Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia

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Sir,

Recent work has demonstrated success in treating MRSA bacteraemia using daptomycin + antistaphylococcal β-lactams.\textsuperscript{1,2} With the subsequent introduction of ceftaroline, the use of ceftaroline alone or in combination with daptomycin or vancomycin may be considered, given its potentially dual benefit of direct anti-MRSA activity plus its class-related enhancement of innate immunity.\textsuperscript{3} We present a case of daptomycin-non-susceptible MRSA septic thrombophlebitis that failed daptomycin + ceftaroline therapy, but was very rapidly cleared with vancomycin + ceftaroline. In vitro analysis showed superior killing by vancomycin + ceftaroline compared with daptomycin + ceftaroline.

A male in his 40s with end-stage renal disease secondary to diabetic nephropathy receiving haemodialysis was admitted with relapsed MRSA bacteraemia due to haemodialysis catheter-associated septic thrombophlebitis of the right subclavian vein, superior vena cava and right atrium. Treatment with daptomycin (12 mg/kg) + ceftaroline (400 mg) intravenously every 8 h was begun. Tranoesophageal echocardiography showed no evidence of valvular involvement. The patient had no symptoms, including fever other than fatigue and lethargy, and vital signs were normal. The haemodialysis catheter was removed and haemodialysis treatments were performed using temporary femoral vein lines that were placed and removed with each treatment for the duration of the bacteraemia. Despite 5 days of daptomycin + ceftaroline therapy and exhaustive radiographic and echocardiographic assessments that failed to reveal additional identifiable foci of infection that could be surgically addressed, bacteraemia was persistent and the daptomycin MIC increased from 0.5 to 2 mg/L. The vancomycin MIC remained at 1 mg/L and the ceftaroline MIC was 0.5 mg/L. Therapy was changed to 750 mg of vancomycin intravenously after dialysis, and ceftaroline was continued. Bacteraemia cleared within 24 h. Vancomycin serum trough concentrations on days 4, 7, 9 and 11 of therapy were 21, 22, 17 and 24 mg/L, respectively. After seven consecutive days of negative blood cultures, a new permanent haemodialysis catheter and peripherally inserted central catheter were inserted and the patient was discharged to complete 8 weeks of vancomycin + ceftaroline therapy with weekly vancomycin trough serum concentrations of 15–20 mg/L. He has remained free of bacteraemia and hospitalization for all other causes 20 months later.

For daptomycin-non-susceptible MRSA 8096 that failed to clear with daptomycin + ceftaroline therapy, daptomycin, ceftaroline and vancomycin MICs were determined according to CLSI guidelines.\textsuperscript{4} and vancomycin population analysis (10\textsuperscript{6} cfu/mL) on brain heart infusion (BHI) agar was compared with Mu3 (ATCC 700689) for determination of heterogeneous vancomycin-intermediate Staphylococcus aureus (hVISA) phenotype, as previously described.\textsuperscript{5} In vitro pharmacokinetic/pharmacodynamic modelling using a one-compartment infection model was performed as previously described simulating normal renal function or end-stage renal disease conditions (creatinine clearance of <10 mL/min).\textsuperscript{6}

MICs of ceftaroline, vancomycin and daptomycin for MRSA 8096 were 0.5, 1 and 2 mg/L, respectively. Vancomycin population analysis profile (PAP) analyses in comparison with Mu3 showed MRSA 8096 to be a non-hVISA, demonstrating a PAP ratio of 0.7396 with respect to Mu3 (Figure 1). Pharmacokinetic/pharmacodynamic modelling of MRSA 8096 showed increased killing by vancomycin + ceftaroline and daptomycin + ceftaroline compared with vancomycin, daptomycin or ceftaroline alone in both normal and impaired renal function (P<0.05). Vancomycin + ceftaroline offered significantly increased killing compared with daptomycin + ceftaroline (P=0.048).

The successful management of the most difficult cases of MRSA bacteraemia with combination antibiotic therapy suggests that combination therapy may be the ideal way of rapidly reducing the bacterial inoculum and preventing emergence of resistance to daptomycin or vancomycin monotherapy. The addition of antistaphylococcal β-lactams to daptomycin appears to enhance bacterial clearance and prevent the loss of daptomycin susceptibility in vitro.\textsuperscript{1,2,7} This has gained increased attention due to the appreciation that in vivo selection pressure by cationic host defence peptides (HDPs) may select for vancomycin or daptomycin resistance in MRSA even in the absence of administered antibiotics during a high-inoculum infection.\textsuperscript{8} The selection may go bidirectionally, with HDPs selecting for daptomycin resistance and vancomycin selecting for HDP and daptomycin resistance.\textsuperscript{9}

Due to drug cost considerations, interest has grown in the pharmacodynamic interactions between vancomycin and β-lactams. Recent work has demonstrated synergy between vancomycin and β-lactam antibiotics, including ceftaroline, against MRSA, even in cases of reduced vancomycin susceptibility.\textsuperscript{10} The case described above was of great interest because it represented a situation where daptomycin + ceftaroline was unable to clear the bacteraemia and there was no surgically removable focus. Faced with few other options, vancomycin + ceftaroline was used and achieved bacteraemia clearance in 24 h. In vitro testing demonstrated excellent activity of vancomycin + ceftaroline against this isolate, superior to the activity of daptomycin + ceftaroline.
The fact that MRSA 8096 was not an hVISA (PAP ratio to Mu3, 0.9) raises the possibility that vancomycin + ceftaroline therapy may be a preferred option for non-hVISA daptomycin-non-susceptible MRSA (selected with prior daptomycin use). Daptomycin + ceftaroline or daptomycin + antistaphylococcal β-lactam may be preferred for daptomycin-susceptible or daptomycin-non-susceptible hVISA or VISA (selected by prior vancomycin use). This brief study unveils the importance of determining daptomycin and vancomycin heteroresistance phenotypes in future combination therapy studies for MRSA bacteraemia. In cases of daptomycin-non-susceptible vancomycin-susceptible MRSA without hVISA phenotype, vancomycin + ceftaroline may offer an option that might not otherwise be considered as a salvage regimen.

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Prolonged treatment with large doses of fosfomycin plus vancomycin and amikacin in a case of bacteraemia due to methicillin-resistant Staphylococcus epidermidis and IMP-8 metallo-β-lactamase-producing Klebsiella oxytoca

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Sir,
Fosfomycin is an old, but potent, antibiotic in the current global fight against antibiotic resistance, mainly for carbapenem-resistant Enterobacteriaceae, but also for Gram-positive bacteria, such as MRSA. However, information about the effectiveness and safety of the drug in severe systemic infections is scarce. We present a case of systemic infection in which methicillin-resistant Staphylococcus epidermidis and carbapenem-resistant Klebsiella oxytoca were isolated.

A 68-year-old Caucasian man was admitted to La Merced Hospital (Osuna, Seville, Spain) for elective colectomy in July 2011. A written consent to publish this case was obtained. His medical history included arterial hypertension, dyslipidaemia, cerebrovascular disease (a frontal ischaemic stroke 2 years earlier) and benign prostatic hyperplasia. In 1998, he had undergone an abdominoperineal resection, radiotherapy and chemotherapy due to a rectal cancer. Since then, he had suffered radiation cystitis. In June 2011, he was diagnosed with cancer recurrence and a total colectomy was performed. Forty-eight hours later, an intra-abdominal infection forced the performance of a wide small bowel resection. As a result, the patient developed short bowel syndrome, for which he had to receive prolonged total parenteral nutrition. A three-way Foley catheter had to be maintained because of a protracted haematuria. On day 114 of hospitalization, the patient developed fever with no evident source. Physical examination revealed conjunctival haemorrhages. Imipenem (1 g/8 h intravenously), vancomycin (1 g/12 h intravenously) and amikacin (1 g/24 h intravenously) were initiated. Methicillin-resistant S. epidermidis...