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【 CASE REPORT 】

# Emergence of Carbapenem Non-susceptible *Campylobacter coli* after Long-term Treatment against Recurrent Bacteremia in a Patient with X-linked Agammaglobulinemia

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**Abstract:**

We herein report a case of recurrent *Campylobacter coli* bacteremia in a 37-year-old Japanese man with X-linked agammaglobulinemia (XLA). The patient experienced seven episodes of *C. coli* bacteremia over one year, with an erythematous rash intermittently emerged on the lower limbs. Although hospitalization for intravenous treatment was repeatedly recommended, he obstinately declined it. Following long-term oral antibiotic treatment with tebipenem and faropenem for the persistent infection, *C. coli* showed elevated minimum inhibitory concentrations to meropenem, a key drug for severe campylobacteriosis. Physicians should note that the overuse of antibiotics can lead to the emergence of carbapenem-non-susceptible *Campylobacter* strains.

**Key words:** bacteremia, *Campylobacter coli*, carbapenem, faropenem, soft tissue infection, tebipenem

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## Introduction

Among *Campylobacter* spp., *Campylobacter coli* is the second-most frequent pathogen of community-onset *Campylobacter* infection, followed by *Campylobacter jejuni* (1). Based on previous reports, usually less than 1% of *C. coli* infections are complicated with bacteremia (2-7). However, the incidence of systemic infection with *C. coli* might be underestimated due to its slow growth and the infrequency of blood culture examinations for outpatients with enterocolitis (8, 9). Thus, the clinical characteristics of *C. coli* bacteremia have not been fully uncovered. Compared with *C. fetus*, which has a specific affinity for vascular tissues, *C. coli* rarely evokes bacteremia and extra-intestinal complications. Immunocompromised patients, however, may fail to survive without appropriate treatment (10).

We herein report an adult patient with X-linked agammaglobulinemia (XLA) who was suffering from repetitive *C. coli* bacteremia without any gastrointestinal symptoms. Through a prolonged treatment course, the pathogenic organism gradually lost its susceptibility to carbapenem.

## Case Report

A 37-year-old man (body weight, 53 kg) with genetically-diagnosed XLA due to a mutation in the Bruton tyrosine kinase gene had undergone intravenous immunoglobulin (Ig)-replacement therapy every 3 weeks since he was 3 years of age. Six months earlier, Ig-replacement therapy had been switched from intravenous administration to subcutaneous injection. The serum IgG levels had been maintained approximately between 870 and 1,000 mg/dL. The patient was not receiving any prophylactic antibiotics.

At the end of May 2015, he suddenly suffered from a swelling of his left leg with an accompanying high fever. The patient was diagnosed with cellulitis and was treated with cefazolin at a neighborhood clinic for one week. However, the high fever and swollen leg persisted, and the patient visited our outpatient department. On arrival, his left

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**Table. Minimum Inhibitory Concentrations (MIC) of *Campylobacter coli*.**

| | June 2015 | February 2016 | May 2016 |
|---|---|---|---|
| Meropenem[a] | ≤0.125 | 1 | 4 |
| Azithromycin[a] | >4 | >4 (>256[b]) | >4 |
| Minocycline[a] | ≤0.5 | ≤0.5 | ≤0.5 |
| Levofloxacin[a] | >2 | >8 | >8 |
| Metronidazole[b] | n.p. | 0.06 | 0.06 |
| Chloramphenicol[b] | 2 | 2 | 2 |

[a]MicroScan Walkaway 96 plus System (Beckman Coulter)

[b]E-test (SYSMEX bioMerieux).

MIC of meropenem continued elevating throughout the course.

n.p.: not performed

lower leg appeared reddish and swollen. He denied any other symptoms, including any gastrointestinal complaints. Serum C-reactive protein was elevated (up to 6.19 mg/dL); otherwise, no remarkable findings were obtained. For a further examination and treatment, hospitalization was proposed to the patient, but he refused. After blood was drawn for a bacterial culture, he returned home. One week later, the patient visited us again, since the results of the blood culture examination were positive for Gram-negative spiral rods, with a 2.33-day incubation period (BacT/ALERT system; bioMérieux, Marcy l'Etoile, France). The patient received a daily administration of cefazolin at the clinic in the meantime; however, the swelling and claudication still persisted, and he was ultimately admitted to our hospital.

On admission, he was afebrile, and his vital signs were stable. There were still no gastrointestinal symptoms, and blood cultures remained positive for the Gram-negative spiral rods. The organism was identified as *C. coli* based on the matrix-assisted laser desorption/ionization-time of flight mass spectrometry using a MALDI Biotyper (Bruker Daltonics, Bremen, Germany) with a score of 2.231 and a positive result for *glyA* gene by polymerase chain reaction test (11). A stool culture was also positive for *C. coli*. The results of antimicrobial susceptibility testing are shown in Table. A whole-body investigation by computed tomography revealed no remarkable findings of visceral infection, and the results of transthoracic echocardiography were not suggestive of infective endocarditis. Magnetic resonance imaging of his lower legs revealed high intensity at the subcutaneous tissues on short TI inversion recovery, but there was no evidence indicating the formation of an abscess or osteomyelitis. After treatment with meropenem (1 g every 8 hours), the swelling of his lower left leg gradually improved, and the bacteremia disappeared. Two weeks later, the patient was discharged with continued treatment by oral tebipenem-pivoxil (200 mg, twice daily) for 3 weeks.

Two months after discharge, the patient experienced a recurrence of the swollen legs, and tebipenem-pivoxil was again orally administered for three weeks. Nevertheless, three months later, the patient experienced a high fever with leg swelling and continuing recurrent *C. coli* bacteremia. For the subsequent five months, even though the symptoms remained, the patient adamantly refused to be re-admitted to the hospital. During this time, oral administration of tebipenem-pivoxil and faropenem (200 mg, twice daily) was continued, and the minimum inhibitory concentration (MIC) for meropenem was found to be elevated (Table). Approximately one year after the onset of the initial episode of *C. coli* bacteremia, he complained of abdominal discomfort. A gastroscopic examination revealed an elevated gastric mucosal lesion that was pathologically diagnosed as gastric cancer. He eventually agreed to be admitted for endoscopic mucosal resection of the gastric malignancy as well as antibiotic treatment for the recurrent bacteremia.

The MIC level for meropenem of the pathogen was further increased on admission (Table). The patient underwent antibiotic therapy with intravenous biapenem (600 mg, every 12 hours) and oral minocycline (100 mg, twice daily) for 2 weeks. The persistent bacteremia resolved, and the antibiotics were switched to oral metronidazole (250 mg, 4 times daily) for an additional 4 weeks. After discharge, the antibiotic treatment was continued with oral minocycline for 10 weeks in total. Subsequently, no recurrent episodes have been reported in more than one year. The clinical course of the patient is shown in Figure.

## Discussion

We presented a case of multiple episodes of *C. coli* bacteremia in an adult patient with XLA. Over one year, the patient had at least seven episodes of *C. coli* bacteremia, with an erythematous rash that intermittently emerged on his lower limbs. Due to his refusal for hospitalization therapy, we were unable to provide the appropriate antibiotic treatment. As a result, the meropenem MIC of the pathogen apparently increased in association with the long-term antibiotic treatment mainly by oral antimicrobials.

The emergence of multidrug-resistant *Campylobacter* strains has become a global health problem (12, 13). Most *Campylobacter* spp. remain susceptible to a range of antibiotics (6), but strains resistant to third-generation cephalosporins, macrolides, and fluoroquinolones have been increasingly reported (14-16). Carbapenem is recommended as an empiric agent for *Campylobacter* bacteremia (7, 10, 17, 18); however, the causative organism in the present case demonstrated an increasing MIC level for meropenem after the prolonged antibiotic therapy. In Japan, the recommended dose of tebipenem is 4 to 6 mg/kg twice daily for children, while the optimum dose for adults is not described on the drug package insert. Faropenem is administered at 150 to 300 mg three times a day. In this case, both of the drugs were given at 200 mg twice daily, which may have been an under-dose for the infection. Although carbapenem-resistance in *Campylobacter* species has yet to be well defined by authorities, our case suggested possible resistance subsequent to drug exposure in a clinical situation. In case of refractory *Campylobacter* infections, com-

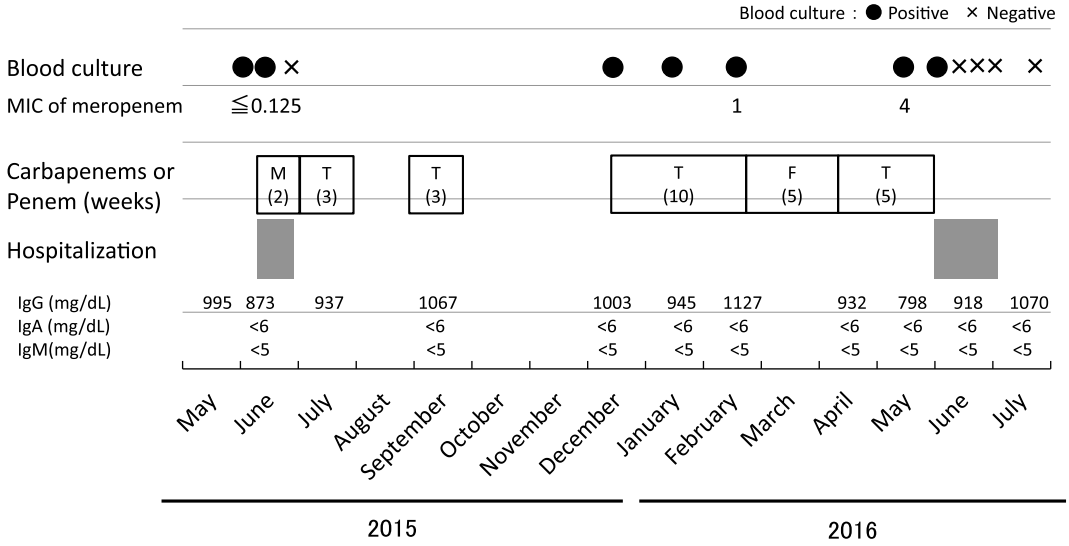


**Figure. Clinical course of the patient. The patient was admitted to the hospital for two weeks in June 2015 and four weeks in June 2016. Over one year, various kinds of carbapenems (M: meropenem, T: tebipenem-pivoxil) and penems (F: faropenem) were administered for the treatment of recurrent *Campylobacter coli* bacteremia. MIC: minimum inhibitory concentration (μg/mL)**

bination therapy may be preferred. In addition, aminoglycosides may be a favorable choice for the treatment of multidrug-resistant *Campylobacter* infections. The rate of aminoglycosides-resistant organisms is approximately 3% (19, 20); therefore, treatment with aminoglycosides is recommended, particularly in the case of severe infections (1, 21).

XLA predisposes patients to severe hypogammaglobulinemia due to the inadequate maturity of B lymphocytes (22). Interestingly, previous studies have revealed a peculiar association with XLA patients and *Campylobacter* systemic infection (8, 23). In a large cohort study, all of the recurrent cases were those with humoral immunodeficiency; as such, a relationship between systemic campylobacteriosis and XLA may exist (14). Worldwide, more than 20 cases of *C. coli* or *C. jejuni* bacteremia in patients with XLA or hypogammaglobulinemia were reported before 2010 (8). In Japan, three cases of *C. coli* bacteremia in XLA patients (24-26) and one case of *C. jejuni* bacteremia in a patient with hypogammaglobulinemia have been reported (27). Patients with XLA are regularly given Ig-replacement therapy to maintain the serum level of IgG for infection prevention. However, replacement therapy is not sufficient to prevent infection with enteropathogenic organisms, such as *Campylobacter* spp. or *Helicobacter* spp. (28), particularly because IgA, which plays an important role in the elimination of gut bacteria, is not provided with such therapy (29). Indeed, *C. coli* bacteremia occurred even in the presence of high serum IgG levels in our case, similar to the findings in an Italian patient with XLA (23). Thus, gut immunity via IgA is likely a key factor in the prevention of this rare infection (30).

The clinical manifestations of *C. coli* bacteremia have only rarely been reported. Previous studies have shown that patients with immunocompromising factors, like our patient, tend to suffer from recurrent *C. coli* bacteremia without gastrointestinal symptoms (7, 31). Cutaneous involvement is less recognized and may often be overlooked as a presentation of *Campylobacter* bacteremia (32). The incidence of cellulitis ranges from 3% to 20% and is particularly frequent in the lower extremities with recurrent episodes of bacteremia (18), as was also seen in this case.

In conclusion, this case highlighted several important issues. First, a carbapenem-non-susceptible *C. coli* strain appeared subsequent to prolonged antibiotic treatment for recurrent infection. Second, patients with XLA are at risk for systemic campylobacteriosis. Finally, Ig-replacement therapy alone is inadequate for the prevention of *Campylobacter* bacteremia, and another method that can enhance gut immunity may be required.

**The authors state that they have no Conflict of Interest (COI).**

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