recommended by the American Thoracic Society–Infectious Diseases Society of America guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* pneumonia [6]. The pharmacodynamic parameters that best express vancomycin bactericidal activity are the time during which serum concentration is greater than the MIC for the organism [2] and the area under the curve divided by the MIC [7]. In neutropenic patients, pharmacodynamic principles suggest that an optimal regimen of a time-dependent killing agent with little postantibiotic effect, such as vancomycin, should achieve serum concentrations greater than the MIC 100% of the time. This may be easily obtained with therapeutic drug monitoring or when vancomycin dosages are adapted to the patient's weight (i.e., 30 mg/kg/day) [8]. On the other hand, with the fixed dosages of vancomycin used in the study by Jaksic et al. [1] (1 g every 12 h), many patients may not achieve this pharmacodynamic parameter. Could the authors detail the range of vancomycin trough serum concentrations obtained in the health care centers where vancomycin serum levels were monitored?

In addition, given that the duration of neutropenia is an acknowledged risk factor for infectious complications [9], the delayed absolute neutrophil count recovery in patients receiving linezolid is of concern, despite the authors' assumption that "it may be attributable to physiological processes during recovery from acute bacterial infection" [1, p. 605]. Indeed, these physiological processes would not explain why neutrophil count recovery was significantly delayed in patients receiving linezolid, compared with those receiving vancomycin. Reports of linezolid myelotoxicity could be a serious limitation to the use of this agent in neutropenic patients [10].

Acknowledgments

Potential conflicts of interest. P.T. and C.C.: no conflicts.

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References

1. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis **2006**; 42:597–607.
2. Murray BE, Nannini EC. Glycopeptides (vancomycin and teicoplanin), streptogramins (quinupristin-dalfopristin), and lipopeptides (daptomycin). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases, 6th ed. Vol. 1. Philadelphia: Churchill Livingstone, **2005**:417–34.
3. Le Normand Y, Milpied N, Kergueris MF, Harousseau JL. Pharmacokinetic parameters of vancomycin for therapeutic regimens in neutropenic adult patients. Int J Biomed Comput **1994**; 36:121–5.
4. Kergueris MF, Le Normand Y, Jahan P Milpied N. Application of USC*PACK clinical programs to vancomycin in neutropenic patients. Int J Biomed Comput **1994**; 36:163–5.
5. Sakoulas G, Moellering RC Jr, Eliopoulos GM. Adaptation of methicillin-resistant *Staphylococcus aureus* in the face of vancomycin therapy. Clin Infect Dis **2006**; 42(Suppl 1):S40–50.
6. American Thoracic Society–Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **2005**; 171:388–416.
7. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis **2006**; 42(Suppl 1):S35–9.
8. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. Clin Infect Dis **1994**; 18:533–43.
9. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **2002**; 34:730–51.
10. Halpern M. Linezolid-induced pancytopenia. Clin Infect Dis **2002**; 35:347–8.

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Clinical Infectious Diseases 2006; 42:1813–4

Reply to Tattevin and Camus

To the Editor—In the letter by Tattevin and Camus [1], 2 interesting points were raised. The first concerns optimization of the vancomycin dosage. Although optimization of the vancomycin dosage may improve the efficacy of treatment, our study was not designed to address this question; rather, the study was designed to compare the 2 investigated medications in the usually recommended and prescribed doses for febrile, neutropenic patients with cancer, who can present with infections of varying sites and etiologies. For this reason, prespecified pharmacokinetic parameters were not defined, and systematic measurements of the vancomycin serum concentrations were not set by the protocol. The protocol directed sites to have 1 unblinded coinvestigator verify vancomycin serum concentrations and to adjust the dose, if necessary, in accordance with local practice guidelines. Because the study was not intended to look at dose optimization, sites were not required to send in concentration data. Therefore, we cannot address the pharmacokinetic/pharmacodynamic relationship with respect to vancomycin therapy, but we definitely can assess, in an unbiased way, the efficacy and tolerance of the drugs studied in their usually administered doses.

The second point concerns the delayed absolute neutrophil count recovery in certain subsets of patients who received linezolid. We were intrigued by the shorter time to defervescence and trends observed in prospectively defined hematologic events. Although the trends of hematological events were not statistically significantly different in the overall patient population, we requested the post-hoc analysis that led to discovery that delayed neutrophil recovery was limited to the subset(s) of patients with good response to antimicrobial treatment, as shown by shorter time to defervescence. In contrast, there was no difference in time to defervescence in the fever of unknown origin (FUO) subset; the FUO subset also had no difference in time to neutrophil recovery (as shown in figure 2 of our study). This finding sheds a different light on the concern

expressed by Tattevin and Camus [1] and in some other (anecdotal) reports. This paradoxical finding was the basis for the hypothesis that delayed neutrophil recovery was not directly related to linezolid use. If linezolid itself had caused delayed neutrophil recovery, this should definitely have also been the case in the 183 patients with FUO (89 of whom were randomized to receive linezolid and 94 of whom were randomized to receive vancomycin). As presented in the article [2], in the FUO patient subset, no difference was detected in neutrophil recovery between linezolid recipients and vancomycin recipients, and this finding was paralleled by a lack of difference in the time to defervescence. Therefore, we were puzzled by the fact that, among patients with better response to linezolid (in the modified intent-to-treat and microbiologically evaluable subset), we found some trend of transient delay in neutrophil recovery. This led us to speculate about possible reasons for this observation. One explanation to this phenomenon could be an enhanced attraction of the neutrophil to the site of infection, thus causing a shift in the neutrophil kinetics. We believe that this observed phenomenon is interesting and warrants further study.

Acknowledgments

Potential conflicts of interest. B.J., G.M., and J.P.-O. have received research grants from Pfizer, and C.S.H., L.B.L., and K.J.T. are employed by Pfizer.

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Reference

1. Tattevin P, Camus C. What can we learn from studies comparing linezolid with vancomycin in neutropenic patients when vancomycin dosages are not optimized [letter]? Clin Infect Dis **2006**; 42:1813–4 (in this issue).
2. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis **2006**; 42:597–607.

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Clinical Infectious Diseases 2006; 42:1814–5