Editorial Response: Choosing Amphotericin B Formulations—Between a Rock and a Hard Place

When choosing lipid formulations of amphotericin B to be used in treatment, physicians and pharmacies have been forced to choose on the basis of either price or adverse reactions. There have been no adequate studies comparing the efficacy of any 2 amphotericin B formulations in proven cases of mycosis; all comparisons performed so far have been either with historical controls of limited value or with empirical therapy. Although amphotericin B has come to be used in febrile neutropenic patients who have not responded to as little as 72 h of antibacterial therapy, there are no studies that have established the efficacy of antifungal therapy at this juncture, with or without prior fluconazole prophylaxis. Without knowing whether amphotericin B is needed at all, concluding that 2 formulations are equally efficacious is meaningless.

See article by Wingard et al. on pages 1155–63.

While the paper by Wingard et al. [1] does not solve this sad dilemma, the paper does add helpful quantitative data on comparative toxicity. There are already published comparisons of toxicity between the old deoxycholate formulation and either amphotericin B colloidal dispersion (ABCD) [2] or liposomal amphotericin B (AmBisome) [3], but there have been no published comparisons of the toxicity of amphotericin B lipid complex (ABLC) and liposomal amphotericin B. Fujisawa (Deerfield, IL) which markets liposomal amphotericin B in the US and which no doubt paid hundreds of thousands of dollars for this study, has an incentive to show that their product is less toxic because it is certainly more expensive. The 1998 average wholesale price for a 5 mg/kg dose of these drugs for a 70 kg person was $560 for ABLC and $1316 for liposomal amphotericin B. At 3 mg/kg, the average wholesale price of liposomal amphotericin B was $940. The actual price of either drug naturally depends on purchasing agreements between hospital systems and the suppliers.

Regardless of obvious commercial interest in the outcome, this well-designed, randomized, double-blinded trial has provided useful data; namely, that ABLC at a dose of 5 mg/kg was more toxic than liposomal amphotericin B at a dose of either 3 or 5 mg/kg. Exactly which differences were statistically significant is more difficult to say because of the study’s design.

The global end point was based on efficacy, and no difference was found. Differences in toxicity were evaluated by numerous \( \chi^2 \) and Fisher’s exact tests. Although a \( P = .01 \) was selected because of multiple comparisons, this is not adequate to correct for the multiple subset analyses performed. A somewhat disquieting alternative would have been to decide before the study began that efficacy was unlikely to be meaningful and to power the study solely to examine criteria for toxicity.

Laying aside the statistical issues, the results of the study are internally consistent across categories of toxicity and encompass both infusion-related toxicity and renal toxicity. The question that the results pose can be framed like this: is the reduced toxicity of liposomal amphotericin B to a particular patient compelling enough to justify the extra dollars? Logically, the answer should depend on the individual patient. Considering chills and fever are usually worst on the first day and that these patients were not allowed to take premedication to reduce fever that day, the physician will want to ask whether premedicating the patient will be sufficient to blunt infusion-related reactions. Patients with advanced respiratory or cardiac failure may have a mild reaction and become hypoxic and hypotensive. Nephrotoxicity of ABLC is often very modest and can be reversed rapidly after ABLC is discontinued. However, patients who receive other nephrotoxic agents or who have other renal disorders can sometimes become azotemic quite rapidly when they are treated with ABLC. Severe azotemia complicates management and causes significant morbidity and mortality, particularly when hemodialysis becomes necessary. The cost of monitoring patients for azotemia will not differ between ABLC and liposomal amphotericin B because both are nephrotoxic and patients who receive them must be monitored.

Despite the logic of making decisions based upon individual patient needs, the cost differences between amphotericin B formulations have caused the decision about whether to use them to be moved from the bedside to the boardroom. Not only is liposomal amphotericin B more expensive than ABLC, both are much more expensive than the old deoxycholate formulation. Hospitals will have to continue to make rules about how their physicians select an amphotericin B formulation. The rules should reflect the needs of their particular patient populations. The job has been rendered somewhat easier by the study of Wingard et al., which gives us numerical data on the differences in the toxicities of the 2 compounds. Although we would rather know differences in efficacy than toxicity, this paper is a step in the right direction.

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References

