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CASE REPORT

Infective endocarditis due to *Enterobacter cloacae* resistant to third- and fourth-generation cephalosporins

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We report the case of using a long-term combination of meropenem and amikacin to treat infective endocarditis caused by *Enterobacter cloacae* resistant to third- and fourth-generation cephalosporins. Multi-drug resistant Gram-negative bacilli, such as the *E. cloacae* in our study, may become possible pathogens of infective endocarditis. Our experience with this case indicates that long-term use of a combination of β-lactam and aminoglycosides might represent a suitable management option for future infective endocarditis cases due to non-*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella* spp. (HACEK group) Gram-negative bacilli such as ours.

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Introduction

Infective endocarditis (IE) is a serious infectious disease that carries a high mortality rate.[1,2] Long-term use of antibiotics is required, and surgical intervention is also necessary in many cases. Gram-positive cocci such as *Streptococcus* spp. and *Staphylococcus* spp. are mainly responsible for infective endocarditis. On the other hand, there are few reported cases of IE due to Gram-negative bacilli (GNB).[3] In these rare GNB IE cases, groups of GNB consisting of *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* spp. (HACEK) are the predominant cause.[3] In contrast, *Enterobacter* spp., a non-HACEK GNB, has been reported to be an extremely rare pathogen of IE. In fact, 49 of all 2761 cases of IE were shown to be due to non-HACEK GNB, and only two were due to *Enterobacter cloacae*.[4] Although rare, IE due to non-HACEK GNB including *E. cloacae* is known to be highly severe.[4]

Multidrug-resistant GNB has become a major public health threat. Beta-lactamase producing GNB is especially important pathogens because of their resistance to antibiotics. The AmpC β-lactamase gene is naturally carried by certain enterobacteriaceae such as *Enterobacter* spp. Exposure to β-lactam can induce the expression of AmpC β-lactamases in these species, with consequent resistance to third-generation cephalosporin and mutations resulting in persistent resistance.[5] Extended spectrum β-lactamase (ESBL) is also well known as a cause of multidrug-resistance in GNB. Productions of ESBLs often can lead to resistance of fourth-generation cephalosporins.[5]

We present the survival case of IE due to *E. cloacae* resistant to third- and fourth-generation cephalosporins. The treatment protocol followed in this case demonstrates that a successful outcome is possible with long-term antibiotic medicines and without surgical intervention.

Case report

A 74-year-old Japanese man, suffering from a fever above 38°C for 2 weeks, was admitted to a hospital. The patient was previously diagnosed with liver cirrhosis (LC) due to hepatitis B virus infection at the age of 70; however, treatment was not sought at the time. Chest/abdominal radiographies and an abdominal ultrasonography upon admission revealed normal findings. Blood testing showed a white blood cell (WBC) count of 11.7×10^9/L and a C-reactive protein (CRP) level of 105 mg/L, yet there were no other significant findings to reveal the focus of infection. Intravenous ceftriaxone, 2 g every 24 hours, was administered from the day of admission; however, the fever continued to persist for 10 days and the patient was transferred to our hospital for further examination.

Upon admission to our hospital, the patient's temperature was 39.0°C. A Grade IV/VI systolic heart murmur was most evident at the cardiac apex. Petechiae were observed in the skin of the lower legs and in palpebral conjunctivae. Laboratory findings showed a WBC count of 8.3×10^9/L with no shift to the left, a platelet count of 96×10^9/L, and a CRP level of 82.1 mg/L. The serum albumin level was 21 g/L, total bilirubin was 7.1 mg/L and prothrombin time was 19.6 seconds. Transthoracic and transesophageal echocardiography revealed moderate mitral regurgitation and vegetation with 14 × 8 mm on the posterior leaflet of the mitral valve. Brain magnetic resonance imaging showed three embolic cerebral infarctions. Chest/abdominal computed tomography showed 2 × 3 cm of splenic infarct and ascites. Blood was collected three times after admission, and blood cultures were performed. Blood cultures revealed *E. cloacae* in all three samples. All three cultures were demonstrated to be the bacterium resistant to third- and fourth-generation cephalosporins by the antimicrobial susceptibility test. The antimicrobial susceptibility test also showed that *E. cloacae*, in this case, was sensitive to aminoglycosides and carbapenems. The patient was diagnosed with IE due to *E. cloacae* resistant to third- and fourth-generation cephalosporins and Child—Pugh class C LC.

A meropenem dose of 1.0 g IV every 8 hours and an amikacin dose of 800 mg IV every 24 hours were administered from the day of admission to our hospital. After the initial administration of meropenem and amikacin, the fever rapidly declined, and blood cultures collected on the second day of the administration of antibiotics were negative. WBC counts were decreased and CRP levels declined gradually. Brain magnetic resonance imaging and systematic computed tomography, and transthoracic and transesophageal echocardiography were repeated every 4 weeks after admission to our hospital. Eight weeks after treatment, the size of splenic infarction was reduced and no other embolic infarction was observed and the vegetation on the mitral valve had disappeared. Administration of meropenem and amikacin was terminated 12 weeks after the initiation of treatment. At the time of writing, the patient had been well for 6 months without relapse.

Discussion

Some specialists recommend that cases of IE associated with non-HACEK GNB should be managed by early surgery, combined with long-term (>6 weeks) therapy consisting of combinations of β-lactams and aminoglycosides, others have reported that the mortality rate is identical in surgical and nonsurgical cases as well as in patients treated with dual- as opposed to single-antibiotics.[4] Our patient was managed with a long-term combination of antibiotics and no surgical intervention. This protocol may represent a suitable management option for future IE cases due to non-HACEK GNB, although a large series of case studies is needed to demonstrate generalizability. Indeed, recently, Moon et al showed that surgical intervention was not needed in the treatment of IE due to *E. cloacae* in their case.[6] This report indicates that management with antibiotics alone was suitable for IE cases caused by *E. cloacae*. We used carbapenem for treatment. We believe that it may be beneficial to use broad-spectrum β-lactams in the empirical treatment of severe GNB infections, because resistant strains of GNB, including β-lactamase-producing GNB, are increasing in number.[7]

E. cloacae in this case was resistant to third- and fourth-generation cephalosporins. *E. cloacae* have chromosome-encoded AmpC β-lactamase genes, and can naturally produce AmpC β-lactamase. In contrast, fourth-generation cephalosporins are comparatively stable to AmpC β-

lactamases, and therefore have been regarded as a suitable option for the treatment of *Enterobacter* infections.[5] Although the results from the disk diffusion test by the Clinical and Laboratory Standards Institute we performed showed that clavulanic acid did not affect the growth of this strain (data not shown), the production of ESBLs in *E. cloacae* in this case remains to be suspected, especially because the double disk assay can be influenced by the presence of AmpC β-lactamase.[5,8]

Regarding the duration of treatment, although there is no evidence to suggest how long antibiotics should be used in non-HACEK GNB IE, a longer duration of antibiotic treatment would be ideal because, according to established guidelines, GNB IE should be treated with antibiotics for more than 4 weeks to cure and prevent relapse.[3] Our patient was managed without surgical treatment because of the patient's severe LC, although this choice was controversial. It has been reported that severe liver cirrhosis should not be treated with cardiac surgery, but, on the other hand, some specialists suggested that cardiac operations could be performed safely in patients with mild and advanced liver cirrhosis, although postoperative complications are common.[9,10] A large series of case studies are needed to reveal whether surgical treatment should be administered under the same conditions as those in our patient. Gut translocation of *E. cloacae* may have caused bacteremia and finally IE in our patient; however we were unable to identify its site of entry.[11]

In conclusion, we present a case of IE due to *E. cloacae* resistant to third- and fourth-generation cephalosporins successfully treated using a combination of meropenem and amikacin for 12 weeks. Multi-drug resistant GNB, such as the *E. cloacae* in our case, may become possible pathogens of IE. We believe that a long-term combination of β-lactam and aminoglycoside may represent a suitable management option for future IE cases due to non-HACEK GNB.

Conflict of interest

All contributing authors declare no conflict of interest.

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