Correspondence

Amphotericin B–Related Nephrotoxicity Has an Economic Impact on Hospitals and Health Systems

SIR—The recent report by Harbarth et al. [1] is an interesting attempt to assess the clinical and economic outcomes associated with renal toxicity after treatment with amphotericin B. The study uses survival analysis to model the effects of nephrotoxicity on length of hospital stay, costs of hospitalization, and mortality rate.

Harbarth et al. [1] note that their single-center results are markedly different from the findings of previous reports [2]. Specifically, findings of Harbarth et al. [1] are different those of our retrospective, multicenter study, which demonstrated significant increases in the length of hospital stay and costs for patients who experienced nephrotoxicity after receiving treatment with conventional and liposomal amphotericin B.

There may be several reasons for these differences in addition to the methodological ones identified by Harbarth et al. [1]. One main difference lies in underlying patient demographic characteristics. All of the patients from our study were febrile and neutropenic [3]. More than 50% of the patients in our study were bone marrow transplant recipients. This contrasts with the more heterogeneous population analyzed at LDS Hospital (Salt Lake City).

A second important difference is that >75% of patients enrolled in the study by Walsh et al. [3] received ⩾2 concomitant nephrotoxic agents. This critical risk factor and potential confounding variable was not incorporated in the study by Harbarth et al. [1]. Lack of concomitant therapy with nephrotoxic agents may, in part, explain the 12% incidence of nephrotoxicity found by Harbarth and colleagues.

Also, our analysis was performed to evaluate the pharmacoeconomics of conventional and liposomal amphotericin B within the context of a randomized, double-blind, multicenter clinical trial. The objective of our study was not to evaluate the impact of nephrotoxicity solely. Instead, because the clinical study was not powered to measure economic differences from an intent-to-treat perspective, costs associated with pivotal clinical outcomes (namely nephrotoxicity) were examined to allow for economic comparisons between treatment groups.

A separate analysis of a different cohort of patients treated with lipid formulations of amphotericin B was conducted recently to determine factors that affect hospital costs [4, 5]. Stepwise regression analysis showed that length of hospital stay, nephrotoxicity, number of concomitant medications, receipt of dialysis, allogeneic bone marrow transplantation, and duration of treatment (in days) with study drug all affected hospital costs after the initiation of lipid-based therapy.

Overall, we believe that the analysis by Harbarth et al. [1] is valuable in promoting the use of additional techniques to examine the impact of treatment-related adverse events on hospital costs. However, its findings with respect to the net impact of amphotericin B–induced nephrotoxicity should be applied with caution across various patient populations, clinical settings, institutions, and treatment decisions.

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Reply

SIR—We appreciate the thoughtful comments of Prendergast and Tong [1] regarding our article [2]. We have 2 comments in response.

First, we did examine the independent effect of other nephrotoxic agents on the incidence of renal failure, as reported in a previously published article [3]. In these detailed analyses, treatment with cyclosporine and the mean daily amphotericin B dose were found to be independently associated with the development of nephrotoxicity. Use of amikacin tended to increase the risk of nephrotoxicity, whereas use of tacrolimus, furosemide, or vancomycin was not an independent predictor of nephrotoxicity in that cohort study [3].

Second, we would like to underscore one of the main messages of our article [2], which is that the statistical methods used for estimating the cost impact of an adverse event have a major effect on the results. Costs attributed to adverse events, such as nephrotoxicity, should include only those costs incurred after occurrence of the adverse event. Observing an association between high hospital costs and nephrotoxicity is not a reliable indicator that nephrotoxicity is the direct cause of the higher costs, because many confounding factors probably exist that are common causes of higher cost and nephrotoxicity, including factors that are unmeasured. It is not safe to assume that this confounding is removed simply by building a multivariable regression model, particularly when criteria used for variable inclusion are based solely on statistical significance. The recent study [4] cited by Prendergast and Tong [1] found that nephrotoxicity was one of the factors associated with increased costs in a multivariable regression model, when all costs incurred after study entry, both before and after the adverse event, were grouped together. Another finding from this study worth noting is that the agents that were compared in the clinical trial (amphotericin B lipid complex and liposomal amphotericin B) exhibited similar efficacy but dramatically different incidences of adverse events (e.g., the incidences of nephrotoxicity were 42% and 14%–15%, respectively). However, total poststudy entry costs (excluding the cost of the study drug) across treatment groups were similar, a finding parallel to a study by Cagnoni et al. [5]. Thus, unconfounded, intent-to-treat analyses do not support the contention that nephrotoxicity has a large causal effect on hospital costs.

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Human Granulocytic Ehrlichiosis Presenting as Acute Abdomen in an Adult

Sir—Rickettsial illnesses manifest in many ways, and our knowledge of disease caused by these organisms is still evolving. We read with interest the report by Seydev et al. [1] of human monocytic ehrlichiosis (HME) that caused acute appendicitis in a pregnant woman. Rocky Mountain spotted fever (RMSF) can present with symptoms mimicking appendicitis [2], and another recent article described a child with human granulocytic ehrlichiosis (HGE), acute abdomen, and suspected appendicitis [3]. To date, there have been no reports in the literature of HGE presenting as acute abdomen in an adult. Here, we present such a case.

A 46-year-old white man was hospitalized for diffuse abdominal pain and fever. His only significant medical history was occasional abuse of >1 substance at a time. Five days before admission to the hospital, he noted acute onset of fever and "flulike symptoms." He gradually improved and attended a party on the night before admission, where he used cocaine and consumed alcohol. Subsequently, he developed diffuse, severe abdominal pain that was localized in the right lower quadrant (RLQ). He denied a recent history of nausea, vomiting, diarrhea, and dysuria. He was heterosexual and denied having had unprotected sex, used injection drugs, or recently traveled. He wasn't receiving medication.

In the emergency department, his temperature was 38.8°C, his pulse rate was 102 beats/min, his blood pressure was 130/80 mm Hg, and his respiration rate was 18 breaths/min. He appeared uncomfortable, with rebound tenderness in the RLQ and voluntary guarding; results of stool guaiac-based testing for occult blood were negative.

Abdominal radiographs showed dilated small bowel loops. Abdominal CT revealed terminal ileum wall thickening consistent with ileitis. The patient's WBC count was 9900 cells/mL (82% neutrophils), and his hemoglobin level was 14.9 g/dL. Results of chemistry testing were normal, except for an albumin level of 3.3 g/dL and an alanine aminotransferase level of 47 U/L. Ciprofloxacin and metronidazole therapy was started, and the surgery department was consulted. Their impression was that the patient had acute terminal ileitis. He was admitted for intravenous hydration therapy and bowel rest and continued to receive antibiotic treatment and to undergo monitoring.

During the 24 h after admission, severe abdominal pain persisted, which required intravenous narcotics. His temperature increased to 40.0°C. Further questioning revealed that, 1 week before the onset of symptoms, he was bitten by a tick in a rural park in upstate New York. He removed and kept the "large" tick. He denied having had any subsequent rash. An eschar at the site of the tick bite was noted