mg and 12.5 days, respectively. In the phase I dose-escalation study, which excluded patients with a baseline se-
rum creatinine level of >2.0 mg/dL, a doubling of or >50% increase in the serum creatinine level (up to 2.5 mg/dL) occurred in 17% of patients [32]. Although the cumulative dose and treatment duration for those patients were not stated in the study, the authors did not note any relationship between the total ABCD dose and serum creatinine value. It is unclear whether the daily dose administered affects the onset and degree of nephrotoxicity.

Summary—ABCD. In comparison with ABLC, ABCD has been less studied in fungal infections other than candidiasis or aspergillosis. As an example, few HIV-positive patients with cryptococcal meningitis have been treated with ABCD, even though ABCD appeared to be most efficacious in a murine model of cryptococcosis comparing the three lipid-based products [27]. Similar to the finding for ABLC, subgroup analysis of those patients whose AmBd treatment for invasive aspergillosis failed suggests that ABCD has a potential role as salvage therapy. However, variable dosing for ABCD makes the optimal treatment dose uncertain for most infections, with the possible exception of candidemia. No data are currently available from any prospective comparison of ABCD with AmBd in the treatment of documented infections.

One blinded, randomized study of invasive aspergillosis has been completed, while another is ongoing, evaluating treatment of azole-resistant oropharyngeal candidiasis in HIV-positive patients. In addition, two trials of low-dose ABCD (1 mg/[kg · d]) as antifungal prophylaxis in neutropenic patients are ongoing; one is of open-label use in mismatched bone marrow transplant recipients for 30 days, while the other compares ABCD to fluconazole (400 mg/d) for neutropenia following bone marrow transplantation or chemotherapy.

On the basis of comparative data with AmBd, the incidence of IRAEs (e.g., fever and chills) associated with ABCD may be higher than with ABLC. The recommended infusion time for ABCD is also 2.5 times longer than with ABLC. Similar to ABLC, ABCD has been demonstrated to be less nephrotoxic than AmBd. However, accurate assessment of the relative nephrotoxicity between the two lipid formulations requires direct comparison between ABLC and ABCD. In addition, both formulations have demonstrated hepatotoxic potential consisting of an elevation in alkaline phosphatase and serum bilirubin levels, without significant change in hepatic transaminase levels.

AmBisome

AmBisome (L-AmB) has been licensed for use in Europe for >5 years but only recently became available commercially in the United States. AmBisome received FDA approval in August 1997 for the treatment of patients with aspergillus, candidal, and/or cryptococcal infections refractory to AmBd or in patients intolerant of AmBd. An additional approved indication is for the empirical treatment of febrile neutropenia.

In comparison with use of ABLC and ABCD, the use of AmBisome has been evaluated in a greater number of patients. Published data include 4 open-label compassionate-use studies, 7 case reports, 1 open-label noncomparative study of HIV+ patients with cryptococcal meningitis, and 1 report on the data from two comparative studies in febrile neutropenic adult and pediatric patients [34–39, 67–75]. More recently, three comparative studies have been presented as abstracts at professional meetings; one study compared L-AmB with AmBd for the treatment of cryptococcal meningitis [76], while the other compared high-dose vs. low-dose L-AmB for the treatment of invasive aspergillosis [77].

The third abstract presented results from a large prospective, double-blind, randomized trial evaluating the efficacy and safety of L-AmB vs. AmBd for the empirical treatment of febrile neutropenia in 687 patients [78]. Results of the study were also presented to the FDA Antiviral Advisory Committee on 16 July 1997 as pivotal phase III data supporting the new drug application of AmBisome. In addition to the above studies, L-AmB has been prospectively evaluated as antifungal prophylaxis in two randomized, double-blind, placebo-controlled studies in bone marrow transplant recipients as well as liver transplant recipients [79, 80].

Efficacy—open-label use. Cumulative experience with >1,500 patients has been published in the English language as open-label-study reports, case reports, and abstracts [14, 34–39, 67–85]. However, of those, less than one-third of patients have been treated for proven systemic disease. Hematologic malignancies have been the primary underlying disorder, and the most common treatment indication is for febrile neutropenia. Documented infections in L-AmB patients were due most commonly to Aspergillus species, followed by Candida species. The overall response rates were 60% and 74% for aspergillosis and candidiasis, respectively. Similar to ABCD, varying dosages were used in the various studies, averaging 3 mg/(kg · d).

Efficacy—comparative trials. One study prospectively compared L-AmB with AmBd in the treatment of cryptococcal meningitis in HIV-positive patients [76]. A total of 28 patients were randomized to receive either L-AmB (4 mg/kg; n = 15) or AmBd (0.7 mg/kg; n = 13) daily for 3 weeks, followed by fluconazole (400 mg/d) for 7 weeks. The study groups were similar with respect to lumbar opening pressure and CSF cryptococcal antigen titers, while more patients in the L-AmB group had altered mental status at enrollment in the study.

The primary study endpoint was time to CSF sterilization, and time to clinical response was the secondary objective. The median time to sterilization of the CSF was shorter with L-AmB than with AmBd therapy (14 days vs. >21 days). When the study groups were compared on day 14 of therapy, a significantly greater number of L-AmB patients had CSF culture conversion (67% vs. 11%). However, the time to clinical response (median, 15 days) as well as the clinical failure rate (23%) during initial therapy did not differ between groups.

None of the L-AmB vs. two AmBd recipients discontinued therapy because of toxicity. This lack of toxicity and the earlier mycologic response with L-AmB suggest a potential role of
L-AmB in the treatment of cryptococcal meningitis. The overall clinical response rate and the time of CSF culture conversion noted in this comparative study for L-AmB are similar to the findings of a noncomparative open-label study [37].

High-dose (HD) vs. low-dose (LD) L-AmB treatment of invasive aspergillosis has been studied in neutropenic cancer patients [77]. Patients were randomized from 18 European institutions to receive 4 mg/kg (HD) vs. 1 mg/kg (LD) of L-AmB daily. Only results from an interim analysis of 70 patients were available. Definite aspergillosis was present in 31% (LD) and 23% (HD) in the respective study groups. More than 90% of the cases involved the lungs. The median duration of treatment was 20 and 19 days with a cumulative dose of 1,260 mg and 4,020 mg in the LD and HD groups, respectively.

Surprisingly, the clinical and radiological responses slightly favored the LD group (68% vs. 49% and 63% vs. 54%, respectively). However, overall survival and mortality rates due to invasive aspergillosis were similar in both groups. Given the small number of documented infections, it is difficult to assess the benefit of LD therapy. In addition, an accurate assessment of the treatment response is problematic since patients who had received L-AmB treatment for only 1 day were included in the interim study analysis. More conclusive results await final data analysis.

One published report presented the combined results from two prospective randomized multicenter European trials comparing L-AmB with AmBd for the empirical treatment of febrile neutropenia [75]. Both studies compared AmBd at a dosage of 1 mg/(kg·d) vs. L-AmB at dosages of 1 mg/(kg·d) (LD) and 3 mg/(kg·d) (HD). Patients were enrolled in the study if they were neutropenic (<0.5 × 10^9 neutrophils/L) and remained febrile with a temperature of ≥38°C for 96 hours despite broad-spectrum antibacterial therapy.

A total of 134 adult patients and 204 pediatric patients were enrolled in the two studies; 102 patients were randomly assigned to receive AmBd, while 118 received LD L-AmB and 118 received HD L-AmB. Most patients had underlying hematologic malignancies. Antifungal prophylaxis with itraconazole, fluconazole, and/or an oral polye was permitted until the day of enrollment. Administration of nonsystemic antifungals was continued for nearly half of the patients in each treatment group. Antifungal therapy was prescribed at the discretion of the treating physician to at least one-third of the patients in each group. Safety was the primary study endpoint. Efficacy was the secondary endpoint, assessed by response and failure rates.

Response was defined by a minimum of 3 consecutive days without fever (temperature of <38°C), with accompanying neutrophil recovery to 0.5 × 10^9/L. Failure was defined by any one of the following: addition of another systemically active antifungal medication, development of a systemic fungal infection, or unresolved fever at study end. Treatment ended with the resolution of fever, recovery of neutrophils to ≥0.5 × 10^9/L for 3 consecutive days, death, unresolved toxicity, or request (from patient or physician) for withdrawal from the study. A total of 335 patients (202 children and 133 adults) were evaluable for efficacy.

Response to treatment was observed in 49 patients (49%) in the AmBd arm, 68 (58%) in the LD L-AmB arm, and 75 (64%) in the HD L-AmB arm; however, statistical significance was noted only for the HD L-AmB group in comparison with AmBd. As expected, the median time to response (7, 8, and 10 days) appeared to correspond closely to the median time of neutrophil recovery for the respective treatment groups (AmBd, LD L-AmB, and HD L-AmB). Subgroup analysis of patients with no neutrophil recovery again indicated a significantly higher response rate in the HD L-AmB group than in the AmBd arm (61% vs. 32%; 32 of 100; P = .03).

Treatment failure due to fungal infections was observed in 6 patients: 4 had positive blood cultures for Candida species (2 in the AmBd group and 2 in the LD L-AmB group), while 2 developed pulmonary aspergillosis 2 weeks after the study drug was discontinued (1 in each of the L-AmB arms). Definitions for proven or presumed fungal infections were not clearly stated. In addition, the outcomes for those patients were not stated. The remainder of the patients whose treatment failed had unresolved fever at the end of the study.

Given that antiviral as well as nonsystemic antifungal therapies were used at the discretion of the treating physician, the relative efficacy of empirical treatment in those without proven fungal diseases is difficult to assess. In addition, survival at 30 days was not different among study groups (∼87%). It is interesting that both cases of proven pulmonary aspergillosis developed in the L-AmB treatment arms, with none observed in the AmBd group. Significantly more AmBd patients experienced side effects than did those receiving LD L-AmB or HD L-AmB (46% [65 of 102] vs. 36% [42 of 118] and 43% [51 of 118]; P < .01).

The most frequently reported side effects were first-dose-related fever and rigors, hypokalemia, and nephrotoxicity. Allergic reactions, including rash, flushing, bronchospasm, facial edema, rigors, and back pain, occurred with 2% of administered AmBd doses, followed by 0.8% of HD L-AmB and 0.6% of LD L-AmB doses. Nephrotoxicity, as defined by a 100% or more increase in baseline serum creatinine, occurred significantly more in the AmBd than the LD and HD L-AmB arms (24% vs. 10% and 12%; P < .01). Subgroup analysis of 81 patients who did not receive other concomitant nephrotoxic medication indicated a much lower incidence of nephrotoxicity (zero to 3%) in the L-AmB arms, while the incidence remained unchanged for patients receiving AmBd.

Serum creatinine levels stabilized or reversed in those patients who switched from AmBd to L-AmB secondary to renal toxicity. Liver function abnormalities, specifically in alkaline phosphatase, serum bilirubin, and transaminase levels, were not different between treatment arms. In light of the small total number (6 of 335; 1.7%) and the lack of demonstrable difference in fungal infections among treatment arms, the reversibility of AmBd-induced nephrotoxicity, and similar survival rates, future studies will need to address the cost-benefit ratio of using liposomal product for the empirical treatment of febrile neutropenia in this patient population.
A larger prospective, multicenter trial comparing L-AmB with AmBd for empirical treatment of febrile neutropenia was recently completed in the United States [78]. Results from this trial are available in abstract only but were presented to the FDA Antiviral Advisory Committee on 16 July 1997 as pivotal phase III data supporting the new drug application of Ambisome. Data presented in the abstract, at the FDA hearing in July, and in the package insert serve as the basis for the discussions below [86, 87].

Inclusion criteria for study patients were the following: an age of 2–80 years, absolute neutrophil count of <500, and fever for at least 96 hours despite broad-spectrum antibacterial therapy. A total of 687 patients were randomized to receive either L-AmB (n = 343) or AmBd (n = 344) in a double-blind fashion. Approximately one-third of the patients in each arm were stratified into the high-risk category, which included patients who underwent allogeneic bone marrow transplantation, had relapsed acute leukemia, and had previously received empirical therapy with AmBd.

The initial daily treatment dose was 3 mg/kg for L-AmB vs. 0.6 mg/kg for AmBd; daily dosages could be increased up to 6 mg/kg and 1.2 mg/kg, respectively, according to protocol guidelines. Dosage reduction was allowed for toxicity, to 1.5 mg/(kg·d) for L-AmB and 0.3 mg/(kg·d) for AmBd. Empirical treatment was to continue until neutrophil recovery and up to 3 days following recovery, for a maximum of 42 days. The treatment duration for confirmed infection was extended to 14 days after cultures returned to negative. The mean duration of treatment was ~10 days for both groups.

Composite success rate was the primary study endpoint, which had to include all of the following: survival at 7 days posttreatment, resolution of fever during neutropenia, resolution of mycologically confirmed study-enrollment fungal infections, absence of emergent fungal infection during or within 7 days posttreatment, and no premature discontinuation of drug secondary to toxicities. L-AmB and AmBd treatment resulted in equivalent composite success rates (50% and 49%).

The secondary efficacy endpoint was the incidence of emergent fungal infections. The number of proven fungal infections was lower in the L-AmB recipients than in AmBd recipients (11 [3.2%] vs. 27 [7.8%]); however, the total number of emergent fungal infections (proven and presumed) was the same in each group (n = 43; 12.5%). Criteria for proven infections were defined according to the Mycoses Study Group grading system; however, criteria for presumptive diagnosis were not specified. Candidemia and invasive pulmonary aspergillosis accounted for the majority of proven infections, while the majority of presumed infections were pulmonary. Survival at 7 days posttreatment was similar between groups (93%, L-AmB; 90%, AmBd); long-term survival rates were not determined.

A significantly lower incidence of IRAEs such as fever, chills/rigors, and cardiorespiratory events was noted on study day 1 among L-AmB recipients. Study drugs were administered over 2 hours, with no premedication given prior to initial infusion. Nephrotoxicity was defined as a doubling of the serum creatinine value at baseline for adults, provided that the peak serum creatinine concentration was >1.2 mg/dL. The incidence of nephrotoxicity was significantly less in patients receiving L-AmB than in AmBd recipients (19% [64 of 343] vs. 34% [116 of 344]; P < .001). Of note, the mean peak serum creatinine value was 1.24 mg/dL and 1.52 mg/dL for L-AmB and AmBd, respectively. No difference in the frequency of hepatotoxicity was noted between study groups.

On the basis of the above study results, L-AmB was considered equivalent to AmBd for the empirical treatment of febrile neutropenia. For proven emergent fungal infections, L-AmB appears superior to AmBd; however, the short-term survival rate is not improved. Whether or not treatment with an expensive liposomal formulation results in a meaningful difference in long-term survival rates is unknown. Finally, while L-AmB was shown to be less nephrotoxic than AmBd by study definition, the clinical significance of the difference in mean peak serum creatinine values between study groups is debatable.

Toxicity. L-AmB appears to have a remarkably low rate of IRAEs, compared with that reported for ABLC and ABCD; most studies reported an incidence rate of <5% [34–39, 67, 73, 79–82]. However, the incidence of fever, chills, and rigors associated with initial infusion was near 20%, compared with >50% for AmBd in a large comparative trial of empirical treatment for febrile neutropenia [78]. In addition, the infusion time used with L-AmB is shorter than that for ABLC and ABCD in most studies. With daily dosages of 0.5 mg/kg to 6 mg/kg, the drug usually has been infused over 30–60 minutes, with no test dose administered prior to the first infusions. However, on a few occasions, low-back pain during infusion has been reported, which improved or disappeared with an increase of the infusion time to 2–3 hours [80–82]. Of note, L-AmB was infused over 2 hours in the largest prospective comparative trial performed to date, with an unexpectedly higher reported incidence of IRAEs [78].

Other rare events noted during infusions of L-AmB include confusion, headaches [79, 81, 82], and dyspnea [81–83]. The latter pulmonary reaction appears to differ from those reported with AmBd in that dyspnea was not associated with bronchospasm, fever, chills, or rigors [88, 89]. Anaphylaxis has also been reported in at least three cases in the literature, with signs and symptoms consisting of vomiting, epigastric pain, abdominal tightness, bronchospasm, facial flushing, and sweating [84, 85]. The onset of reaction was within seconds of the start of infusion and resolved within 4 hours after the infusion was discontinued. A test dose prior to initial infusion was not called for in the product packaging, despite the latter reaction.

Similar to findings with ABLC and ABCD, nephrotoxicity associated with L-AmB therapy appears to be significantly less than with conventional AmBd therapy. Overall, the reported incidence of nephrotoxicity, depending upon definition and dosage used, ranges from zero to 31%. When L-AmB was given at 1 mg/(kg·d) for the empirical treatment of febrile
neutropenia, none of the patients who did not receive concomitant nephrotoxic drugs experienced nephrotoxicity [75]. Furthermore, safety data from a phase II/III clinical trial indicate that 85% of the 71 L-AmB recipients who had normal serum creatinine values at the start of therapy still had normal values at the end of treatment. Eleven of those patients received cumulative doses exceeding 5 g. Although no apparent difference in the incidence of nephrotoxicity was noted between LD and HD L-AmB therapy in the previous two large comparative studies, another investigator observed a significantly greater incidence in patients receiving 4 mg/(kg·d) vs. 1 mg/(kg·d) of L-AmB (44% vs. 9%) [77]. As a result, the daily dose of L-AmB is expected to be an important factor associated with the risk of nephrotoxicity.

Other toxicities associated with L-AmB therapy that were also reported with the other lipid-based products are abnormalities in hepatic function, manifested by elevation of the alkaline phosphatase level and conjugated bilirubin. Unlike with the other two products, transaminase values were also noted to increase with L-AmB treatment. A retrospective report on the use of L-AmB as salvage therapy in 133 episodes of infection found hepatic dysfunction possibly attributable to L-AmB in 17% of the episodes; two cases were severe enough to require discontinuation of therapy, with subsequent resolution of abnormalities. The maximum peak levels of aspartate transaminase, alkaline phosphatase, and bilirubin were 510 IU/L, 1,362 IU/L, and 310 nmol/L, respectively [36]. In another large series of patients described by Ringden et al., 26% of 197 treatment episodes were associated with an increase in alkaline phosphatase level; the abnormalities were observed primarily in liver transplant recipients [81].

**Summary—L-AmB.** L-AmB is the most studied of any lipid-based AmB product. However, efficacy data regarding proven systemic fungal infections are limited; empirical therapy for febrile neutropenia has been the primary indication. The dosage studied varies by indication: 1 mg/kg for prophylactic therapy, 1–6 mg/kg for empirical therapy, 3 mg/kg for cryptococcal meningitis, and up to 5 mg/kg for aspergillosis. L-AmB treatment resulted in earlier CSF sterilization but similar clinical response and failure rates when compared with AmBd prospectively in the treatment of cryptococcal meningitis in HIV-positive patients.

Despite a much faster infusion rate (30–60 minutes) used in most studies, L-AmB has been associated with the lowest incidence of IRAEs among the lipid-based products. However, occasionally, the infusion time may need to be extended to 2–3 hours for patients who complain of low-back pain related to the infusion. More important, dyspnea and anaphylaxis necessitating discontinuation of therapy rarely have been reported. L-AmB is less nephrotoxic than AmBd when given at doses three times that of AmBd in adult and pediatric patients. Renal function remains normal at the end of L-AmB treatment in a majority of patients whose serum creatinine level is normal at the start of therapy.

Other toxic effects noted with L-AmB are elevations in transaminase, alkaline phosphatase, and bilirubin levels. Although these abnormalities may occur in up to 26% of patients treated, all appear to be reversible. Drug is discontinued only on rare occasions; no cases of fatal hepatitis have been reported.

**Comparison of ABLC, ABCD, and L-AmB**

All three lipid-based AmB products differ in the type of phospholipid and the phospholipid:AmB ratio, which may be important determinants of fungicidal activity and toxicity [20]. Dosage equivalency among the three products has not been established. Adding to the uncertainty are the variable dosages used in clinical trials within and among different products. Pharmacokinetic properties in terms of plasma and tissue levels also differ among the products. However, the clinical significance of such differences has not been addressed.

Overall, treatment with all three lipid-based AmB products has been evaluated for candidiasis, aspergillosis, cryptococcosis, coccidioidomycosis, mucormycosis, and fusariosis, in descending order of frequency. Published data on ABLC and ABCD are derived primarily from compassionate-use studies of patients refractory to or intolerant of conventional AmBd therapy, while the use of L-AmB has been largely as empirical therapy for febrile neutropenia. When used at five times the AmBd dose for empirical treatment of febrile neutropenia, L-AmB reduced the number of proven emergent fungal infections, yet the short-term survival rate was not altered [78].

For the treatment of proven infections, the response rates, in general, are lower for aspergillosis than for candidiasis; however, the results of open-label trials indicate that the rate of clinical cure with use of L-AmB is greater than that reported with ABLC and ABCD. In addition, both ABLC and L-AmB have been compared prospectively with AmBd for the treatment of cryptococcal meningitis in a small number of HIV-positive patients. Neither lipid product resulted in a better clinical response than with AmBd when used at a daily dosage 3–5 times greater than the dosage of AmBd. In fact, a higher number of patients receiving ABLC had consistently positive CSF cultures at the end of treatment; in contrast, CSF sterilization occurred significantly sooner with L-AmB than with conventional AmBd therapy.

The difference in mycologic response to ABLC and L-AmB must be confirmed with a larger number of patients. To date, few HIV-positive patients with cryptococcal meningitis have been treated with ABCD. Furthermore, ABLC has also been compared prospectively with AmBd for the treatment of invasive candidiasis. No improvement in efficacy was seen with ABLC when given at five times the AmBd daily dose for the treatment of candidemia. No comparative trial report has been published to date evaluating ABCD vs. AmBd prospectively for the treatment of documented infections; one recently completed randomized study that compared ABCD (6.0 mg/[kg·d]) and AmBd (1.0 mg/[kg·d]) for the treatment of invasive aspergillosis in 175 patients awaits data analysis. However, no clinical trial data are available at this point
directly comparing the efficacy and safety of ABLC, ABCD, and L-AmB.

Given the paucity of efficacy data from controlled and comparative trials, several important issues concerning the available efficacy results deserve comment. Definitions for “evaluable” patients as well as treatment response are not provided routinely, which may impact on the comparison of response rates among studies. In addition, response rates were not consistently reported with proven vs. suspected fungal infections. Furthermore, dosages used with ABCD and L-AmB have been variable among studies. Critical factors such as cumulative dose or duration and presence of neutropenia also were inconsistently reported. In those studies that stratified treatment response with neutropenia, higher rates of treatment failure were observed with all three lipid products in patients who were persistently neutropenic throughout the treatment course. Finally, mycologic follow-up was not performed in most studies to document eradication of the organisms.

While treatment with each of the three products resulted in lower risk of nephrotoxicity when given at daily dosages up to five times that of conventional AmBd, it is unknown whether one lipid product is superior in this regard. It does appear that acute IRAEs occurred less frequently in L-AmB-treated patients than in those receiving ABLC, ABCD, or conventional AmBd. Of note, only ABCD requires a test dose prior to initial therapy, according to the product packaging. L-AmB has been infused as fast as 30–60 minutes, more rapidly than ABLC (2.5 mg/[kg·h]) and ABCD (1 mg/[kg·h]), which is an attractive feature for ambulatory home infusion therapy. Close monitoring of both hepatic and renal function during treatment with all three products seems prudent at this point because of the potential for liver function abnormalities.

Given the heterogeneity of the patient populations and the varying indications, dosages, and treatment durations, comparison between products is difficult. Thus, until direct comparative studies are performed with respect to clinical efficacy and toxicities, each lipid-formulated AmB product must be evaluated separately.

Costs and Role of Therapy

Allocation of limited health care dollars to the use of such high-acquisition-cost lipid-based agents can be considered only if they prove to have superior efficacy and reduced toxicities in comparison with conventional AmBd or other effective therapeutic options. According to the average wholesale price dated December 1997, the drug-acquisition cost is the highest for L-AmB, followed by ABCD and then ABCD, all of which are significantly more costly than conventional AmBd. The daily drug-treatment cost for a 70-kg adult patient given L-AmB at a dose of 5 mg/kg vs. AmBd at a dose of 1 mg/kg, on the basis of the average wholesale price, is $1,300 and $24, respectively. Comparatively, therapy with ABLC for the same patient at 5 mg/(kg·d) costs $570. Depending on the dosage used, the daily cost for ABCD varies. Based on the manufacturer’s recommended dosing (3 mg/kg up to 6 mg/kg), the daily cost of drug ranges between $330 and $660 for the same patient.

While the drug-acquisition costs for the lipid products are exceedingly high, when performing cost-effectiveness analysis one needs to balance the acquisition cost with (1) the costs associated with the failure to prevent fungal infections, in cases of empirical treatment, (2) the cost of nephrotoxicity, and (3) the cost of premedications used to minimize IRAEs.

Efficacy evaluations of these products have focused primarily on candidiasis and aspergillosis. Limited data from one prospective controlled trial on candidemia indicated that when used at five times the AmBd dose, ABCD was not more efficacious. In contrast, ABCD appeared to be more efficacious than AmBd in a retrospective concurrent-control study of aspergillosis. However, more AmBd recipients remained persistently neutropenic during the study, potentially influencing treatment response. In addition, when patients receiving AmBd who had postmortem-diagnosed aspergillosis were excluded, the difference in response rates did not reach statistical significance. Thus, neither ABLC nor ABCD demonstrated superior efficacy when directly compared with AmBd. However, they appear to have a potential role in salvage therapy for those cases refractory to treatment, defined by receipt of at least 500 mg of AmBd.

Accordingly, none of the lipid-based products should be considered as first-line therapy for documented invasive mycoses. Relatively less expensive and nonnephrotoxic alternative therapies should be considered when appropriate. For example, fluconazole should be considered for the treatment of uncomplicated candidemia due to C. albicans and in maintenance therapy for cryptococcal meningitis in HIV-positive patients. Fluconazole therapy given orally in cases in which absorption is adequate further enhances this drug as a cost-effective therapeutic option.

An additional indication for antifungal therapy is empirical treatment in neutropenic patients unresponsive to antibacterial therapy. As demonstrated in the largest prospective, randomized, comparative study involving L-AmB and AmBd, the total number of emergent fungal infections (proven and presumed) was small, and these occurred at the same rate (12.5%); however, there were fewer proven infections in the L-AmB arm, with no effect on the short-term survival rate [78].

On the basis of the study results, the additional direct treatment cost associated with the use of L-AmB to reduce the incidence of invasive fungal infections by ~5% was in excess of $2.6 million. A recent meta-analysis of 24 randomized controlled trials with 2,758 neutropenic cancer patients receiving prophylactic or empirical antifungal therapy revealed a lack of survival benefit, despite significant reduction in the incidence of invasive fungal infection [90]. In the current setting of limited health care resources, better predictors to identify those neutropenic patients at highest risk for the development of invasive fungal infections are urgently needed. In addition, future studies should perform cost-benefit analyses that include data on length of hospital stay and long-term survival rates in order to aid clinicians in making the most cost-effective therapeutic decision.
All comparative studies indicate that lipid-based AmB products are associated with less nephrotoxicity; however, none addresses the incidence of irreversible renal dysfunction, which is a pivotal safety endpoint to justify use of such expensive agents. Although the incidence of nephrotoxicity with AmBd has been reported to be in the range of 15%–90%, permanent renal dysfunction is rare [91].

Despite the high acquisition cost and lack of superior efficacy, the lipid-based products may prove to be cost-effective by minimizing the risk of nephrotoxicity and other morbidities, thus reducing the overall health care costs for the treatment responders. One ongoing multicenter study is attempting to address these pharmacoeconomic issues by comparing the quantity of resources consumed (i.e., intensive care stay, need for dialysis, relapse or treatment failure, and diagnostic procedure costs) for ABCD vs. AmBd recipients. Until pharmacoeconomic analyses document the value of these drugs or such drugs clearly are found to be more clinically effective, the use of such products should be highly restricted to those intolerant of or refractory to AmBd treatment.

Conclusion

At present, if a lipid-based AmB product is considered for use, L-AmB, ABLC, and ABCD appear to be similar with respect to their efficacy against candidiasis and aspergillosis and the associated risk of nephrotoxicity. The latter two products cost significantly less than L-AmB. ABLC appears to afford a lower incidence of reversible infusion-related toxicities than does ABCD (not on the basis of direct comparative study), but at a slightly higher drug-acquisition cost. L-AmB is the only product with an approved indication for the empirical treatment of febrile neutropenia in patients unresponsive to antibacterial therapy. However, the clinical utility of L-AmB for this indication is hampered by its exceedingly high cost and unknown effect on long-term survival rate.

While these novel formulations of AmB represent a significant advance in drug-delivery technology to minimize toxicities, their overall value in the treatment of infection is controversial. More controlled trials will need to be performed in order to determine the clinical situations in which the most benefits can be derived from the use of these new products, such that the direct costs can be readily justified.

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