Sepsis in a 4-Month-Old Boy Due to Carbapenem-Resistant Enterobacteriaceae Characterized by AmpC β-Lactamase with Porin Loss

Abstract
The incidence of carbapenem-resistant Enterobacteriaceae (CRE) infections is increasing, and these infections are associated with both morbidity and mortality. However, little is known about CRE infections in children. This article is a case report describing a 4-month-old boy with Langerhans histiocytosis who developed septic shock due to a CRE infection. The mechanism of carbapenem resistance was identified as AmpC β-lactamase hyperproduction with porin loss. The patient was treated with antibiotics, volume resuscitation, and vasopressors; however, he died of multiorgan failure due to CRE infection. Clinicians should be aware of the prevalence of CRE and the importance of prevention strategies against infection with multidrug-resistant bacteria, even in pediatric populations.

Keywords: Carbapenem resistant, children, porin, sepsis, β-lactamase

Introduction
The emergence of carbapenem-resistant Enterobacteriaceae (CRE) has become a worldwide problem,[1,2] and CRE infections are associated with significant morbidity and mortality.[1,2] The mechanisms of developing resistance to carbapenems include the production of carbapenemase or metallo-β-lactamase and the combination of β-lactamase hyperproduction with porin loss.[3] In children, especially infants, the previously reported mechanisms of carbapenem resistance were almost exclusively carbapenemase and metallo-β-lactamase production; reports of β-lactamase hyperproduction with porin loss are quite limited.[4] Here, we report the case of a 4-month-old boy whose blood cultures revealed CRE with carbapenem resistance due to AmpC β-lactamase hyperproduction with porin loss.

Case Report
In another hospital, a boy with a rash and low activity 7 days after birth was administered ampicillin and cefotaxime for 2 weeks as treatment for sepsis. When the patient was 1 month of age, he was admitted to our hospital for the treatment of rash and fever. He was treated for sepsis with cefotaxime, vancomycin, and acyclovir. On day 2, cytomegalovirus DNA was detected in his urine, blood, and cerebrospinal fluid, so ganciclovir was added to his treatments. Following these treatments, cytomegalovirus DNA was no longer detected. On day 15, the ganciclovir administration was discontinued due to severe pancytopenia. On day 40, the patient had a neutropenic fever, so he was given piperacillin/tazobactam from day 40 to day 50. On day 47, he was diagnosed by skin biopsy as having Langerhans histiocytosis. He received chemotherapy from day 57. However, after receiving chemotherapy, he developed another neutropenic fever, so he was treated with meropenem. On day 80, he developed a neutropenic fever again, with hypotensive shock. He was treated with volume resuscitation and a vasopressor, and vancomycin was added to his treatments. Blood cultures revealed carbapenem-resistant Enterobacter aerogenes. Based on susceptibility testing results [Table 1], ciprofloxacin was added to the patient’s treatment. On day 84, he died of multiorgan failure secondary to sepsis of *E. aerogenes*.

The results of susceptibility testing are shown in Table 1. Mean inhibitory concentrations were determined using disk diffusion methodology. The...
Mechanisms of carbapenem resistance include the production of carbapenemase and/or metallo-β-lactamase and the hyperproduction of AmpC or ESBL with porin loss. There are a few studies about CRE infections in children. The patient in this case was a 4-month-old infant. The 16S rRNA gene sequence from blood culture matched *E. aerogenes*, and the AmpC disk test results were positive. However, the results of a plasmid-mediated AmpC β-lactamase PCR were negative. PCR tests for the known carbapenemase-resistant genes of ESBL and carbapenemase were also negative. The levels of OmpC and OmpF significantly decreased. Thus, we considered the mechanism of carbapenem resistance to be chromosomal AmpC β-lactamase hyperproduction with porin loss.

It has been reported that risk factors of CRE infection in children are the same as those in adults and include long-term hospital care, previous antibiotics use, and an immune-compromised condition. From India, it was reported that, in children, risk factors for mortality from bloodstream infections of CRE, which mostly had carbapenemase production as their mechanism of carbapenem resistance, include intensive care admission, intubation, inotropic support, and respiratory failure. In the present case, the patient had multiple risk factors for CRE infection, specifically immune-compromised condition due to Langerhans histiocytosis and chemotherapy, long-term health care, and repeated prior exposure to broad-spectrum antibiotics, such as piperacillin/tazobactam and meropenem, due to febrile neutropenia. The patient subsequently died from sepsis caused by CRE infection, and he had risk factors for mortality from CRE infection that was identical to those of a previous report, including intensive care admission, intubation, and inotropic support. However, in contrast to the previously reported case, the mechanism of carbapenem resistance of the CRE in this case was different; it was determined to be AmpC hyperproduction with porin loss.

Current treatment options for CRE infection include tigecycline and colistin. Tigecycline is contraindicated in children who are <8 years of age due to tooth discoloration and enamel hypoplasia. In addition, the pharmacokinetic and clinical data of tigecycline and colistin in children are quite limited. Previously, it was reported that treatment combinations composed of two or three effective antibiotics had lower mortality rates. The patient in the present case received ciprofloxacin based on the results of antibiotic susceptibility tests; in spite of this treatment, he died from multiorgan failure due to CRE infection. The outcome may have been different if the patient had received combination therapy including colistin or tigecycline. Children are less likely to receive broad-spectrum antibiotics compared with adults; however, for cases with potential risk factors for CRE infection, such as long-term hospital care and prior antibiotic use, it is important to consider the possibility of infection due to CRE. Even in children, the administration of broad-spectrum antibiotics can cause the development of carbapenem resistance, including the acquisition of AmpC or ESBL enzymes with porin loss. Infection control and prevention strategies for antimicrobial drug resistance need to be emphasized.

### Discussion

Discussion of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information Table 1: Antibiotic susceptibility test

| Antibiotics | MIC (µg/ml) | Susceptible/intermediate/resistant |
|-------------|-------------|-----------------------------------|
| Ampicillin  | ≥32         | Resistant                          |
| Amoxicillin/Clavulanic acid | ≥32         | Resistant                          |
| Cefotaxime  | ≥64         | Resistant                          |
| Ceftazidime | ≥64         | Resistant                          |
| Cefepime    | 2           | Susceptible                        |
| Cefmetazole | ≥64         | Resistant                          |
| Imipenem    | ≥8          | Resistant                          |
| Meropenem   | ≥8          | Resistant                          |
| Amikacin    | ≤2          | Susceptible                        |
| Gentamicin  | ≤1          | Susceptible                        |
| Minocycline | ≥16         | Resistant                          |
| Ciprofloxacin| 0.5         | Susceptible                        |
| Levofloxacin| 1           | Susceptible                        |
| Sulfamethoxazole/trimethoprim | 40 | Susceptible                        |

Defined as “susceptible,” “intermediate,” or “resistant” based on the Clinical and Laboratory Standards Institute standards M100-S25. MIC: Minimum inhibitory concentration

Clinical isolates exhibited resistance to imipenem and meropenem and were also resistant to penicillin and cephalosporin. The cultures had positive results in an AmpC disk test, but test results from carba NP and plasmid-mediated AmpC β-lactamase PCR were also negative. The levels of OmpC and OmpF significantly decreased. Thus, we considered the mechanism of carbapenem resistance to be AmpC β-lactamase hyperproduction with porin loss. There are a few studies about CRE infections in children. The 16S rRNA gene sequence from blood culture matched *E. aerogenes* (1369/1369 bp).

### Discussion

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information.
to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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