We thank Eschenauer et al [1] for their comments and interest in our article [2]. However, the term “calming the perfect storm” in their title minimizes the concerns posed by our scientific discussion and reflects a lack of appreciation of the complexities of the dangerous physiology at work in the establishment of methicillin-resistant Staphylococcus aureus (MRSA) endovascular infections. In addition, there are several discrepancies in their statements that should be noted.

The authors state that the 2006 study conducted by Fowler et al [3], rather than the study conducted by Levine et al [4], should have been referenced to indicate that the median time to clearance of MRSA bacteremia is 7–9 days with vancomycin or daptomycin. We agree that current practice has not changed the duration of MRSA bacteremia over the course of 15 years, emphasizing the necessity to rethink our current treatment approach [3, 4].

However, the authors seemed to have missed one of the main points of the article with their above comment. Vancomycin and daptomycin are “one-dimensional” antibiotics, meaning that they provide direct inhibition or killing of bacteria without harnessing the antimicrobial peptides of the innate host response [5]. Contrastingly, β-lactams are “2-dimensional” antibiotics in that they not only inhibit or kill the bacteria, but also synergize with innate immune peptides to provide added killing. These concepts may provide some explanation for why we see a differential treatment effect and differences in duration of bacteremia between MRSA and methicillin-susceptible S. aureus. We presented some of the early data on efficacy of ceftaroline for MRSA bacteremia, including combination therapy with daptomycin and ceftaroline [2]. We reemphasize the importance of understanding the science behind antimicrobial activity and resistance so that clinicians can think more strategically about optimal treatment options.

Furthermore, the authors state that the publication by Kullar et al [6] was biased due to employee authorship and speaking/consulting fees. However, this publication was performed during Dr Kullar’s fellowship through an investigator-initiated grant, which is initiated and completed by the investigator(s), with the company...
only providing funding and not having direct study involvement [7]. Dr Kullar was neither employed by the company that funded the study, nor received speaking/consulting fees.

The retrospective studies [6, 8, 9] discussed by Kullar et al [2] comparing daptomycin to vancomycin provide real-world data on the treatment of MRSA bacteremia. Eschenauer et al state that in the Moore et al [9] study, 69% of patients in the daptomycin arm had already cleared their bacteremia prior to being switched to daptomycin. However, this is not correct as the study revealed that 60% of patients were switched to daptomycin due to documented vancomycin failure, and approximately 50% of the 59 daptomycin-treated patients were still bacteremic when they were switched from vancomycin to daptomycin. Of note, the median time to switch from vancomycin to daptomycin was 5 days [9]. These data actually bias against daptomycin, not the reverse. We acknowledge that a limitation of the study by Murray et al [8] is the exclusion of patients with intravenous catheter MRSA bacteremia and renally impaired patients, and there is further research warranted in optimizing therapy in these populations.

We state that daptomycin combination therapy should be considered for rapid clearance of MRSA bacteremia. Particularly, Eschenauer et al commented that daptomycin/rifampin combination has been shown to be antagonistic. This comment reflects a lack of appreciation of the complexities of pharmacodynamics, as rifampin has indeed been shown to be antagonistic in vitro yet synergistic against the same exact isolate in vivo [10]. The role of rifampin clinically is complex and poorly defined and we included it in the general discussion of the importance of combination therapy, without specifics on where it may be best suited.

As we state in our article, rapid clearance of MRSA bacteremia within 3–4 days is crucial to improve patient outcomes and can be done with currently available antimicrobials. We hope that clinical trials are designed using the information presented in our article that can definitively demonstrate this, as has already been done in our individual clinical practices several years ago. Our paper supports that this goal is attainable via source control, the utilization of optimal bactericidal therapy, and rapid diagnostics. MRSA bacteremia, with mortality rates approaching 30%, is hardly a disease we need to be “calm” about.

Notes

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