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Case Commentary: Imipenem/Cilastatin and Fosfomycin for Refractory Methicillin-Resistant *Staphylococcus aureus* Infection: a Novel Combination Therapy

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ABSTRACT Given that it is unlikely that randomized clinical trials will yield answers for treating the most challenging bacteremic infections caused by methicillin-resistant *Staphylococcus aureus*, clinicians, microbiologists, and pharmacists will have to cooperate to discover novel ways to select successful individualized antimicrobial therapy for these patients. An example of such a strategy was demonstrated in the identification and utilization of imipenem/cilastatin plus fosfomycin to treat a particularly recalcitrant MRSA bacteremia and spinal abscess.

KEYWORDS MRSA, antimicrobial combinations, bacteremia

The case report of successfully using imipenem/cilastatin (IC) with fosfomycin to treat a case of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia with a deep-seated abscess with vertebral osteomyelitis translates laboratory microbiology into clinical use in a very complex case where there are not, and likely never will be, substantial clinical data (1). With the description of a remarkably long bacteremia of more than 1 month's duration and a growing infection despite appropriate vancomycin or daptomycin, single antimicrobial therapy would generally be destined to fail, with emergence of resistance to these antibiotics being highly possible. Indeed, prolonged exposure to vancomycin can select for daptomycin-nonsusceptible MRSA (2), and persistence *in vivo*, with the selection pressure of cationic antimicrobial peptides even without the administration of any exogenous antibiotics, has also been shown to select for MRSA with reduced daptomycin susceptibility (3).

Treatment options in this case would have included some combination of antimicrobial therapy: daptomycin with a beta-lactam that would depend on regional availability (e.g., ceftaroline versus ceftobiprole, an antistaphylococcal beta-lactam, or cefazolin) (4–8); daptomycin plus fosfomycin (9–11), or perhaps daptomycin plus trimethoprim-sulfamethoxazole (12). Regarding consideration of vancomycin, the CAMERA-2 trial showed that a cephalosporin rather than a penicillin should be used to avoid the risk of acute kidney injury (13). Indeed, the take-home message of that study was not that combination therapy is not beneficial, but rather that not all combination therapies carry the same risk-benefit profile. Theoretically, telavancin might be considered given its dual mechanism of action at the membrane and cell wall, although the results of the halted clinical trial with this agent were never published (14). The IC-fosfomycin combination was chosen here based on Etest synergy testing, a more rapid method than conventional kill curves or checkerboards, which are too labor-intensive in clinical laboratory settings (1).

The use of antibiotics with mechanisms of action conferred at different steps in cell wall synthesis makes intuitive sense, and the use of Etest synergy testing to drive the decision of using these agents is novel and capable of being done by most clinical laboratories. This case encourages a more extensive evaluation of such methods in

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guiding decisions regarding antimicrobial therapy in challenging clinical cases of *S. aureus* bacteremia, where more than one antibiotic may be needed. The use of two beta-lactams demonstrating MRSA activity has been carried out *in vitro*, although no clinical evidence has been published (15, 16).

This case illustrates that in the most challenging cases of MRSA bacteremia, "outside-the-box" diagnostic and therapeutic steps must be taken to achieve clinical success. Such steps cannot be identified from treatment guidelines or other official documents that are increasingly relied upon to make system-wide antimicrobial stewardship decisions. Paradigms of monotherapy for all MRSA bacteremia appear to be in need of re-evaluation in order to avoid weeks-long trial-and-error therapy in order to achieve more rapid success. It remains to be determined if clinical trials offering level I guiding evidence can ever achieve the granularity to capture the clinical nuances required in the management of this case. It would be interesting to consider how this case would have played out if combination daptomycin plus a beta-lactam or imipenem plus fosfomycin had been used from the early stages. Might the patient have survived? One wonders if heart failure, which was presented as the cause of death, was the result of the progression of an endovascular infection such as endocarditis, given the increased risk of endocarditis in patients with vertebral spine infection (17). A future challenge for infectious disease physicians will be to identify these patients early in their course of their illness rather than relying on therapeutic failure to identify them, perhaps through emerging biomarker signatures (18).

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