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Results from the study by Hachem et al<sup>11</sup> are similar to those reported by Wingard et al,<sup>34</sup> in that the use of ABLC as primary antifungal therapy was associated with significantly more nephrotoxicity than L-AmB. However, this difference was not observed in patients receiving salvage therapy. In addition, although meta-analysis results showed an increased probability of developing nephrotoxicity when the primary treatment arm was included in the analyses, the OR and RR were considerably less than those observed with the Wingard study. As indicated earlier, the Hachem study looked at severely ill patients with advanced hematologic malignancies, who may have had reduced renal function, confounding the nephrotoxicity analysis between ABLC and L-AmB.

Despite reduced rates of adverse reactions compared with conventional amphotericin B, patients receiving antifungal therapy with ABLC and L-AmB still experience few infusion reactions and renal toxicity.<sup>8,23,29</sup> Using a murine candidiasis model, Andes et al<sup>1</sup> found that lipid formulations of amphotericin B distribute preferentially to the mononuclear phagocytic system. The interaction of free amphotericin B drug released from lipid vehicles with macrophages may be responsible for observed infusion reactions.<sup>1</sup> However, macrophage nitric oxide synthase expression and tumor necrosis factor- $\alpha$  production is reduced by lipid formulations of amphotericin B.<sup>14</sup> In addition, ABLC and L-AmB appear to downregulate or have no effect on genes coding for proinflammatory cytokines, which could explain the lower levels of infusion-related reactions compared with conventional amphotericin B.<sup>30</sup> Lipid formulations of amphotericin B may have reduced nephrotoxicity because the drug is distributed to tissues of the reticulo-endothelial system, sparing the kidneys. Furthermore, in the kidneys, less amphotericin B is released from the lipid carrier, because the synthetic phospholipids have a greater affinity for amphotericin B than does cholesterol in renal epithelial cell membranes.<sup>32</sup> Toxic effects and vasoconstriction associated with conventional amphotericin B are diminished as a result of lower amounts of amphotericin B reaching kidney cells.

## Conclusions

Renal failure associated with the use of conventional amphotericin B results in longer hospital stays, increased treatment costs, and higher mortality rates.<sup>3</sup> The development of lipid formulations of amphotericin B has improved delivery of the drug and decreased the incidence of adverse reactions and nephrotoxicity associated with conventional amphotericin B. A comprehensive review and analysis of studies comparing amphotericin B formulations demonstrate that lipid forms help preserve renal function and improve survival in patients critically ill from invasive fungal infections.<sup>29</sup> Considering the costs associated with renal failure, the ability to use lipid formulations of

amphotericin B becomes increasingly important in patients requiring broad-spectrum antifungal therapy. Our meta-analysis raises questions about the previously known relative nephrotoxicity of ABLC or L-AmB. In addition, no conclusive differences in response and outcome have been reported in patients with invasive fungal infections treated with ABLC or L-AmB. Therefore, cumulative evidence suggests that ABLC or L-AmB can be administered to immunocompromised individuals for the treatment or prophylaxis of invasive mycoses, with comparable efficacy and safety.

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