cordant was identical means that therapy was not confounding the association between penicillin resistance and outcome. A conclusion about the efficacy of penicillin therapy cannot be drawn from these results, not only because the studies were not randomized controlled trials, but also because these analyses were not adjusted for heterogeneity of prognostic factors between the concordant and discordant groups. Our meta-analysis was not designed to address the issue of penicillin treatment failure because of the paucity of relevant data in available studies.

Fourth, we addressed the issue of confounding thoroughly in our article [2] in the Methods, Results, and Discussion sections. We agree with Drs. Klugman and Yu [1] regarding their concerns that our results may be misinterpreted; thus, we emphasize what we have stated in our article: our meta-analysis does not dictate a shift in current antimicrobial treatment for pneumococcal pneumonia; rather, it indicates that penicillin resistance is a prognostic factor.

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History of Cerebrovascular Events: A Relative Contraindication to Ertapenem Treatment

To the Editor—Seizures have been reported to be a rare adverse effect associated with the parenteral β-lactam antimicrobial agent ertapenem [1]. We describe 2 patients treated with ertapenem who developed seizures; each patient’s history included an old cerebrovascular accident.

Patient 1 was an 85-year-old man who had been admitted to the hospital for treatment of a urinary tract infection. His history included diabetes mellitus, hypertension, chronic renal failure, benign prostatic hypertrophy, and an old cerebrovascular accident. Laboratory values determined at hospital admission included a urea level of 116 mg/dL and a creatinine level of 4 mg/dL. A urinary culture was positive for Klebsiella species. Therapy with ertapenem (500 mg/day) was initiated. On the fourth day of treatment, the patient experienced 3 seizures. A brain CT demonstrated peripheral and central brain atrophy and an old infarction in the left-middle cerebral artery distribution. Antibiotic treatment was modified. Seizures did not recur.

Patient 2 was a 71-year-old man who had been admitted for treatment of a urinary tract infection. His history included diabetes mellitus, hypertension, chronic ischemic heart disease, and an old cerebrovascular accident. Laboratory values obtained at hospital admission included a urea level of 95 mg/dL and a creatinine level of 1.95 mg/dL. A urinary culture included an old cerebrovascular accident. The antibiotic treatment included an old cerebrovascular accident. The antibiotic treatment was modified; seizures recurred the next day and were treated with anti-epileptics, with no recurrence thereafter. The patient recovered and was discharged from the hospital.

Infections due to extended-spectrum β-lactamase (ESBL)—producing enterobacteriaceae have increased markedly in recent years. This trend is expected to continue, and in some institutions, it is already increasing exponentially [2]. Antibiotic options for the treatment of ESBL-producing organisms are extremely limited; carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms [3], and seizures have been associated with use of imipenem and meropenem in <1% of patients treated [4]. A safety analysis of meropenem, including data from 46 clinical trials involving hospitalized patients, has shown that the incidence of seizures during treatment exposures in patients with infections other than meningitis was 0.46% for the total number of seizures and 0.08% for drug-related seizures [5]. Calandra et al. [6] reported that the incidence of seizures during treatment with imipenem was as high as 3%.

Of 2046 patients enrolled in 5 Phase IIa and 8 Phase IIb/III clinical trials who were treated with 1 g of ertapenem, seizures were rare (0.2%–0.5% of patients); almost all patients who experienced a seizure had an underlying CNS disease or a known seizure disorder [1]. Results of a pooled analysis of adverse event data from trials involving adults with complicated bacterial infection who received ertapenem included headaches in 2.2% and seizures in 0.5% [7]. A Medline search revealed only 1 case in a patient who underwent peritoneal dialysis and who developed refractory seizures after receiving 2 doses of ertapenem [8].

In our hospital, a 1000-bed hospital, 100 patients had received ertapenem in the
prior 12 months, including the 2 patients described above who experienced seizures while exposed to the drug. Both patients’ histories included a previous cerebrovascular accident. The presence of an underlying CNS disease—an old cerebrovascular accident (thrombotic or embolic), in particular—was the unique risk factor for the development of seizures [6]. Elderly patients in internal medicine wards are currently among the most common sources of colonization with ESBL-producing microorganisms. A substantial number of these patients have had a stroke in the past. Carbenamems appear to be the last resource to treat nosocomial infections caused by ESBL enterobacteriaceae. Therefore, it is our opinion that prescribing information for ertapenem should list an old cerebrovascular accident specifically as a relative contraindication to drug use.

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Influence of Candida Colonization on the (1–3)-β-D-Glucan Assay

To the Editor—Upton et al. [1] and Ostrosky-Zeichner and Finkelman [2] mentioned our recent article [3] when discussing the influence of Candida colonization on the performance of the (1–3) β-D-glucan assay Fungitell (Associates of Cape Cod) (BG) in the diagnosis of invasive fungal infection (IFI). In our experience, Candida colonization is unlikely to cause false-positive results in the BG assay [3]. We found 3 false-positive results among 29 patients without IFI; none of the 3 patients had mucositis. Although 2 of the 3 patients were colonized by Candida species, other patients who had heavy Candida colonization had negative BG results. The occurrence of false-positive results in the detection of BG is an important problem that reduces the specificity of the test [4]. Two strategies can be followed to reduce the number of false-positive results: first, combination of all available diagnostic fungal marker tubes, mannan, or PCR findings, may help identify the false-positive results, because in our experience, it is unlikely for 2 tests to have the same false-positive results; second, an analysis of the kinetics of BG levels (provided that serial samples are obtained during the period of risk) helps in the identification of false-positive results, because, in these patients, BG levels show abrupt increases and decreases in the absence of antifungal treatment [3].

We believe that the BG assay is a promising fungal marker for serial prospective screening of IFIs in the clinical setting, particularly in immunosuppressed subgroups of persons at high risk for IFI, such as neutropenic, critically ill patients and transplant recipients. In these populations, the incidence of IFI is high, and consequently, incidences of positive predictive value and negative predictive value are also likely to be high [5]. Currently, the value of BG and its impacts on the early diagnosis, preemptive treatment strategies, and therapeutic monitoring of IFI will only be established in the clinical setting with prospective studies that include matched controls in which high-risk subpopulations are prospectively screened for the presence of surrogate fungal markers. Semiquantitative surveillance cultures for yeast are important for evaluation of these validation studies. Patients should be screened twice weekly while the risk persists, preferably when screening is combined with risk stratification strategies, as described by Prentice et al. [6]. Another convenient and desirable approach is the separate analysis of the utility of BG in relation to the different etiologic agents of IFI. Because all of the current different surrogate markers of IFI have limitations and discrepancies, comparative prospective studies with matched controls using a combination of all available diagnostic fungal markers are warranted.

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