Reply to Kaasch et al

To the Editor—We thank Kaasch and colleagues for their comments [1] on our article describing the effect of vancomycin minimum inhibitory concentration (MIC) on the prognosis of left-sided endocarditis caused by methicillin-susceptible Staphylococcus aureus (MSSA) [2].

Kaasch et al cite a meta-analysis by van Hal et al [3], who did not find an association between vancomycin MIC and outcome of MSSA bacteremia. The meta-analysis analyzed 3 studies of patients with MSSA bacteremia [4–6]. Price et al [4] included 14 of 45 patients treated with vancomycin, which is suboptimal in this setting. In addition, we do not know the distribution of the vancomycin MIC according to methicillin susceptibility. Schweizer et al [5] evaluated the relationship between agr dysfunction and mortality among 814 cases, although 60% were methicillin-resistant Staphylococcus aureus and 86% were treated with vancomycin. Holmes et al [6] evaluated the effect of vancomycin MIC on mortality in 261 patients with MSSA bacteremia: Higher vancomycin MIC led to higher mortality among flucloxacinil-treated patients, as in our study. In conclusion, the results of van Hal’s subanalysis must be interpreted with caution because of population heterogeneity, study design, and frequent use of vancomycin to treat MSSA. Two recent studies not included in that meta-analysis found similar results to ours for complicated bacteremia [7] and mortality [8] of MSSA bacteremia according to vancomycin MIC.

Regarding our article [2], some of the variables not included in the model are associated with mortality in S. aureus bacteremia rather than in S. aureus endocarditis. The incidence of in-hospital mortality according to duration of bacteremia (P = .585), persistent bacteremia (P = .315), duration of fever (P = .688), and vegetation size (P = .158) was similar between the groups. The median Charlson score was low in both groups, with no significant differences. Disease severity at onset was included in the composite variables (septic and nonseptic complicated endocarditis).

We determined vancomycin MICs using the Etest (bioMérieux, Marcy l’Etoile, France) (Figure 1). Reference strain ATCC 29213 was used for quality control, and the assay variation was <5%. MIC/minimum bactericidal concentration values for each strain were also tested using broth microdilution (data not shown) following Clinical and Laboratory Standards Institute recommendations [9]. Vancomycin MICs with the Etest were consistently higher than with microdilution, as reported elsewhere [10, 11]. The mode of our vancomycin MIC was 1 µg/mL by broth microdilution and 1.5 µg/mL by Etest, as in the article cited by Kaasch et al [11]. Consequently, the Etest is widely accepted for determination of vancomycin MIC, given the good correlation between broth microdilution and the Etest for providing consistent and predictable results [3, 10, 11].

It is true that S. aureus isolates with higher vancomycin MICs have decreased recently in several regions, suggesting that this finding is not local. Also relevant is that survival curves deviate after 2 weeks of treatment. This is typical in patients with endocarditis and a major difference with bloodstream infection–related mortality, in which the first hours of treatment are critical for improved prognosis. The claim that this divergence is related to management issues is speculative. Mortality in these patients was related to the virulence of the pathogen, whereas only 1 patient died of a nosocomial infection.

Finally, Kaasch et al state that the relationship between vancomycin MIC and mortality of S. aureus bacteremia or endocarditis treated with a β-lactam cannot be explained from a biological perspective. We disagree. Many biological factors (clonal complexes, agr dysfunction, agr phenotypes, specific resistance and virulence genes) have been associated with increased vancomycin MIC in MSSA, and there is growing evidence of a correlation between higher vancomycin MIC and more aggressive S. aureus clones [12].

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

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Figure 1. Minimum inhibitory concentration (MIC) distribution of the 93 methicillin-susceptible Staphylococcus aureus strains from patients with left-sided infective endocarditis treated with cloxacillin (Etest).
References


