other β-lactam antibiotic” was not all correct. Of the 4 subgroup analyses (ie, ce-
fepine vs. ceftazidine, cefepine vs. pi-
peracillin-tazobactam, cefepine vs. imi-
penem-meropenem, and cefepine vs. cef-
triaxone-cefotaxime), only the cefepine versus piperacliln-tazobactam subgroup, which included 3 studies [5–7], was sta-
tistically significant.

Cases of neurotoxicity, which included encephalopathy and nonconvulsive status epilepticus, were used to explain the in-
creased mortality in the cefepine group [2]. We could not find any description of a sus-
ppected case of neurotoxicity in the studies analyzed that could have contrib-
uted to the death of a patient in the ce-
fepine group. However, Biron et al [6] reported 6 patients from the cefepine 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-lac-
tams and/or carbapenems [11–13], did not make much sense, especially when the reported rates of adverse effects were sim-
ilar between the 2 treatment groups in many studies analyzed [3–9].

Yahav et al [2] attributed inadequate antimicrobial efficacy in vivo to the in-
crease in mortality. Their meta-analysis [2] found no difference in clinical failure be-
tween treatment with cefepime and treat-
ment with the comparator drugs. Al-
though their analyses “did not reveal a specific cause for the increased mortality” [2, p. 344], they insisted on finding rea-
sions to explain the statistically significant difference in the mortality rates without providing much clinical evidence. There-
fore, 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 sub-
stitute for well-designed trials [14]. What Yahav et al [2] concluded should not be taken as the final word.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Thao D. Nguyen,1,2 Byron Williams,2 and Norela Ocampo2

1Department of Pharmacy Services and Infectious Disease Services, White Memorial Medical Center, Los Angeles, and 2Pharmacy and Outcomes Science, School of Pharmacy, Loma Linda University, Loma Linda, California

References

1. Paul M, Yahav D, Fraser A, Leibovic L. Ce-
fepine and all-cause mortality. Clin Infect Dis
5. Bow EI, Roststein C, Noskin GA, et al. A ran-
domized, open-label, multicenter comparative study of the efficacy and safety of piperacliln-
tazobactam and cefepine for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis
6. Biron P, Fuhrmann C, Cure H, et al.; CEMIC (Study Group of Infectious Diseases in Can-
8. Bohme A, Shah PM, Stille W, Hoelzer D. Pi-
peracillin/tazobactam versus cefepime as ini-
tial empirical antimicrobial therapy in febrile neutropenic patients: a prospective random-
9. Chandrasekar PH, Arnow PM. Cefepime ver-
sus ceftazidine as empiric therapy for fever in neutropenic patients with cancer. Ann Pharmacother
10. Tamura K, Matsuoka H, Tuskada J, et al.; Kyu-
shu Hematology Organization for Treatment (K-HOT) Study Group. Cefepime or carba-
penem treatment for febrile neutropenia as a single agent is as effective as a combination of 4th-generation cephalosporin + amino-
11. Francisa M, Maganti R. Cephalosporin-in-
duced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother
12. Slaimer SE, Cars O, Norrbys SR. Neuro-
toxicity of β-lactam antibiotics: predisposing factors and pathogenesis. J Antimicrob Che-
14. Machtay M, Kaiser LR, Glatstein E. Is meta-
analysis really meta-physics? Chest 1999; 116:
539–42.

Is the Minimum Inhibitory Concentration of Vancomycin an Infallible Predictor of the Clinical Outcome of Staphylococcus aureus Bacteremia Treated with Vancomycin?

To the Editor—We read with interest the study of Soriano and coworkers [1] that described the relationship between the clinical outcome of Staphylococcus au-
reus bacteremia and the minimum inhibi-
tory concentration (MIC) of vancomycin. In this prospective clinical study undertaken in a Spanish university hospital, it was observed that among 168 patients treated with vancomycin for an S. aureus bacteremia, a higher MIC of vancomycin (>2.0 mg/L) was independently associated with a significantly greater risk of death at 30 days (odds ratio [OR], 6.39; 95% con-
fidence interval [CI], 1.68–24.3; P < .001), compared with an MIC of 1.0 mg/L. In-
terestingly, these findings, which led the authors to suggest the need for the eval-
uation of the possible superiority of new antistaphylococcal agents versus vanco-
mycin when a strain has a vancomycin MIC >1 mg/L, are in clear contrast with those of a recent English study that par-
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_{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_{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_{min} of 15 mg/L. The C_{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.

Acknowledgments

Potential conflicts of interest. E. P. has been on the speakers’ bureau for Pfizer and Novartis. P. V. has been a consultant to, has been on the speakers’ bureau for, and has received grant support from Pfizer and Novartis.

Federico Pea* and Pierluigi Viale*

*Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, and †Clinical of Infectious Diseases, Department of Medical and Morphological Research, Medical School, University of Udine, Italy

References


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 \( \geq 1.5 \) \( \mu \)g/mL. Their main finding was that an MIC of vancomycin <1.5 \( \mu \)g/mL was associated with a significantly greater risk of death, compared with an MIC of vancomycin \( \geq 1.5 \) \( \mu \)g/mL. This result seems contradictory with our previous finding.