the prescribing habits of practitioners [1]. Until recently, vancomycin has been the major therapeutic agent used in these situations and has performed well. An alternative to vancomycin is welcome and necessary for 4 major reasons. First, resistance among enterococci has prompted the development of guidelines that emphasize the need to restrict vancomycin use for hospitalized patients. Second, the inherent toxicities of vancomycin, such as red man syndrome and nephrotoxicity, necessitate care in administration of the drug and monitoring of patients’ renal function. Third, as Dr. Siegel [1] suggests, vancomycin must be administered intravenously. Finally, the emergence of S. aureus strains that have intermediate resistance to vancomycin was described several years ago, first in Japan [2] and then in the United States [3]. In July 2002, an article in Morbidity and Mortality Weekly Report reported a strain of S. aureus with an MIC of vancomycin of >128 µg/mL [4]. The organism was susceptible to linezolid, trimethoprim-sulfamethoxazole, and tetracycline.

Linezolid can be administered intravenously or orally. In fact, because of its 100% bioavailability, orally administered linezolid (600 mg) yields plasma concentrations that are much greater than the MIC90 for MRSA for the entire 12-h dosing interval. For example, the mean steady-state plasma concentrations of linezolid are ~12 µg/mL at 6 h after administration of 600 mg po q12h (Zyvox; Pharmacia) [5]. Thus, as indicated in previously published studies [6, 7], a variety of MRSA infections initially can be treated with intravenously administered therapy, followed by oral therapy. Unanswered questions regarding linezolid include its efficacy in the treatment of endocarditis and osteomyelitis. At this point, neither indication is approved, and additional studies are necessary. In addition, neutropenia and thrombocytopenia have been described in patients receiving linezolid [8]. To date, these events have been reversible and have tended to occur in patients receiving prolonged treatment. It is unclear whether this will be a problem for patients who are neutropenic or thrombocytopenic at the onset of linezolid treatment. In a recent study of 240 patients who received linezolid, these adverse events were not observed [6]. Another potential problem is the emergence of antimicrobial resistance during treatment, which has been reported in association with both vancomycin therapy and linezolid therapy in patients with enterococcal infections [9, 10]. In addition, as previously mentioned, vancomycin-resistant strains of S. aureus recently have been reported. Thus far, there has been one report of linezolid resistance in an S. aureus isolate recovered from a patient receiving oral treatment [11]. Resistance primarily has occurred in patients who did not have a foreign body (e.g., a peritoneal dialysis catheter) removed during treatment. Although this is not surprising to infectious disease physicians, it emphasizes the importance of the removal of infected intravenous catheters or prosthetic devices. Removal of such items not only improves the efficacy of an antibiotic, but it also reduces the likelihood of antimicrobial resistance developing.

As addressed by Dr. Siegel [1], linezolid has an advantage in terms of cost, both because of its oral bioavailability and because it should be cheaper than intravenously administered vancomycin. Costs of hospitalization, home-based administration of intravenous therapy, and the cost of linezolid tablets vary greatly in different regions of the nation. Thus, precise cost analysis may be difficult to perform on a national scale, although I do not dispute the figures calculated by Dr. Siegel [1]. As the cost of oral linezolid decreases in the future, there will be an increasingly dramatic cost advantage favoring the use of linezolid.

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Signs of Meningeal Irritation: What Is Their Diagnostic Accuracy?

Snr.—Thomas et al. [1] are to be congratulated for the elegant prospective study in which they examined the diagnostic accuracy of classic signs of meningeal irritation in adult patients who had...
suspected meningitis. They showed that nuchal rigidity, Kernig’s sign, and Brudzinski’s sign do not have diagnostic value for suspected meningitis. However, their conclusions should not be generalized, especially for bacterial meningitis, because only 3 of the 80 patients in their study had severe meningeal inflammation (i.e., a CSF WBC count of >1000 cells/mL). Of note, in the latter subset of patients, nuchal rigidity had a sensitivity and a negative predictive value of 100%.

Moreover, 2 other points made by Thomas et al. [1] deserve comment. First, nearly one-fourth of the patients enrolled in their study were immunocompromised hosts. Severely immunocompromised patients usually do not develop an adequate inflammatory response, and local signs of infection, such as nuchal rigidity, may be absent. This is why it is essential to perform a lumbar puncture in immunocompromised patients who have fever or headache, to recognize and to provide prompt treatment of meningitis that manifests without meningeal signs. Second, with regard to the etiology of microbiologically confirmed CSF infection in the 18 studied patients, 8 patients had Enterovirus infection, and 6 patients had cryptococcal meningitis. Kernig’s and Brudzinski’s signs are present in only approximately one-third of the patients who are affected by Enterovirus meningitis [2]. The same is true also for cryptococcal meningitis in patients with AIDS: fewer than one-third of such patients have nuchal rigidity [3]. Therefore, it is misleading to study the diagnostic accuracy of meningeal signs without stratification of immunocompetent and immunocompromised subjects into separate subgroups.

In conclusion, as stated by Thomas et al. [1], better bedside diagnostic tests are needed. However, contrary to their assertion, in clinical practice, the need for a lumbar puncture does not rely on the presence or absence of these meningeal signs.

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References

Reply
Sir—In response to the letter by Antinori [1], I would like to state that I agree with most of his comments, but I should respond to some of the specific issues he raises. It is true that Kernig’s sign, Brudzinski’s sign, and nuchal rigidity had low diagnostic sensitivity in our prospective cohort of adults with suspected meningitis [2]. It is also true that, of 297 adults with suspected meningitis in our cohort, only 80 (27%) had meningitis documented on the basis of CSF WBC count (i.e., a CSF WBC count of >6 cells/mL); 18 patients had microbiologic evidence of CSF infection, and only 3 had bacterial causes of infection. This spectrum of etiologies is consistent with the spectrum noted in current clinical practice for adults with suspected meningitis in the emergency department, and it does not affect the generalizability of the results.

Clinicians do not restrict the diagnostic use of bedside meningeal signs to patients with bacterial meningitis or patients who are immunocompetent; these signs are used for all patients with suspected meningitis. This broad group of patients includes persons with and persons without CSF inflammation, and only a small proportion of such patients have meningitis with microbiologically documented bacterial causes, as our prospective study corroborated. However, it is precisely this broad group of patients for whom clinical decisions regarding lumbar puncture need to be made. On the basis of our prospective assessment of patients with this common clinical syndrome, there appeared to be little diagnostic value for the classic meningeal signs; nuchal rigidity had 100% negative predictive value only for the 4 patients who had the most severe meningeal inflammation (i.e., a CSF WBC count of >1000 cells/mL). This reflects the common problem of spectrum bias in the interpretation of diagnostic test results. Our conclusion, which is based on prospective assessment of the diagnostic accuracy of these bedside clinical signs, remains the same: these signs do not have sufficient diagnostic accuracy to reliably assist the clinician in the decision to perform a lumbar puncture in real-life situations involving unselected adults with suspected meningitis. Better bedside diagnostic signs are needed.

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