because it occurred in the midst of the usual seasonal increase in the number of cases of enteroviral meningitis together with cases of herpes simplex virus 1 (HSV-1) encephalitis, which occurs sporadically throughout the year. HSV-1 encephalitis may be differentiated from WNE by the presence of focal abnormalities on the electroencephalogram and/or on CT/MRI scans. Most cases of enteroviral meningitis are not accompanied by encephalitis, but enteroviral infections of the CNS are frequently accompanied by nonexudative pharyngitis, loose stools, or a maculopapular rash. Neither of these viral infections that infect the CNS is accompanied by lymphocytopenia. Although our series is limited, we believe that profound and prolonged lymphocytopenia in patients with encephalitis is an important diagnostic clue of WNE. In patients with encephalitis, aseptic meningitis, profound lymphocytopenia in patients with encephalitis is an important diagnostic clue of WNE. In patients with encephalitis, aseptic meningitis, profound lymphocytopenia, clinicians should rule out enteroviral meningitis and HSV-1 encephalitis and should order specific WNE serological testing.

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Controlled Trials of Amphotericin B Lipid Complex

SIR—In the January 2000 issue of Clinical Infectious Diseases, we read, with some puzzlement, the letter [1] “Controlled Trials of Amphotericin B Lipid Complex and Other Lipid-Associated Formulations.” The authors, Winston and Schiller, state: “We participated in 2 randomized, controlled trials of ABLC [amphotericin B liquid complex] therapy for neutropenic patients…. The first trial was a randomized study comparing the efficacy and safety of ABLC and fluconazole as prophylaxis for fungal infections in bone marrow transplant recipients. Unfortunately, this trial was prematurely discontinued because of unacceptable nephrotoxicity when ABLC prophylaxis was used for patients receiving cyclosporine prophylaxis. Patients who received ABLC prophylaxis also had frequent chills and fever; these toxicities were not observed in patients who received fluconazole prophylaxis.”

Dr. Winston was an investigator for such a proposed study in 1994. Actual enrollment of patients in the comparative phase of the study was never initiated; therefore, we are puzzled by Dr. Winston’s comments regarding nephrotoxicity data from a comparative study that never took place.

The second study cited by Winston and Schiller, a study comparing amphotericin B with ABLC (Abelcet; Liposome, Princeton, NJ) for the empiric treatment of patients with febrile neutropenia, was initiated in the United States. Enrollment in this study was discontinued in 1995 because of study-design issues and related investigator protocol violations. The study was also discontinued as a result of the Liposome Company’s internal management decision to focus the clinical development of Abelcet on the treatment of confirmed fungal infection in patients who cannot tolerate or who do not respond to conventional antifungal therapy.

Given the high percentage of protocol violations in the study, a formal analysis of these data has not been conducted, and findings from such a database would be potentially misleading. Despite the early termination of this study, Dr. Winston was provided with the individual data listings for patients enrolled at this site. The data to which Drs. Winston and Schiller refer reflect a very limited patient enrollment at their center (12 patients treated with amphotericin B and 13 treated with amphotericin B lipid complex). In such a limited number of patients, a comparison of the safety and efficacy of treatment for febrile neutropenia would not be expected to demonstrate a statistically significant difference in outcome. Indeed, the Mycosis Study Group’s recently completed study of treatment with AmBisome versus conventional amphotericin B required the enrollment of >700 patients to have statistical power to detect potential differences between the 2 products when they are used for the empiric treatment of fungal infections in patients with febrile neutropenia [2].

During the past 4 years, >80,000 patients who have had proven infection and who have either failed or developed in-
tolerance (including renal intolerance) to treatment with amphotericin B have been treated with Abelcet. Our experience with these patients and the findings from other clinical studies of Abelcet previously reported in Clinical Infectious Diseases and other medical journals support findings that Abelcet is effective and has an acceptable safety profile for the treatment of patients with fungal infections.

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Reference

Reply
Str—In the package insert for amphotericin B lipid complex (ABLC; Abelcet; Liposome, Princeton, NJ), there is a precautionary statement that data from a prospective study of prophylactic ABLC for the treatment of patients undergoing bone marrow transplantation have suggested that concurrent use of cyclosporine and ABLC may be associated with increased nephrotoxicity [1]. This statement is based on data from the prophylactic study of ABLC in bone marrow transplant recipients that we mentioned in our recent letter [2].

According to our records, 29 patients from the University of California at Los Angeles (UCLA) Medical Center participated in the multicenter, randomized trial comparing ABLC with amphotericin B as empirical antifungal therapy for patients with febrile neutropenia. Fourteen patients were given ABLC, and 15 patients were given amphotericin B. A successful response occurred in 8 patients (57%) who were given ABLC and in 9 patients (60%) who were given amphotericin B. Nephrotoxicity (defined as doubling of the baseline serum level of creatinine) occurred in 7 patients (50%) who were given ABLC and in 8 patients (53%) who were given amphotericin B. We agree that this is a limited number of patients. However, the 50% incidence of nephrotoxicity associated with ABLC is not insignificant and is similar to the incidence observed with the use of ABLC in another recent study of patients with febrile neutropenia [3].

To our knowledge, ~200 patients were enrolled in the multicenter study before the study was prematurely discontinued by the Liposome Company. Despite investigators’ repeated requests for the opportunity to review the data on all patients who entered the trial, the Liposome Company declined to provide the data. We are not aware of any protocol violations that would preclude a meaningful review and analysis of these data.

Dr. Boyle’s reference to the large number of patients who have been treated with ABLC outside of a controlled study ignores one of the most important points that we emphasized in our letter [1] and that Dr. Walsh emphasized in his paper [4]. Randomized, double-blind multicenter trials should be the standard for the assessment of the comparative efficacy and safety of newer antifungal agents. Indeed, in such a recent randomized trial involving 244 patients with febrile neutropenia [3], significantly more patients who were treated with ABLC, compared with patients who were treated with liposomal amphotericin B (AmBisome; NeXstar, San Dimas, CA), experienced drug-related nephrotoxicity (42% vs. 15%; P < .001), chills (80% vs. 21%; P < .001), and fever (58% vs. 22%; P < .001). More patients who were treated with ABLC (32%) discontinued therapy prematurely because of drug-related toxicity than did patients who were treated with AmBisome (14%).

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