Combination of ceftaroline and daptomycin as treatment for complicated osteomyelitis

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SUMMARY

Osteomyelitis is an infection involving bone. *Staphylococcus aureus* is the pathogen most frequently implicated; less frequently involved are other gram-positive organisms, such as *Staphylococcus epidermidis,* and also gram-negative organisms. The antibiotic of choice for treatment of osteomyelitis caused by methicillin-resistant staphylococci (MRS) is vancomycin, although other alternatives such as daptomycin or teicoplanin are also considered. Osteomyelitis caused by MRS can be difficult to treat safely and effectively. This case report describes the successful use of daptomycin combined with ceftaroline for the treatment of osteomyelitis caused by methicillin-resistant *S. epidermidis* (MRSE) in a 54-year-old woman, emphasising the clinical pharmacist's role in antimicrobial stewardship programmes. This alternative combination has been studied in the treatment of methicillin-resistant *S. aureus* (MRSA), but it may also be useful in MRSE.

BACKGROUND

Staphylococcus epidermidis is among the most frequent constituents of normal skin flora.[1 2] These organisms are common contaminants in clinical specimens and are increasingly being recognised as agents of clinically significant infection, including bacteraemia and endocarditis. Patients at particular risk for coagulase negative staphylococci (CoNS) infection include those with prosthetic devices (eg, pacemakers, intravascular catheters) and immunocompromised hosts.[3]

According to the guidelines[4] the treatment of choice for osteomyelitis caused by methicillin-resistant *S. epidermidis* (MRSE) is vancomycin, despite the risk of nephrotoxicity and the need for monitoring. Other alternatives could be used such as daptomycin, fusidic acid, linezolid, cephalosporins, clindamycin, dalvabancin or telavancin.

To predict vancomycin effectiveness, the most useful pharmacodynamic parameter is the ratio of the vancomycin area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) of ≥400.[5] However, in patients with a serious infection and an MIC ≥2 mg/L for vancomycin, the use of an alternative therapeutic agent may be needed.[6] In these cases, daptomycin should be used. The Infectious Diseases Society of America (IDSA) guidelines for the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections recognise daptomycin as an antibiotic option for the treatment of osteomyelitis,[4] and the study by Mallizos *et al*[2] noted successful rates of 80% in patients with osteomyelitis treated with daptomycin. The optimal dose of daptomycin is uncertain; doses ranging from 6 to 10 mg/kg/day were used in the study above.

Daptomycin non-susceptibility is unusual in the clinical setting and it seems to be linked to multiple mutations in a number of genes, which affect the wall load, membrane fluidity and metabolism.[7] The combination of daptomycin and a β-lactam such as ceftaroline may be beneficial against daptomycin-susceptible and daptomycin-non-susceptible MRSA, increasing the negative charge of the bacterial cell surface leading to better daptomycin binding. Therefore, it may prevent the development of daptomycin resistance.[8 9]

The use of the combination of ceftaroline and daptomycin has been described in the following indications[10]: bacteraemia, infective endocarditis (IE) and MRSA prosthetic valve IE. However, evidence about the effectiveness and duration of this combination in the treatment of osteomyelitis is limited.

This type of infection has a complicated management and physicians sometimes seek advice from the hospital antimicrobial stewardship programme (ASP) teams. These multidisciplinary groups are responsible for finding the optimal selection, dosage and duration of antimicrobial therapy that result in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.[11] Our antimicrobial ASP team was established in 2016, and clinical pharmacists are part of the team. They are actively involved in antimicrobial management, controlling the appropriate use of antimicrobial agents and optimising prescription behaviours.[12]

Herein, we present the case of a patient diagnosed with MRSE osteomyelitis. The susceptibility test showed an MIC of 2 mg/L for vancomycin; therefore daptomycin was prescribed (MIC ≤1 mg/L). After 5 days of treatment with daptomycin no response was observed; in order to prevent the emergence of resistance to daptomycin, ceftaroline was added (MIC ≤0.5 mg/L) resulting in an adequate response.

Consequently, we consider it relevant to describe this case in order to highlight that this alternative antimicrobial combination should be taken into account by physicians and pharmacists in the treatment of MRSE osteomyelitis.

CASE PRESENTATION

A 54-year-old woman was admitted to the Traumatology Department with a diaphyseal fracture of

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Table 1 Sensitivity of *Staphylococcus aureus* and *Staphylococcus epidermidis* isolated

Bacterial organism isolated	Methicillin-resistant Staphylococcus aureus			Staphylococcus epidermidis
Material collected	Surgical wound		Prosthesis material	Surgical wound
Date	14/8/2017	20/8/2017	10/10/2017	14/5/2018
Amoxicillin/clavulanate	R	R	R	R
Cefoxitin	R	NT	NT	NT
Ceftaroline				S
Ciprofloxacin	NT	NT	NT	R
Clindamycin	S	S	S	R
Cloxacillin	R	R	NT	NT
Daptomycin			S	S
Gentamicin	S	S	NT	R
Erythromycin	S	NT	NT	R
Levofloxacin	R	R	R	R
Linezolid	S	S	S	S
Oxacillin	NT	NT	R	R
Penicillin	NT	R	R	NT
Rifampicin	NT	S	S	NT
Teicoplanin	NT	S	NT	S
Tetracycline	S	NT	NT	NT
Trimethoprim/sulfamethoxazole	S	S	S	R
Vancomycin	S	S	S	S

NT, not tested; R, resistance; S, sensitive.

the tibia and fibula after an accidental fall. She had a history of type 2 diabetes mellitus and spondyloarthritis. Her usual treatment included enalapril/hydrochlorothiazide 20/12.5 mg/day, metformin 450 mg twice daily, amlodipine 10 mg/day, prednisone 5 mg/day and omeprazole 20 mg/day. On admission, the limb was immobilised and a minimally invasive plate osteosynthesis (MIPO) was performed. The patient received a single dose of cefazolin 2 g as preoperative antibiotic prophylaxis followed by three doses of cefazolin 1 g after the intervention. On the third day of hospitalisation an adequate progression of the surgical wound was observed and the patient was discharged with follow-up visits with her primary care physician.

Ten days after the discharge, although the patient remained asymptomatic, she was re-admitted to the emergency department due to suppuration of the surgical wound. Laboratory work-up showed a C-reactive protein (CRP) value of 28.7 mg/L (reference range 0–5 mg/L), but the rest of the infection values were normal. Oral amoxicillin/clavulanic 875/125 mg three times a day was empirically prescribed until the result of the wound culture was obtained.

INVESTIGATIONS

MRSA was isolated from the surgical wound. Surgeons presented the case to the ASP team and treatment with oral linezolid 600 mg/12 hours for 6 weeks was recommended according to the antibiogram (table 1). The patient presented an adequate response.

However, 1 week after antibiotic discontinuation the wound worsened, with suppuration present at the physical examination, and the patient reported pain. The physicians decided to remove the osteosynthesis and implant an external fixator. The prosthetic material was cultured and showed growth of MRSA with a sensitivity profile similar to that of the first culture (table 1). At that point, the strategy of the ASP team was to re-introduce linezolid 600 mg/12 hours combined with rifampicin 600 mg daily because it has excellent anti-staphylococcal activity and bioavailability. The patient reported gastrointestinal adverse effects due to the rifampicin and consequently the drug was discontinued. Linezolid was maintained for 8 weeks with an improvement of the surgical wound, and the pain disappeared.

Unfortunately, symptoms such as pain, clinical signs of inflammation and a pre-tibial blister in the region of the surgical wound occurred after antibiotic discontinuation. Intravenous vancomycin 1 g/12 hours for 15 days was prescribed. There was an improvement in the patient's condition and, subsequently, she was discharged with sulfamethoxazole/trimethoprim (800/160 mg three times a day) and rifampicin orally (300 mg/12 hours) for 2 months. In order to avoid gastrointestinal adverse events, the clinical pharmacist recommended dividing the dosage of rifampicin into two administrations per day and to add a prophylactic anti-emetic treatment.

TREATMENT

A significant clinical improvement was observed; however, CRP values remained high (18 mg/L) and a sequestrum was visible on X-ray. Surgical debridement with an intramedullary application of vancomycin cement was then performed. Cultures were collected during the surgical intervention and MRSE was isolated. A susceptibility test of *S. epidermidis* showed an MIC for vancomycin of 2 mg/L. Due to treatment failure, and the good penetration of daptomycin in the bone and joints, the ASP team considered initiating treatment with daptomycin 10 mg/kg/day (MIC ≤1 mg/L) as an alternative therapy. The patient was prescribed daptomycin 900 mg/day. Although the antibiogram was sensitive to daptomycin, after 5 days of treatment no clinical improvement was observed, the tibia scar presented serohaematic exudate and the infra-patellar region presented a paler erythematous eruption. On suspicion of possible non-susceptibility to daptomycin, the clinical pharmacist was asked to review the available evidence of alternative antibiotic agents to add to daptomycin in order to prevent the occurrence of resistance. A literature reviewed found that the combination of

daptomycin with a β-lactam such as ceftaroline demonstrated a synergistic effect because it seemed to increase the bactericidal activity against MRS.[9] Ceftaroline was tested as sensitive (MIC ≤0.5 mg/L) and the ASP team recommended the addition of this agent to the therapeutic regimen.

OUTCOME AND FOLLOW-UP

Intravenous ceftaroline 600 mg every 8 hours was combined with daptomycin 900 mg/day for 3 weeks. Once clinical improvement was observed the clinical pharmacist proposed de-escalation to a single agent and ceftaroline was maintained in monotherapy for 1 week more.

The patient was closely monitored for renal function and creatinine phosphokinase (CPK) levels during the therapy, as well as haematological parameters. No adverse events were reported throughout the course of treatment. The patient finished the treatment in June 2018.

Currently, the patient continues to attend follow-up visits to the Traumatology Department; she remains asymptomatic and has not shown any signs of infection.

DISCUSSION

Combinations of β-lactams and daptomycin against *S. aureus* have demonstrated synergistic effects which result in changes in the cell surface charge and lead to increased daptomycin binding.[8 9 13] In addition, this combination appears to be beneficial in decreasing the emergence or selection of resistant subpopulations. Therefore, this association may be of particular value in the setting of difficult-to-treat infections where isolates with reduced susceptibility to glycopeptides or lipopeptides have emerged on therapy.[13]

Due to the fact that ceftaroline demonstrates activity against MRSA,[11] the use in combination with daptomycin has been studied. Its use has been described in bacteraemia,[14 15] infective endocarditis[16 17] and MRSA prosthetic valve IE indications.[18]

The case series conducted by Sakoulas *et al*[15] described 26 cases series of staphylococcal bacteraemia who were treated with ceftaroline in combination with daptomycin, which includes 22 MRSA cases, two methicillin- sensitive *S. aureus* cases (MSSA) and two to MRSE cases. Doses ranged from 6–10 mg/kg for daptomycin and from 200 mg every 12 hours to 600 mg every 8 hours for ceftaroline. After a median of 2 days, blood cultures cleared with combination therapy in 25 patients (96%). Fourteen percent of these bacteraemias had associated osteomyelitis and the MRSE cases were bacteraemia associated with right-sided IE prosthetic valve.

The study by *Geriak et al*[16] compared the use of daptomycin plus ceftaroline versus standard therapy in monotherapy (vancomycin or daptomycin) in patients with bacteraemia due to MRSA. Their results showed that therapy with daptomycin and ceftaroline may be associated with a reduction in in-hospital mortality compared with monotherapy treatment.

It should be noted that the experience of this combination is primarily with *S. aureus* and not with CoNS. Therefore, ceftaroline may not be the only agent in this regard; other β-lactams may provide similar synergistic effects.[10]

In terms of treatment duration, the IDSA guidelines recommend a minimum of 8 weeks of antibiotic therapy for MRSA osteomyelitis.[4] However, there are no specific studies on combination therapy in osteomyelitis. According to Sakoulas *et al*,[15] the median duration of daptomycin plus ceftaroline combination therapy was 16 days although some patients received additional de-escalated, step-down antibiotics, replacing daptomycin plus ceftaroline, to complete a median total duration of 42 days of therapy. In the patients who presented with associated osteomyelitis, the median duration of combination therapy was 13 days to complete on average 53 days of therapy. Geriak *et al*[16] reported a treatment duration of 11 days, and Baxi *et al*[18] maintained 6 weeks of ceftaroline/daptomycin therapy. In our patient the combination therapy was maintained for 3 weeks, and ceftaroline monotherapy for 1 week more.

The MRSA guidelines recommend that patients with refractory bacteraemia or those who have failed vancomycin could receive a β-lactam in combination with high-dose daptomycin; however, the duration of combination therapy or the potential for de-escalation are not clearly addressed.[4] According to Geriak *et al*,[16] de-escalation is almost universally adopted with an average duration of treatment of 11 days. However, Sakoulas *et al*[15] observed that de-escalation should be adopted once patients are deemed to be stable, which occurs on average at 16 days.

It is important to know whether de-escalation can be done without compromising efficacy. The study by Barber *et al*[14] indicated that combination therapy may not be necessary for the entire course of treatment. De-escalation therapy may be considered a reasonable alternative to long-term combination therapy in patients with an early clinical response. However, additional investigations are warranted to determine the optimal timing of de-escalation.

Thus, it seems that once an infection is adequately controlled, and there are no outstanding surgical management issues, it may not be necessary to complete an entire parenteral course of antimicrobial therapy with daptomycin plus the β-lactam or ceftaroline, because this combination therapy can be very cumbersome and expensive outside an acute care hospital setting. More studies are needed to establish the duration of combination therapy or the potential for de-escalation.

The inclusion of pharmacists in different healthcare settings, such as in ASP teams, and their cooperation with physicians promotes the safe and cost-effective use of antibiotics.

Learning points

- The combination of daptomycin and ceftaroline may be considered an alternative in the treatment of methicillin-resistant *Staphylococcus epidermidis* (MRSE) osteomyelitis refractory to vancomycin therapy.
- A synergistic effect between daptomycin and ceftaroline has been confirmed.
- The duration of combination therapy and its de-escalation are not clearly established.
- More studies are needed to establish the correct management of this antimicrobial combination in this setting.
- Clinical pharmacists integrated into antimicrobial stewardship programmes can play a key role to support the safe and cost-effective use of antimicrobial agents.

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REFERENCES

1 Darley ESR, MacGowan AP. Antibiotic treatment of gram-positive bone and joint infections. *J Antimicrob Chemother* 2004;53:928–35.
2 Malizos K, Sarma J, Seaton RA, *et al*. Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry. *Eur J Clin Microbiol Infect Dis* 2016;35:111–8.
3 Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. *Clin Microbiol Rev* 2014;27:870–926.
4 Liu C, Bayer A, Cosgrove SE, *et al*. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis* 2011;52:e18–55.
5 Rybak MJ, Lomaestro BM, Rotschafer JC, *et al*. Therapeutic monitoring of vancomycin in adults: summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2009;29:1275–9.
6 Mohr JF, Murray BE. Point: vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* 2007;44:1536–42.
7 Gómez Casanova N, Siller Ruiz M, Muñoz Bellido JL. Mechanisms of resistance to daptomycin in Staphylococcus aureus. *Rev Esp Quimioter* 2017;30:391–6.
8 Choo EJ, Chambers HF. Treatment of methicillin-resistant Staphylococcus aureus bacteremia. *Infect Chemother* 2016;48:267–73.
9 Gonzalez-Ruiz A, Seaton RA, Hamed K. Daptomycin: an evidence-based review of its role in the treatment of gram-positive infections. *Infect Drug Resist* 2016;9:47–58.
10 Cosimi RA, Beik N, Kubiak DW, *et al*. Ceftaroline for severe methicillin-resistant *Staphylococcus aureus* infections: a systematic review. *Open Forum Infect Dis* 2017;4:84.
11 Tamma PD, Cosgrove SE. Antimicrobial stewardship. *Infect Dis Clin North Am* 2011;25:245–60.
12 Sakeena MHF, Bennett AA, McLachlan AJ. Enhancing pharmacists' role in developing countries to overcome the challenge of antimicrobial resistance: a narrative review. *Antimicrob Resist Infect Control* 2018;7:63.
13 Werth BJ, Sakoulas G, Rose WE, *et al*. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate Staphylococcus aureus in a pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother* 2013;57:66–73.
14 Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. *J Antimicrob Chemother* 2015;70:505–9.
15 Sakoulas G, Moise PA, Casapao AM, *et al*. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clin Ther* 2014;36:1317–33.
16 Geriak M, Haddad F, Rizvi K, *et al*. Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant Staphylococcus aureus bacteremia. *Antimicrob Agents Chemother* 2019;63:2483–518.
17 Rose WE, Schulz LT, Andes D, *et al*. Addition of ceftaroline to daptomycin after emergence of daptomycin-nonsusceptible Staphylococcus aureus during therapy improves antibacterial activity. *Antimicrob Agents Chemother* 2012;56:5296–302.
18 Baxi SM, Chan D, Jain V. Daptomycin non-susceptible, vancomycin-intermediate Staphylococcus aureus endocarditis treated with ceftaroline and daptomycin: case report and brief review of the literature. *Infection* 2015;43:751–4.