

## Reply to Koehler et al

TO THE EDITOR—We appreciate the interest Koehler et al expressed in our review of combination antimicrobial therapy against *Enterococcus faecalis* [1], particularly as it pertains to infective endocarditis (IE) [2]. The authors raise important clinical points on the optimal treatment options and the necessity of combination therapy in IE and highlight a key conclusion of our review paper: current data are limited and further studies are required [1].

First, Koehler et al question the necessity of combination therapy for *E. faecalis* IE. Early clinical data suggested that clinical cures in the treatment of IE were only 50% compared to those in streptococci [3]. Subsequent experiments showed that the addition of gentamicin or streptomycin was bactericidal in vitro and increased cure rates, becoming the standard of care [3–11]. Moreover, current data that support the use of ampicillin monotherapy for IE are limited to case reports and animal studies. A case report of high-level aminoglycoside-resistant *E. faecalis* IE demonstrated cure in a 75-year-old male (nonsurgical candidate) after the continuous infusion ampicillin dose was increased from 16 g to 24 g/day to achieve bactericidal activity [12]. While case reports may serve as hypothesis-generating literature, they are at risk of publication bias as many negative studies (ie, treatment failures) are unreported. Likewise, animal models have demonstrated some treatment success, but findings need to be corroborated in humans [13]. Furthermore, vegetations in animal models are developed over the course of 1–2 days, whereas human vegetations may develop over weeks and have varying degrees of biofilm vs planktonic bacteria, not comparable to that of animal studies.

Second, Koehler et al raise questions regarding the mechanistic basis of the synergism. The mechanism of synergism between aminoglycosides and cell wall agents were elegantly studied by

Moellering et al, suggesting that the alteration in cell wall synthesis conferred by the B-lactam agent (and also vancomycin) increased the amount of aminoglycoside that reached its intracellular ribosomal target yielding a bactericidal effect [14]. This effect has been shown to be beneficial both in vivo and in vitro [14]. On the other hand, the double B-lactam synergism stems from a penicillin-binding protein (PBP) effect, in which saturation of 2 different PBPs creates a synergistic bactericidal effect despite lack of susceptibility to individual agents by conventional minimum inhibitory concentrations (MIC). This phenomenon also reminds us that MIC determination has important limitations, and interpretation of these values is not straightforward in situations when antibiotic options are limited. This issue has become overwhelmingly apparent in the treatment of multidrug-resistant gram-negative and gram-positive infections in the last decade. Only a full understanding of the mechanistic basis of resistance allows for novel strategies to be implemented and tried in clinical scenarios.

Finally, Koehler et al question the validity of the clinical studies on *E. faecalis* IE. We agree that prospective, randomized clinical trials would be ideal to provide robust recommendations for the treatment of all infections. However, the reality is different, and in many instances, only limited data provide bases for recommendations. The Spanish cohort described by Fernandez-Hidalgo et al [15] is the best evidence of the efficacy of the ampicillin–ceftriaxone combination. Although some of the data were collected retrospectively, the study attempted to identify patients in a prospective manner. The overwhelming result of that study was that the ampicillin–gentamicin combination was associated with statistically higher frequency of renal toxicity without major differences in clinical outcomes compared to the ampicillin–ceftriaxone combination. Moreover, the combination was selected in patients after careful in vitro and animal experiments that

suggested that this combination could be effective. Although, we agree that the use of ceftriaxone could pose collateral damages to the microbiota and increased colonization by *Clostridium difficile* and others, the nephrotoxicity of the ampicillin–gentamicin combination seems to be a major clinical limitation for patients who require prolonged therapy. The recent publication of the POET trial [16] raises the interesting possibility of using an early switch to oral agents in selected cases of *E. faecalis* IE, decreasing the toxicity of current regimens.

In summary, we agree that more clinical data are needed to validate our approaches for the treatment of *E. faecalis* IE. However, in the absence of such data, judicious translation of studies with robust mechanistic basis along with strong translational science is the best strategy to improve the care of our patients.

## Note

**Potential conflicts of interest.** K. L. L. has received research funding or acted as an advisor or consultant for Merck, Davol/BARD, Actavis, Melinta Therapeutics, the Medicines Company, and Pfizer. C. A. is employed by the University of Texas Health Science Center; has received grants from Merck and MeMed Diagnostics; and has received royalties from UpToDate and Harrison Principal of Internal Medicine. All other authors reported no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**Clinical Infectious Diseases**® 2019;69(5):901–2

Published by Oxford University Press for the Infectious Diseases Society of America 2019. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/cid/ciz057

## Concerns About the Association Between Poor Clinical Outcomes and the Minimum Inhibitory Concentrations Determined by Etest

TO THE EDITOR—Daptomycin is being increasingly used in the treatment of vancomycin-resistant enterococcus infection, but high daptomycin minimum inhibitory concentrations (MICs) are associated with poor microbiology outcomes and clinical failures [1, 2]. Moreover, Avery et al [3] reported recently that due to the low probability of target attainment (PTA) when the MIC is in the high susceptible range, lowering of the daptomycin susceptibility breakpoints may be necessary to optimize patient outcomes. Based on the above studies, the Clinical and Laboratory Standards Institute (CLSI) adjusted the MIC of 2–4 to the category of susceptible dose dependent.

There is, however, an important concern with the interpretation of the results, based on MICs determined by Etest [3]. Determining daptomycin MICs using broth microdilution (BMD)—and not the Etest—is currently recommended by CLSI [4]. The Etest might be more difficult to interpret for enterococci, compared to staphylococci [5]. The activity of daptomycin also depends on the physiological concentrations of calcium; however, the diffusion of calcium in the agar phase may be problematic. Although calcium concentrations have been shown to affect the MICs determined by Etest [5], a calcium supplement is not specified in the methodology. Instead, a quality control strain is used to verify Etest results [5]. In addition, different brands of Müller-Hinton agar may differ in their calcium concentrations [6], resulting in different MIC distributions by Etest [7]. In fact, only 1 study [8] among the 7 studies reported the Müller-Hinton agar brands and quality control strains [3].

Another reason for caution in extrapolating the results obtained by Etest is that the Etest correlated poorly with BMD, whereby the MIC obtained by Etest

could be 0.5–1 log<sub>2</sub> dilutions higher than BMD [9]. Shukla et al [1] showed that the MIC obtained by Etest had a mean of 1.4 log<sub>2</sub> dilutions higher than BMD for *Enterococcus faecium*. Therefore, the results reported by Avery et al [3]—claiming that a dose of 12 mg/kg might be needed to obtain a PTA >90% for an Etest MIC of 2 mg/L and a dose of 12 mg/kg might be needed to obtain a PTA of 32.4–54.4% for an Etest MIC of 4 mg/L—may translate to BMD MICs of 1 mg/L and 2 mg/L, respectively. Considering the modal MICs of *E. faecium* by BMD as 2 mg/L and 4 mg/L [10], it may, in fact, mean that even a daptomycin dose of 12 mg/kg, the target PD parameter for most of the isolates, may not be reached.

We agree that, according to the pharmacodynamic parameters of daptomycin, higher MICs would result in poorer outcomes. However, given that the BMD is still the gold standard for the MIC testing of daptomycin, using the BMD to validate the result obtained by Avery et al [3] is strongly suggested. If the enterococci isolates or the MICs by BMD are available, the authors may reanalyze the data, which might make it easier to draw inferences and determine appropriate MIC cutoffs.

## Note

**Potential conflicts of interest.** Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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