Continuous Infusion of Amphotericin B Deoxycholate for the Treatment of Life-Threatening Candida Infections

To the Editor:

Dreyfuss and colleagues advocate the use of conventional amphotericin B (CAMB) for the treatment of life-threatening Candida infections in intensive care unit patients (1). Key elements of their plea include the manageable toxicity associated with CAMB, using appropriate salt administration, hydration, continuous infusion, and electrolyte replacement; the lack of evidence that the newer formulations of AMB are more efficacious than CAMB; and financial considerations.

Dreyfuss and colleagues claim that continuous infusion of CAMB resulted in superior mortality compared with rapid infusion. The authors refer to two studies, but toxicity and not treatment efficacy was the primary focus in both (2, 3). The first study was a prospective randomized trial comparing rapid infusion (4 h) with continuous infusion (24 h), aiming at inclusion of 40 patients in each category. The study was powered to detect a difference in creatinine clearance at the end of therapy. An analysis of treatment efficacy was provided using mortality, mortality due to invasive fungal infections, and breakthrough fungemia. A significant difference in efficacy was observed in favor of continuous CAMB infusion (2). However, this study was not blinded, indications for fungal infections, and breakthrough fungemia. A significant difference in efficacy was observed in favor of continuous CAMB infusion (2). The second study was a retrospective study comparing rapid infusion of CAMB in 42 patients (January 2001 to January 2002) with continuous infusion for 39 patients (January 2002 to January 2003) (3). A significant difference in mortality was again found in favor of the continuous infusion–treated patients. However, there were no significant differences in mortality due to invasive fungal infection or in breakthrough fungal infection between the two groups, suggesting that other factors might have contributed to the observed difference (3). We believe that these two studies do not provide sufficient clinical evidence to support the claim that the efficacy of continuous infusion of CAMB is superior to that of conventional rapid infusion. Even comparable efficacy between the two administration schedules has not been shown.

Our concern is underscored by preclinical studies that investigated the pharmacokinetics and pharmacodynamics of CAMB in invasive fungal infection. Experimental models of Candida infection show that the pharmacodynamic parameter that best correlated with outcome is the maximum concentration–to–minimum inhibitory concentration (MIC) ratio \([C_{\text{max}}/\text{MIC}]\) (4). \([C_{\text{max}}/\text{MIC}]\) was also found to correlate best with efficacy in an in vivo model of Aspergillus infection (5). The aim therefore would be to achieve high peak serum concentrations of CAMB, which is best approached by rapid infusion, and not with continuous infusion. Lipid formulations of amphotericin B, such as liposomal amphotericin B, do allow higher peak concentrations to be achieved without dose-limiting renal toxicity.

When comparing the efficacy of CAMB with lipid formulations of the drug, the clinical trials were powered to demonstrate noninferiority, and as a consequence it would be very difficult to demonstrate superiority in any study arm. Also, hydration is considered the standard of care in centers where CAMB is administered through rapid infusion, as there is strong evidence that this provides renal protection.

Although some of us fall in the category of scientists with potential conflicts of interest, our scientific accuracy leads us to conclude that clinical evidence is lacking to justify continuous infusion of CAMB for treatment of life-threatening Candida infections. Our views are in keeping with recent major Candida practice guidelines (6).

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

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Reply

From the Authors:

We thank Pövoa and colleagues and Seyedmousavi and colleagues for their interest in our work (1). We unintentionally missed their previous contribution (2), but fully agree with Pövoa and colleagues that conventional amphotericin B (CAMB) should be the first-line agent for treatment of systemic candidiasis pending confirmation and susceptibility analysis, for cost and possible efficacy considerations.

In their letter, Seyedmousavi and colleagues rightly underline the weaknesses of studies on continuous CAMB but—certainly

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