Reply to Nannini and to a Previous Letter by Hurley

To the Editor—In recent correspondence, Hurley [1] performed an ecologic analysis that suggests that length of hospital stay (LOS) before the onset of bacteremia may have confounded the association between vancomycin resistance and mortality observed in our meta-analysis [2]. We believe his conclusions are misleading.

Ecologic analyses are subject to the so-called ecologic fallacy [3], in which associations observed using group average data are not necessarily a valid reflection of associations seen at the individual patient level. There is evidence from patient-level multivariate analyses that the observed association between vancomycin resistance and mortality cannot be explained by differences in LOS. Of the 6 studies cited by Hurley [1] in which multivariate analyses controlling for vancomycin resistance, LOS, and severity of illness were performed, none found an independent association between LOS and mortality [4–9].

Although we acknowledge the limitations of ecologic studies, we repeated Hurley’s [1] analytic approach, but controlled for vancomycin resistance. We excluded 2 studies cited by Hurley [1] for which insufficient data were provided [10, 11] and 1 of 2 studies [12, 13] that contained duplicate data. In a multivariate linear regression model with 2 exposure variables (LOS and vancomycin resistance) and 1 outcome variable (mortality), the association between LOS and mortality disappears ($P = .91$), whereas vancomycin resistance shows an independent and significant association with death ($P = .0048$).

Therefore, multivariate analyses of individual patient data and multivariate linear regression using group average data fail to support Hurley’s [1] suggestion that the association between vancomycin resistance and death described in our meta-analysis [2] could be explained by a difference in LOS between patients with bacteremia due to vancomycin-resistant enterococci (VRE) and patients with bacteremia due to vancomycin-sensitive enterococci (VSE).

Nannini [14] suggests that 4 studies included in our meta-analysis provided definitions of appropriate therapy and frequency of receipt according to comparison group [5, 15, 16]. In all 3 studies, patients with bacteremia due to VRE were less likely to have received appropriate therapy. These differences between the comparison groups were clinically important, even though, in 1 small study, the difference did not reach statistical significance [5]. These data do not support the suggestion that failure to detect a statistically significant association between vancomycin resistance and mortality among 4 studies included in our analysis can be explained by similar use of appropriate therapy among the comparison groups. On the contrary, and as discussed in our article [2], we agree with Nannini’s [14] suggestion that a plausible explanation for the association between vancomycin resistance and mortality is that patients with bacteremia due to VRE may be less likely than patients with bacteremia due to VSE to receive optimal antimicrobial therapy. However, Nannini [14] implies that, if this explanation is correct, our conclusions should be different. We disagree. We do not believe that the proposed mechanism diminishes the significance of the finding that antimicrobial resistance has important impact on patient outcome.

Nannini [14] also suggests that the association between bacteremia due to VRE and mortality may be confounded by differences in the distribution of enterococcal species among the comparison groups. There is little evidence to suggest that this is the case. Laboratory data regarding the relative virulence of Enterococcus faecium and Enterococcus faecalis have yielded contradictory findings [17–20]. If Nannini’s [14] suggestion that E. faecalis is more virulent than E. faecium is true, then the association between vancomycin resistance and mortality described in our meta-analysis is likely to be an underestimation, because E. faecalis is generally more common among patients with bacteremia due to VSE. In addition, a review of the

---

**Clinical Infectious Diseases** 2006;42:1203–4
© 2006 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2006/4208-0025$15.00

Reprints or correspondence: Dr. Esteban Nannini, Sanatorio Parque, Blvd. Oroño 860, Rosario (2000) Santa Fe, Argentina (enannini@intel.com.ar).

1204 • CID 2006;42 (15 April) • CORRESPONDENCE
studies included in our meta-analysis fails to support Nannini’s argument [14]. Three of the studies adjusted for enterococcal species as a possible confounder, 2 of which restricted their population to patients with Enterococcus faecium infection [5, 9], and 1 of which controlled for differences in enterococcal species in a multivariate regression model [15]. Of these 3 studies, 2 showed a significant association between vancomycin resistance and death [9, 15]; the third showed an association that did not reach statistical significance [5], but the study was underpowered. Although we acknowledge the limitations of existing data, we do not think the currently available evidence supports the hypothesis that the association between vancomycin resistance and mortality observed in our meta-analysis is confounded by differences in the virulence of individual enterococcal species.

Acknowledgments


Carlos A. DiazGranados12 and John A. Jernigan
1Fundación Universitaria de Ciencias de la Salud, Bogota, Colombia; and 2Emory University School of Medicine, Atlanta, Georgia

References