other β-lactam antibiotic” was not all correct. Of the 4 subgroup analyses (ie, cefepime vs. ceftazidime, cefepime vs. piperacillin-tazobactam, cefepime vs. imipenem-meropenem, and cefepime vs. ceftriaxone-ceftaxime), only the cefepime versus piperacillin-tazobactam subgroup, which included 3 studies [5–7], was statistically significant.

Cases of neurotoxicity, which included encephalopathy and nonconvulsive status epilepticus, were used to explain the increased mortality in the cefepime group [2]. We could not find any description of a suspected case of neurotoxicity in the studies analyzed that could have contributed to the death of a patient in the cefepime group. However, Biron et al [6] reported 6 patients from the cefepime group who died of extensive cancer. Chandrasekar and Arnow [9] reported that 24 (75%) of 32 patients who died did so 11 weeks after the completion of the study. Attributing the difference in the deaths of those patients with cancer to rare case reports of toxicity, which have been reported among patients receiving β-lactams and/or carbapenems [11–13], did not make much sense, especially when the reported rates of adverse effects were similar between the 2 treatment groups in many studies analyzed [3–9].

Yahav et al [2] attributed inadequate antimicrobial efficacy in vivo to the increase in mortality. Their meta-analysis [2] found no difference in clinical failure between treatment with cefepime and treatment with the comparator drugs. Although their analyses “did not reveal a specific cause for the increased mortality” [2, p. 344], they insisted on finding reasons to explain the statistically significant difference in the mortality rates without providing much clinical evidence. Therefore, we raise the same question that Machtay et al [14] did 10 years ago: is meta-analysis really meta-physics? Meta-analyses should not be considered a substitute for well-designed trials [14]. What Yahav et al [2] concluded should not be taken as the final word.

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adoxically observed that an MIC of vancomycin <1.5 mg/L was significantly associated with poorer outcome when this antibiotic was used for treating *S. aureus* bacteremia (OR, 12; 95% CI, 1.73–83.2; $P = .001$), compared with an MIC of $\geq 1.5$ mg/L [2]. This unexpected conflict raises an interesting question: is the MIC of vancomycin an infallible predictor of the clinical outcome of *S. aureus* bacteremia treated with vancomycin? Indeed, we believe that vancomycin MIC when considered alone should not be regarded as an infallible predictor of outcome, because assessment of the in vitro bacterial susceptibility is only one of the pieces needed to correctly solve the “antimicrobial therapy puzzle” [3]. In fact, knowledge of drug exposure at the site of infection is at least equally relevant. It has been recently suggested that for a pathogen with an MIC of 1 mg/L, the minimum trough concentration ($C_{\text{min}}$) of vancomycin would have to be $\geq 15$ mg/L to generate the pharmacodynamic target of area under the curve (AUC)/MIC of $400 [4]$. Accordingly, it would be interesting to verify in these patients if the paradoxical relationship with clinical outcome of *S. aureus* bacteremia could be confirmed or refuted when correlating the MIC of vancomycin with the $C_{\text{min}}$ of vancomycin. Additionally, it would be informative to know if vancomycin was administered by conventional twice-daily dosing or by continuous infusion and to know the severity status of the patients. Administration of conventional dosing was in several cases clearly shown to fail to reliably achieve a $C_{\text{min}}$ of 15 mg/L. The $C_{\text{min}}$ at 36–48 hours after the start of therapy was <10 mg/L in 352 (45.1%) of 780 patients who received standard intermittent daily doses separated in 2–4 administrations [5], and the $C_{\min}$ is expected to be even lower in critically ill patients who present pathophysiological and/or iatrogenic conditions that may cause an enlargement of the extracellular space and/or an increase of the renal clearance of hydrophilic antimicrobials [6]. Conversely, continuous infusion coupled with loading, by ensuring targeted serum levels of vancomycin more rapidly than intermittent administration [7], may be the best way to maximize the time-dependent activity of vancomycin in critically ill patients [8], because with the same daily dosage, it may keep higher and more sustained concentrations at the infection site [8, 9]. Interestingly, vancomycin by continuous infusion was independently associated with a lower mortality rate, compared with intermittent infusion (25% vs 54.2%; $P = .02$), in patients treated with vancomycin, because of oxacillin-resistant ventilator-associated pneumonia [10]. We believe that assessment of the clinical outcome of antibiotic therapy on the basis of only in vitro susceptibility of bacterial pathogens may sometimes be misleading, and that conversely, the simultaneous assessment of appropriateness of drug exposure at the infection site might be helpful in averting a paradoxical correlation with clinical outcome that may be difficult to explain.

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**Reply to Price et al and to Pea and Viale**

**To the Editor—**Recently Price et al [1] published the results of their study of 45 consecutive patients with bacteremia attributable to *Staphylococcus aureus*. Similar to our previous report [2], 75% of the strains (34 of 45) had a minimum inhibitory concentration (MIC) of vancomycin $\geq 1.5$ μg/mL. Their main finding was that an MIC of vancomycin <1.5 μg/mL was associated with a significantly greater risk of death, compared with an MIC of vancomycin $\geq 1.5$ μg/mL. This result seems contradictory with our previous finding.

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