
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 [12] 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 failed 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 failed to show a statistically significant association, because there was similarity in the frequency of appropriate antibiotic administration between the comparison groups [5–7, 12]. We believe that this claim is not well supported. Only 3 of the 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.

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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


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A Clinically Dangerous Flaw in Reporting Statistical Significance

To the Editor—Having read the article by Maggiolo et al. [1] on the effect of adherence on the risk of virologic failure, we pinpoint several major flaws in their statistical analyses that can invalidate their conclusions. They stated that, with respect to the number of pills in the prescribed regimen and to the number of daily doses that the prescribed regimen required, “the mean adherence rate was significantly higher for patients receiving once-daily regimens (94.8% [95% CI, 90.2%–99.3%]), compared either with patients receiving a twice-daily regimen (mean adherence rate, 92.0% [95% CI, 90.8–93.2%]; P = .042) or with patients receiving a regimen requiring >2 daily doses (mean adherence rate, 91.9% [95% CI, 89.9%–94.9%]; P = .009)” (p. 161).

First, these statements show a conceptual confusion between significance tests and confidence inference. Although there is a relationship between P values and confidence intervals, strictly speaking they are not the same [2]. Maggiolo et al. [1] do not interpret the reported 95% CIs; they only write that the differences among the adherence rates are statistically significant. What the reported 95% CIs show is extremely important: the 3 intervals overlap. In statistical reasoning, this means that no final conclusion can be drawn and that all values of the population adherence rates within the limits of the three 95% CIs are consistent with the observed data at a confidence level of 95%—that is, population adherence rates may or may not differ, because they share some possible parameter values.