Case Report

Successful treatment of skin and soft tissue infection due to carbapenem-resistant Acinetobacter baumannii by ampicillin–sulbactam and meropenem combination therapy

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S U M M A R Y

In recent years, carbapenem-resistant Acinetobacter baumannii infections have been responsible for outbreaks in medical facilities. A 35-year-old Japanese woman developed a skin and soft tissue infection due to carbapenem-resistant A. baumannii. The isolate was resistant to antibiotics other than ampicillin–sulbactam and colistin, suggesting drug resistance due to carbapenemase production by OXA-23. We selected a combination therapy consisting of intravenous ampicillin–sulbactam and meropenem. No changes were observed in aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, or serum creatinine during therapy, and carbapenem-resistant A. baumannii was not detected in wound exudates 3 days after therapy initiation. In our patient's case, combination therapy with ampicillin–sulbactam and meropenem was effective against skin and soft tissue infection due to carbapenem-resistant A. baumannii. Combination therapy with intravenous ampicillin–sulbactam and meropenem may be an option for skin and soft tissue infections due to carbapenem-resistant A. baumannii.

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1. Introduction

Acinetobacter baumannii causes a wide range of nosocomial infections, including pneumonia, bacteremia, urinary tract infections, secondary meningitis, and skin and soft tissue infections. Traditionally, the most effective antimicrobials against A. baumannii have been carbapenems such as imipenem–cilastatin and meropenem. In recent years, infections due to carbapenem-resistant A. baumannii have been responsible for frequent outbreaks in medical facilities. Carbapenem resistance is mediated primarily by carbapenemases, including class D β-lactamases (OXA-type carbapenemases) and class B metallo-β-lactamases (MBLs). Although the efficacy of a number of antimicrobial combinations has been demonstrated in vitro, only limited data support the use of these agents in animal models of carbapenem-resistant A. baumannii infection. In addition, no randomized clinical trials have evaluated the optimal antimicrobial regimen for treating carbapenem-resistant A. baumannii infections. Therefore, clinicians must use combinations of licensed drugs in the hope that they will act synergistically.

Polymyxin B and colistin are frequently used to treat clinical carbapenem-resistant A. baumannii infections. Although these antibiotics act in vitro against many Gram-negative bacilli, including Acinetobacter spp and Pseudomonas spp, nephrotoxicity and neurotoxicity are common adverse events. Ampicillin–sulbactam is effective against Acinetobacter spp in vitro, and combination therapy with this antibiotic and a carbapenem has been used to treat carbapenem-resistant A. baumannii infections with some success. However, nearly all of these studies have involved cases of pneumonia, urinary tract infection, and sepsis; the efficacy of combination ampicillin–sulbactam therapy for the treatment of skin and soft tissue carbapenem-resistant A. baumannii infection remains unclear. The ideal therapeutic approach to A. baumannii infection should be based on the evaluation of isolate resistance patterns and clonally related carbapenem resistance. Here, we report a case of carbapenem-resistant A. baumannii skin infection successfully treated with a combination of intravenous ampicillin–sulbactam and meropenem.

2. Case report

A 35-year-old Japanese woman with a history of paranoid schizophrenia was admitted to our emergency medical care center
with vertebral compression and patellar fractures. Although mexitillin-resistant *Staphylococcus aureus* (MRSA) was detected in the wound exudate after endoscopic bone fixation surgery, there were no symptoms of infection. Vancomycin (20 mg/kg/day) was administered to prevent MRSA infection. On the third day of vancomycin treatment, carbapenem-resistant *A. baumannii* was isolated from the wound exudate, but MRSA was not found. The patient’s C-reactive protein (CRP) level was 4.28 mg/dl (normal, <0.2 mg/dl), white blood cell (WBC) count was 11.6 × 10^3/μl (normal, 3.5–8.5 × 10^3/μl), blood urea nitrogen (BUN) level was 10 mg/dl (normal, 8–22 mg/dl), serum creatinine (Scr) level was 0.44 mg/dl (normal, 0.40–0.70 mg/dl), aspartate aminotransferase (AST) level was 14 IU/l (normal, 13–33 IU/l), and alanine aminotransferase (ALT) level was 14 IU/l (normal, 8–42 IU/l). Based on these clinical findings, the patient was diagnosed with a skin and soft tissue infection caused by carbapenem-resistant *A. baumannii* and administration of vancomycin was discontinued immediately.

Antimicrobial susceptibility testing revealed resistance to all examined antibiotics, with the exception of ampicillin–sulbactam and colistin and, to a lesser extent, minocycline hydrochloride (Table 1). Combination therapy with ampicillin–sulbactam (ampicillin, 80 mg/kg/day; sulbactam, 40 mg/kg/day) and meropenem (30 mg/kg/day) was initiated in divided doses three times daily. Improvements in CRP and WBC count were observed 2 days after initiating combination therapy. Although carbapenem-resistant *A. baumannii* was not detected in wound exudates after 3 days of therapy, the exudate persisted without improvement. Therefore, continuous combination therapy with ampicillin–sulbactam and meropenem was administered to prevent multidrug-resistant *Pseudomonas aeruginosa* infection. Occasionally, MRSA was detected in the wound exudate, but the patient did not develop infectious disease. No other antibiotics were administered. No changes in AST, ALT, BUN, or SCR were observed during the prolonged combined therapy. No adverse events were observed, the wound healed, and the patient was discharged on day 52 to complete the 45-day course of combination therapy. One month after discharge, no carbapenem-resistant *A. baumannii* was detected in the wound area.

### 2.1. Mechanisms of antimicrobial drug resistance in *A. baumannii*

The minimum inhibitory concentration of antibiotics was determined by the agar dilution method using Clinical and Laboratory Standards Institute guidelines. MBL production was examined by double-disk synergy test. We also screened the isolate for OXA-type carbapenemase genes by multiplex PCR. MBLs were not produced by the carbapenem-resistant *A. baumannii* isolate; however, the isolate harbored the bla*OXA-23-like* and intrinsic bla*OXA-51-like* genes (see Supplementary Material). Although bla*OXA-51-like* resistance occurs only after insertion of an ISAb1a element containing a promoter sequence upstream of the encoding gene, ISAb1a was not found in the carbapenem-resistant *A. baumannii* isolate. These findings suggest carbapenem resistance in the isolated carbapenem-resistant *A. baumannii* strain was at least partially conferred by bla*OXA-23-like* carbapenemase.

### 3. Discussion

In this case of skin and soft tissue infection due to carbapenem-resistant *A. baumannii*, we selected combination therapy involving intravenous ampicillin–sulbactam and meropenem. First, it was necessary to avoid side effects such as nephrotoxicity and neurotoxicity; because our patient had a history of paranoid schizophrenia, side effects would be more difficult to discern in the presence of subjective and objective symptoms. In a large retrospective study of patients with *A. baumannii* infection conducted over an 8-year period, better outcomes were obtained with ampicillin–sulbactam than with polymyxin. Betrosian et al. also reported that, in comparison to the results obtained for colistin used at 3 million units three times daily, high doses of ampicillin–sulbactam exhibited a similar safety and efficacy profile in critically ill patients with *A. baumannii* pneumonia. In a retrospective study of patients with carbapenem-resistant *A. baumannii* bacteremia, the combination of a carbapenem and ampicillin–sulbactam was found to be associated with superior outcomes in comparison to those obtained with carbapenem plus amikacin or carbapenem alone.

Ampicillin–sulbactam is available in a number of countries and may be a suitable option for treating infections caused by *Acinetobacter spp.* The in vitro activity of sulbactam against clinical carbapenem-resistant *A. baumannii* strains ranges from 30% to 45%. These reports demonstrate the efficacy of ampicillin–sulbactam monotherapy for treating serious *A. baumannii* infections and suggest that sulbactam would be suitable for combination therapy with other antibiotics. *A. baumannii* outbreaks worldwide are caused by a limited number of genotypic clusters of multidrug-resistant strains. *A. baumannii* strains carrying the *blaOXA-23-like* Carbapenemase gene are among the most prevalent carbapenem-resistant *Acinetobacter* species in Asian countries. In this case, we found that the carbapenem resistance of the clinical *A. baumannii* isolate was conferred by the *blaOXA-23-like* carbapenemase (see Supplementary Material). Therefore, routine use of combined ampicillin–sulbactam and carbapenem therapy may be effective in the treatment of infectious disease due to the most prevalent carbapenem-resistant *A. baumannii* strains that produce *blaOXA-23-like* Carbapenemase.

In conclusion, combination therapy with intravenous ampicillin–sulbactam and meropenem resulted in both clinical and microbiological cure without significant acute complications or adverse effects. To our knowledge, this is the first report of the successful treatment of a complicated skin and soft tissue infection due to carbapenem-resistant *A. baumannii* using intravenous ampicillin–sulbactam and meropenem. As the frequency of secondary infections caused by multidrug-resistant organisms such as *A. baumannii* continues to rise, more data on the efficacy of combination therapies such as ampicillin–sulbactam and meropenem will be necessary to develop effective treatment regimens for carbapenem-resistant *A. baumannii* infection.

*Ethical approval:* Ethics committee approval and informed consent were obtained.

*Conflict of interest:* No conflict of interest to declare.
Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2013.05.002.

References