consequences of toxicity, it is doubtful that the entire sum would be recouped. On the contrary, Cagnoni et al. [8] estimated that the use of LFABs in a randomized study added approximately $5800 to the average cost of hospitalization. This cost likely underestimates the true financial burden in typical clinical practice, as the doses of LFABs utilized in the study were modest (most patients received 3 mg/kg per day).

Hence, although LFABs have been proven equally efficacious as and less toxic than AmBID, we believe that the economic impact of a global switch away from AmBID would be difficult to justify. Rather, both AmBID and LFABs should be considered alternative gold standards. At hospitals with limited resources, such as ours, it would be financially impossible to replace AmBID with LFABs.

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References


Lipid Amphotericin B Formulations as Comparators in Clinical Trials

Sir—We would like to thank Ostrosky-Zeichner et al. [1] for their compilation of data on lipid formulations of amphotericin B (LFABs). Two years ago, we outlined options for use of a non-US Food and Drug Administration (FDA)-approved comparator in active-controlled trials [2]. One of these options was to supply evidence from the literature and elsewhere regarding the safety and efficacy of the unapproved comparator. Ostrosky-Zeichner et al. [1] have taken the first step toward compiling this evidence for LFABs. However, they also point out that individual LFABs have important differences in pharmacokinetics and safety profiles. Therefore, one cannot view these drugs as interchangeable [3]. These differences may be important in a clinical trial in which one is specifically attempting to measure differences in safety and efficacy between drugs. The current absence of evidence of differences between individual LFABs cannot be interpreted as evidence of the absence of true differences, because these drugs have rarely been compared directly. Drug sponsors who wish to use an LFAB as a comparator in a clinical trial for a disease for which the formulation is not FDA-approved should compile evidence on that specific LFAB and on the selected dose for the specific disease under study.

However, is the question of whether conventional or lipid formulations of amphotericin B should be the gold standard now a moot point? One usually chooses non-FDA–approved comparators in a clinical trial because of lack of other treatment options for the disease under study. In the case of LFABs, the issue was the potential safety benefit of LFABs compared with conventional amphotericin B (C-AmB) in treating diseases for which there were no other available therapies. However, since the previous discussion of alternative trial designs for antifungal drugs, the FDA has approved voriconazole for the primary treatment of invasive aspergillosis [4] and caspofungin for the primary treatment of candidemia and invasive candidiasis [5]. Voriconazole was statistically superior to C-AmB plus other licensed therapy, which included LFABs, in the treatment of invasive aspergillosis. Caspofungin had comparable efficacy to C-AmB in treating candidemia and had a more advantageous safety profile. Fluconazole is also FDA-approved for the treatment of invasive candidiasis and candidemia [6] and has a more favorable adverse event profile than does C-AmB. Although some LFABs may have safety advantages over C-AmB, the toxicities of LFABs are not insubstantial, as Ostrosky-Zeichner et al. [1] point out. The Declaration of Helsinki, an international document that describes ethical considerations in clinical investigations, states that, “In any medical study, every patient—including those in the control group, if any—should be assured of the best proven diagnostic and therapeutic method” (p. 926) [7]. One could assert, then, that using comparators in clinical trials with known safety disadvantages compared with other FDA-approved therapies with similar efficacy for the disease under study would not meet this standard. Although LFABs give clinicians an important option in the treatment of fungal disease, the question remains: should any amphotericin product be the gold standard for use as a comparator in clinical trials of invasive aspergillosis and candi-
with use of aggressive nephrotoxicity-prevention protocols [1]. Although we agree that such trials would be of interest, saline loading is not suitable for all patients, and the need for complicated protocols and monitoring also adds to the cost of such treatment [6].

Both Johnson [1] and Schneemann and Bachli [2] bring up the possibility of using continuous infusions of AmBD. However, as reviewed by Lewis and Wiederhold [7] in their article regarding the study by Imhof et al. [8], continuous infusions of AmBD are not widely accepted for 3 reasons: “(1) comparative data supporting the efficacy of continuously infused AmBD are still limited; (2) dedication of venous access solely to the administration of AmBD is often unfeasible, especially in critically ill patients; and (3) the concentration-dependent pharmacodynamic characteristics of AmB suggest that less-frequently administered, higher daily doses would be more active than the same daily dose of AmBD administered by continuous infusion” [7, p. 871]. For these reasons, and because we believe that the need for complicated maneuvers to administer this difficult-to-use drug can be circumvented by use of alternatives formulations, we do not support this strategy at this time.

Spellberg, Witt, and Beck [3] bring up several points in their letter. The first part of their letter reminds us of the difficulties of performing research in clinical mycology [9, 10]. They next observe that short- and long-term toxicities associated with AmBD are often treatable and reversible. Although we agree that infusion-related reactions are treatable and that AmBD-induced nephrotoxicity is often reversible, nephrotoxicity may resolve slowly or incompletely, the patient’s care may be significantly complicated in the interim, and there does appear to be an associated increase in mortality [11, 12]. Also, the long-term impact of even modest elevations of the serum creatinine level is unknown. Finally, we agree that, although some early pharmacoeconomic estimates seem favorable and others do not, the financial impact and benefits of the use of these agents remain to be studied in more detail [13]. However, we wish to emphasize that these studies should focus, not only on the immediate and easily tangible drug acquisition costs, but on the overall cost of care, as well as on the short- and long-term consequences of using these agents. This is where we believe the impact of LFABs will be of most significance, both for patients and health care administrators.

Finally, Powers and Albrecht [4] correctly observe that the absence of evidence of difference is not the same as the absence of differences. We entirely agree, but we also think that the accumulated evidence supports the conclusion that LFABs are at least as active as AmBD against infection, that any remaining unmeasured differences favor LFABs, and that LFABs are thus appropriate as candidates to replace AmBD as the gold standard formulation of amphotericin B. The excellent question of what would constitute an optimal comparator for any future specific study is a separate issue. As Powers and Albrecht [4] observe, there are indeed an increasing number of options among US Food and Drug Administration–approved therapies for some fungal infections. However, approved comparators do not exist for all defined infections, changes in patterns of resistance could reduce the utility of any given agent, and drug-specific pharmacological issues (e.g., the limitations on the intravenous dosing of voriconazole in patients with reduced renal function) could also limit the number of choices for some patient groups. Thus, we feel that putting forward options and information that might maximize the utility of the amphotericin B is an important step.

In summary—and as we observed in our article [5]—there are circumstances under which AmBD can be used with an acceptable risk-benefit ratio, whereas other situations would appear to favor a lipid formulation [14]. We hope our review continues to ignite local, regional, na-

References