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CASE REPORT

Vertebral osteomyelitis caused by vancomycin-tolerant methicillin-resistant *Staphylococcus aureus* bacteremia: Experience with teicoplanin plus fosfomycin combination therapy

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An 85-year-old female presented with fever and consciousness disturbance for 3 days. The patient's blood culture subsequently revealed persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia despite the administration of vancomycin or teicoplanin monotherapy. Gallium inflammation scan and magnetic resonance image of the spine disclosed osteomyelitis and discitis at the level of L4—5. Surgical debridement was not feasible in this debilitated patient. Because of the creeping minimal inhibitory concentration of vancomycin of the causative isolate (1.5 μg/mL) and clinical failure with glycopeptide monotherapy, we changed the antibiotic therapy to a fosfomycin and teicoplanin combination therapy. The patient showed improved clinical response in terms of her enhanced consciousness as well as subsidence of persisted bacteremia. Despite the potential side effects of fosfomycin (such as diarrhea and

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hypernatremia), it combined with a glycopeptide may be an alternative therapy for invasive refractory MRSA infections.

Introduction

Staphylococcus aureus is the most common causative agent of hematogenous vertebral osteomyelitis among adults, accounting for over 60% of cases.[1] Emergence of the methicillin-resistant *S. aureus* (MRSA) strain has further complicated management of patients with vertebral osteomyelitis. The increasing minimal inhibitory concentration (MIC) of MRSA now accounts for a large proportion of invasive *S. aureus* infections.[2] MRSA-related infections often result in higher mortality rates and longer duration of hospitalization.[3,4] The Clinical and Laboratory Standards Institute lowered the susceptibility breakpoint of *S. aureus* from 4 μg/mL to 2 μg/mL, teicoplanin 8 μg/mL and fosfomycin 64 μg/mL.[5] Vancomycin or teicoplanin has been the antibiotic of choice for MRSA bacteremia. However, many alternative agents and combination therapies are considered as the salvage therapy of MRSA bacteremia when vancomycin treatment fails.[6,7]

Fosfomycin is a phosphoenolpyruvate analog produced by *Streptomyces* that inhibits enolpyruvate transferase, which prevents the formation of the peptidoglycan cell wall.[8] *In vitro* studies have confirmed the effectiveness of fosfomycin in combination with other antistaphylococcal agents, including vancomycin and teicoplanin, when conventional glycopeptide therapy fails.[9] Moreover, high concentrations of fosfomycin in bone tissue have been proved to be effective for treating osteomyelitis.[10]

We describe a case of lumbar osteomyelitis and discitis with persistent MRSA bacteremia refractory to vancomycin treatment. The patient was treated successfully with a combination therapy of fosfomycin and teicoplanin.

Case report

An 85-year-old female had a history of type 2 diabetes mellitus and was bedridden following a cerebral vascular accident. She had recurrent multiple pressure sores over lumbosacral areas. On admission, she was presented with fever and disturbed consciousness for 2 days. Physical examination revealed blood pressure of 89/68 mmHg and heart rate of 98 beats per minute. She had moderate respiratory distress, with a respiratory rate of 22 breaths per minute, and a body temperature of 39.5°C. The patient had multiple pressure sores over the lumbosacral and bilateral ankles area. Her white blood cell count was 26,960/μL, with 85% neutrophils and 9% band forms; platelet count 125,000/μL; and hemoglobin concentration 11.5 g/dL. The patient's biochemistry data were as follows: blood urea nitrogen 26 mg/dL, creatinine 1.26 mg/dL, randomized glucose 186 mg/dL, sodium 143 mmol/L, and potassium 3.3 mmol/L. Serum level of C-reactive protein (CRP) was 19.31 mg/dL. Urinalysis showed pyuria and bacteriuria. Her chest X-ray showed no evidence of active lung infection. Brain computed tomography revealed no intracerebral hemorrhage or evidence of newly onset cerebral infarction. Abdominal sonography revealed no biliary tract lesion. The empirical antibiotic of cefoperazone/sulbactam (2/1 g) was administered intravenously (i.v.) every 12 hours.

On the 4th admission day, urine culture yielded *Escherichia coli* and blood culture revealed MRSA. The antibiotic treatment was changed to ertapenem 1 g i.v. every 24 hours and vancomycin 1 g i.v. drip for 1 hour every 12 hours to cover both agents based on our laboratory susceptibility test (vancomycin MIC: 1.0 μg/mL by E test). One week later, blood cultures yielded MRSA (vancomycin MIC: 1.5 μg/mL by E test) repeatedly. Her urinalysis showed no pyuria in repeated tests and urine culture was negative. Echocardiography disclosed no evidence of infective endocarditis. Vancomycin was changed to teicoplanin (MIC: 1.0 μg/mL by E test) 400 mg once a day i.v. due to renal function deterioration and persisted bacteremia. MRSA bacteremia persisted despite a 2-week course of intravenous teicoplanin therapy. Erythrocyte sedimentation rate (ESR) was 91 mm/h and CRP was 11.7 mg/dL.

Magnetic resonance imaging of the L-spine indicated osteomyelitis and discitis at L4 and L5, with the involvement of bilateral psoas muscles and epidural abscess with low signal intensity on T1-weighted image and low-to-isointense signal on T2-weighted images, enhancement after gadolinium injection (Fig. 1A) and transverse view (Fig. 1B). Surgical debridement was not performed on the patient due to her poor performance status as well as the refusal of the patient's family. The antibiotic regimen was changed to a combination therapy comprising fosfomycin 4 g i.v. every 6 hours and teicoplanin 400 mg once daily. After commencing this combination regimen, blood cultures became sterile 1 week later.

The patient received a 5-week course of fosfomycin plus teicoplanin combination therapy. Serum ESR and CRP decreased to 35 mm/h and 2.1 mg/dL, respectively. The patient was discharged and in our outpatient clinic received a combination therapy comprising intramuscular injections of teicoplanin 400 mg twice a week, oral fusidic acid 500 mg every 8 hours, and rifampicin 300 mg orally every 12 hours for 2 months. She recovered well and there was no bacterial growth in repeated blood cultures.

Discussion

Vancomycin is the drug of choice for invasive MRSA infection. Due to the high mortality rate associated with MRSA infections, many alternative agents and combination

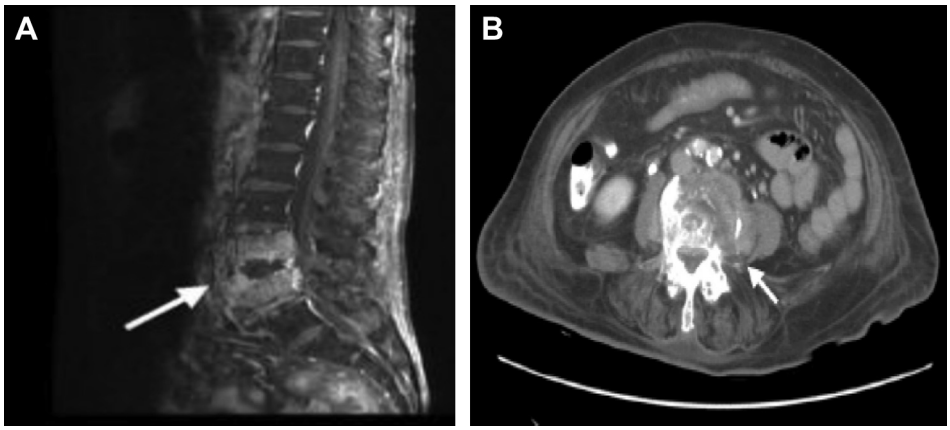

Figure 1. Spinal T2-weighted magnetic resonance images revealed (A) osteomyelitis and discitis at L4 and L5 with gadolinium enhancement (arrow), and (B) epidural abscess and psoas muscle abscess (arrow).

therapies are under development to manage vancomycin-tolerant strains, clinical treatment failure, or severe adverse effects.[6,7] The minimal bactericidal concentration (MBC) determination by the Clinical and Laboratory Standards Institute for the causative *S. aureus* isolate of this patient was 48 μg/mL, and the MBC/MIC ratio was ≥ 32. Therefore, a combination therapy may be considered for such tolerant strains.[6,9,11] Moise et al[12] have proved that MRSA bloodstream isolates from patients treated with vancomycin may demonstrate reduced susceptibility and increased tolerance to vancomycin *in vitro*. For MRSA infections with reduced vancomycin efficacy, consideration may be given to alternative anti-MRSA agents or combination therapies.[12,13]

Fosfomycin is a phosphoenolpyruvate analogue and has been shown to have reliable efficacy against *S. aureus*.[11] *In vitro* studies confirmed the synergistic effect of fosfomycin in combination with other anti-*Staphylococcus* agents, including vancomycin, teicoplanin, and rifampicin, when conventional glycopeptide therapy fails.[11,12] Fosfomycin can penetrate bone tissue and maintain high concentrations, which make it effective for treating osteomyelitis.[10]

Because the patient had lumbar osteomyelitis, discitis, and epidural abscess with persistent MRSA bacteremia after monotherapy with vancomycin or teicoplanin, a combination of fosfomycin plus teicoplanin i.v. was given to our patient during hospitalization. The effectiveness of this combination therapy was shown by the eradication of *S. aureus* bacteremia in repeated blood cultures and a substantial decline in the levels of CRP and ESR.

Although vancomycin is still the drug of choice for MRSA bacteremia, the tolerance or creeping MIC of vancomycin is a major issue about treatment outcome.[11–14] Among the isolates with higher MICs within the susceptible range (≤ 2 μg/mL), slow bactericidal activity and relatively poor tissue penetration of vancomycin may, however, contribute to poor performance and clinical success.[12] In case of glycopeptide treatment failure, a combined therapy can be an effective medical option. In addition to the debilitated status of our patient, her family's unwillingness to surgical intervention made antibiotic therapy the only choice for this patient. Our case demonstrates the effectiveness of a combination therapy comprising glycopeptide and fosfomycin for MRSA bacteremia and vertebral osteomyelitis.

At present, there are no definitive guidelines for the management of vertebral osteomyelitis, discitis, and epidural abscess. No data from randomized, controlled trials to guide decisions about specific antimicrobial regimens or duration of therapy are available.[15,16] Our case showed the clinical effectiveness of fosfomycin plus teicoplanin combination treatment. In addition, intramuscular injections of teicoplanin, and oral administration of rifampicin and fusidic acid may be a choice for long-term maintenance therapy for outpatients and avoidance of prolonged hospitalization.

References

1. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ. Hematogenous pyogenic spinal infections and their surgical management. *Spine* 2000;**25**:1668–78.
2. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. *Clin Infect Dis* 2006;**42**:389–91.
3. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;**26**:166–8.
4. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003;**36**:53–9.
5. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; twenty-second informational supplement, M07-A9*. PA, USA: Clinical and Laboratory Standards Institute; 2012.
6. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med* 1991;**115**:674–80.
7. Baltch AL, Ritz WJ, Bopp LH, Michelsen PB, Smith RP. Antimicrobial activities of daptomycin, vancomycin, and oxacillin in human monocytes and of daptomycin in combination with gentamicin and/or rifampin in human monocytes and in broth

against *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2007;**51**:1559—62.
8. Fosgen A, Walzer M. Antimicrobial activity of fosfomycin in vitro. *J Antimicrob Chemother* 1983;**11**:467—71.
9. Pistella E, Falcone M, Baiocchi P, Pompeo ME, Pierciaccante A, Penni A, et al. *In vitro* activity of fosfomycin in combination with vancomycin or teicoplanin against *Staphylococcus aureus* isolated from device associated infections unresponsive to glycopeptide therapy. *Infez Me* 2005;**13**:97—102.
10. Schintler MV, Traunmüller F, Metzler J, Kreuzwirt G, Spendel S, Mauric O, et al. High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection. *J Antimicrob Chemother* 2009;**64**: 574—8.
11. Vogt K, Rauhut A, Trautmann M, Hahn H. Comparison of fosfomycin and teicoplanin in serum bactericidal activity against Staphylococci. *Drug Res* 1995;**45**:894—7.
12. Moise PA, Smyth DS, Fawal N, Robinson DA, Holden PN, Forrest A, et al. Microbiological effects of prior vancomycin use in patients with methicillin-resistant *staphylococcus* bacteraemia. *J Anitmicrob Chemother* 2008;**61**:85—90.
13. Grif K, Dierich MP, Pfaller K, Miglioli PA, Allergerger F. *In vitro* activity of fosfomycin in combination with various anti-staphylococcal substances. *J Antimicrob Chemother* 2001;**48**: 209—17.
14. Eksi F, Gayyurhan ED, Bayram A, Karsligil T. Determination of antimicrobial susceptibility patterns and inducible clindamycin resistance in *Staphylococcus aureus* strains recovered from southeastern Turkey. *J Microbiol Immunol Infect* 2011;**44**: 57—62.
15. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med* 2010;**362**:1022—9.
16. Chen WC, Wang JL, Wang JT, Chen YC, Chang SC. Spinal epidural abscess due to *Staphylococcus aureus*: clinical manifestations and outcomes. *J Microbiol Immunol Infect* 2008;**41**: 182—8.