Case Report

Ceftaroline and gentamicin for the treatment of daptomycin-non-susceptible meticillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis in a pregnant patient

Nathan R. Unger, Olayemi O. Osinyemi, Robert M. Richardson, Jose Menajovsky and Jennifer Kuretski

1 Nova Southeastern University College of Pharmacy, 11501 North Military Trail, Palm Beach Gardens, FL 33410, USA
2 Triple O Medical Services, P.A., 1515 North Flagler Ave Suite 200, West Palm Beach, FL 33401, USA

Introduction: Vancomycin remains the mainstay in the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia; however, concerns exist about its continued efficacy in the presence of rising MICs. Daptomycin serves as an alternative but has also witnessed increases in reduced susceptibility. Several published case reports have demonstrated the potential utility of ceftaroline as a viable therapeutic option for invasive MRSA infections, including endocarditis.

Case presentation: A 23-year-old pregnant female presented with complaints of foot pain and fevers up to 104 °F. Her past medical history included polysubstance abuse, hepatitis C, intravenous drug use and a right arm abscess 2 years ago due to MRSA. Daptomycin was started empirically due to an allergy (angioedema) to vancomycin. Blood cultures returned positive for MRSA and remained persistently positive for 10 days at which point ceftaroline was added. Subsequent positive blood cultures on day 12 revealed daptomycin-non-susceptible MRSA at an MIC of 4 μg ml⁻¹. Consequently, daptomycin was discontinued and gentamicin was added. Blood cultures were negative by day 14 and the patient completed a total of 2 weeks of gentamicin and 4 weeks of ceftaroline after the first negative blood culture. The baby was born premature at 34 weeks and 2 days due to complications of pregnancy; however, no adverse effects of antimicrobial therapy were noted.

Conclusion: We describe the emergence of daptomycin-non-susceptibility during treatment and the successful eradication of persistent daptomycin-non-susceptible MRSA bacteraemia and endocarditis with a combination of ceftaroline and gentamicin in a pregnant female.

Keywords: bacteraemia; ceftaroline; endocarditis; gentamicin; MRSA; pregnancy; synergy.

Introduction
Vancomycin remains the mainstay in the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) infections; however, concerns exist about its continued efficacy in the presence of rising MICs and its safety profile as clinicians continue to target higher therapeutic levels (van Hal & Fowler, 2013). Daptomycin and linezolid serve as alternatives but have also witnessed increases in reduced susceptibility (Boucher et al., 2009; Sader et al., 2013; Talbot et al., 2006). Ceftaroline has emerged as another therapeutic option for invasive MRSA infections; moreover, it possesses *in vitro* coverage against both Gram-negative and Gram-positive bacteria, including MRSA at an MIC₉₀ of 1 μg ml⁻¹. In fact, ceftaroline retains potent activity against MRSA even in the presence of reduced vancomycin susceptibility (MIC ≥2 μg ml⁻¹), linezolid resistance (MIC ≥8 μg ml⁻¹) and daptomycin non-susceptibility (MIC ≥2 μg ml⁻¹) (Sader et al., 2013). Several published case reports and series (Ho et al., 2012; Jongmsa et al., 2013; Lin et al., 2013; Polenakovik & Pleiman, 2013; Rose et al., 2012) have described the potential utility of ceftaroline as a viable therapeutic option for invasive MRSA infections; however, none of the published literature has included a pregnant patient.

Abbreviations: MRSA, meticillin-resistant *Staphylococcus aureus*
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A 23-year-old Caucasian pregnant (23 weeks) female was initially admitted to an outside facility with complaints of left foot pain sustained during a fall 1 week previously and subjective fevers up to 104 °F. Her past medical history included chronic hepatitis C, polysubstance abuse, intravenous drug use and a right arm abscess 2 years ago due to MRSA. The patient reported allergies to vancomycin (angioedema), rifampin (hives) and clindamycin (rash).

Height and weight on admission were 155 cm and 52 kg, respectively. Pertinent initial vital signs and laboratory results included a temperature of 99.5 °F, a heart rate of 110 beats min⁻¹ and a white blood cell count of 12 200 µl⁻¹. Given complaints of a subjective fever and the past history of MRSA and intravenous drug use, two sets of blood cultures were drawn and the patient was immediately started on intravenous (IV) daptomycin 6 mg kg⁻¹ daily. Gram staining of the initial two sets of blood cultures revealed Gram-positive cocci in clusters, which were later identified as MRSA, and were susceptible to vancomycin (MIC=2 µg ml⁻¹) and daptomycin (MIC =0.25 µg ml⁻¹). Antibiotic susceptibility testing was conducted using automated broth microdilution. A transthoracic echocardiogram revealed a possible small vegetation on the aortic valve, and small vegetations on the mitral and tricuspid valves could not be ruled out. The patient developed respiratory distress on day 2 and a chest X-ray was performed that demonstrated diffuse bilateral ill-defined nodular infiltrates, correlating clinically with the presence of septic emboli. The patient became afebrile, but leukocytosis (up to 17 200 µl⁻¹) persisted through day 3, and daptomycin was increased to 8 mg kg⁻¹ IV daily. A chest X-ray was repeated secondary to pleuritic chest pain and revealed diffuse bilateral ill-defined nodular infiltrates. On day 6 of her overall hospitalization, she had a fever of 102.7 °F with relatively unchanged leukocytosis (15 000 µl⁻¹); in addition, a repeat transthoracic echocardiogram was ordered that did not reveal any valvular vegetations. Blood cultures drawn on days 4, 5 and 8 were persistently positive for MRSA. On day 10, MIC testing for daptomycin and ceftaroline were ordered and, in the interim, ceftaroline 600 mg IV every 12 h was added empirically to the daptomycin. Blood cultures on day 11 were positive and daptomycin was discontinued on day 12 due to an MIC of 4 µg ml⁻¹ by E-test. Ceftaroline (MIC 0.5 µg ml⁻¹ by E-test) was continued, and gentamicin 1 mg kg⁻¹ (based on actual body weight) IV every 8 h was added. Leukocytosis resolved by day 11 and blood cultures were negative on day 14. 4 days after starting ceftaroline and 2 days after the addition of gentamicin. Renal function remained stable throughout therapy and the patient completed a total of 2 weeks of gentamicin and 4 weeks of ceftaroline after the first negative blood culture. No surveillance cultures were ordered after completion of therapy.

A baby girl was delivered via caesarean section at 34 weeks and 2 days due to premature rupture of the membranes, recurrent prolonged decelerations and complex cord entanglement around the fetus’s bilateral lower extremities. The birth weight was 1.95 kg and APGAR scores were 9 (1 min) and 9 (5 min). Meconium and urine drug screens were positive for cocaine and opiates. The infant remained hospitalized for 26 days secondary to treatment of opiate withdrawal; moreover, physical examination and laboratory markers did not reveal any renal toxicity, hearing loss or other adverse effects attributed to antimicrobial therapy.

Discussion

In this case report, we describe the successful eradication of persistent daptomycin-non-susceptible MRSA bacteraemia and endocarditis with a combination of ceftaroline and gentamicin in a pregnant female. When used for the treatment of invasive MRSA infections, ceftaroline has primarily been selected as salvage therapy. In a retrospective study by Polenakovik & Pleiman (2013), the charts of 31 patients who received ceftaroline for MRSA bacteraemia were reviewed. The patients were previously treated unsuccessfully with vancomycin, linezolid and/or daptomycin. Endocarditis was the source of infection in nine patients. Overall, clinical success was seen in 74 % of patients, including 89 % of patients with endocarditis. However, the study only included patients who received a minimum of 7 days of ceftaroline. Comparatively, two other case series (Ho et al., 2012; Lin et al., 2013) reported clinical success rates of 83 % (5/6 patients) and 60 % (6/10 patients). Only a few case reports (Jongsma et al., 2013; Rose et al., 2012) have described the use of ceftaroline for daptomycin-non-susceptible MRSA bacteraemia, one of which was as monotherapy and the other was in combination with daptomycin to elicit an enhanced bactericidal activity.

The ceftaroline regimen utilized in our patient preceded much of the published literature supporting alternative dosing (i.e. 600 mg IV every 8 h) in MRSA bacteraemia. Rather, we elected to employ the use of combination therapy with an aminoglycoside for synergy. When ceftaroline was combined with tobramycin, in vitro time-kill experiments demonstrated synergism resulting in a quick and persistent bactericidal effect against tested MRSA isolates (Vidaillac et al., 2010), which may have facilitated rapid clearance of bacteria. While ceftaroline is considered pregnancy category B, it is important to note that aminoglycosides cross the placenta and may cause fetal harm including nephro- and ototoxicity (pregnancy category D); however, the risk from persistent bacteraemia and endocarditis was of greater concern and the potential consequences for the fetus were minimized by targeting the lower end of the therapeutic range for synergy.

This case report further supports the growing body of evidence highlighting the role of ceftaroline treating in MRSA bacteraemia, particularly in instances of vancomycin and daptomycin failure or intolerance.
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References


