

# Recurrent *Campylobacter jejuni* bacteremia in a patient with hypogammaglobulinemia

## A case report

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### Abstract

**Rationale:** Although some cases of recurrent bacteremia due to *Campylobacter jejuni* have been reported in immunocompromised patients, antibiotic treatment strategies to eradicate *C. jejuni* and prevent recurrent infections in immunocompromised patients have not been established. Authors' experience of such rare cases should be shared for improving patients' outcomes.

**Patient concerns:** An 18-year-old boy with hypogammaglobulinemia, who received intravenous immunoglobulin replacement therapy every 3 weeks, was admitted to hospital repeatedly due to recurrent diarrhea and cellulitis of the leg.

**Diagnoses:** The patient was admitted 6 times, and among them, *C. jejuni* was isolated from blood cultures 4 times and stool cultures 2 times.

**Interventions:** The patient experienced recurrent *C. jejuni* enteritis and bacteremia 5 times despite macrolide therapy. Doxycycline was administered for 3 months after the fifth admission.

**Outcomes:** Ten months after the completion of doxycycline therapy for 3 months, *C. jejuni* enteritis relapsed; however, since then, recurrent infection has not occurred for 10 months.

**Lessons:** Immunocompromised patients can experience recurrent *C. jejuni* infection despite prolonged antibiotic therapy. Further studies to establish appropriate antibiotic therapy for eradicating colonized *C. jejuni* and preventing recurrent infection are needed.

**Abbreviations:** HD = hospital day, HIV = human immunodeficiency virus, IVIG = intravenous immunoglobulin, WBC = white blood cell.

**Keywords:** agammaglobulinemia, bacteremia, *Campylobacter jejuni*, recurrence

## 1. Introduction

*Campylobacter* spp. is one of the most common pathogens causing infectious enterocolitis.<sup>[1]</sup> In humans, most cases of *Campylobacter* infections are caused by *Campylobacter jejuni*, manifested as a self-limiting enterocolitis.<sup>[1]</sup> Patients with human immunodeficiency virus (HIV) infections and immunocompromised patients, including those with hypogammaglobulinemia, are especially susceptible to *Campylobacter* infections.<sup>[2]</sup> Infections in these patients were reported to be severe, prolonged, and

recurrent.<sup>[2]</sup> *Campylobacter* spp. is the most common cause of infectious diarrhea in patients with hypogammaglobulinemia,<sup>[3]</sup> and cases of recurrent bacteremia associated with *C. coli* and *C. lari*, as well as *C. jejuni* have been reported in patients with hypogammaglobulinemia.<sup>[4–6]</sup> In spite of this, an antibiotic treatment strategy for immunocompromised patients experiencing recurrent *Campylobacter* infections has not been established, and no study on the prevention of recurrent *Campylobacter* infections has been implemented.

We report a case of an 18-year-old boy with underlying hypogammaglobulinemia, who experienced recurrent *C. jejuni* bacteremia 4 times in a period of 8 months. His diarrhea resolved with doxycycline administration for 3 months; however, *C. jejuni* enteritis recurred 10 months after the completion of doxycycline therapy. Future studies should be performed to determine appropriate antibiotic therapy for immunocompromised patients experiencing recurrent *Campylobacter* infections. This report was approved by the Institutional Review Board of Seoul St. Mary's Hospital (Approval number: KC16ZISE0757).

## 2. Case presentation

An 18-year-old boy was admitted to the hospital complaining of persistent cough and painful swelling with focal redness on the left shin. The patient had been diagnosed with hypogammaglobulinemia at 1 year of age, and subsequently received intravenous immunoglobulin (IVIG) replacement therapy every 3 weeks. Due to the parents' opposition, genetic studies for X-linked

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		1 <sup>st</sup> admission	2 <sup>nd</sup> admission (2 months later)	3 <sup>rd</sup> admission (1 month later)	4 <sup>th</sup> admission (2 months later)	5 <sup>th</sup> admission (1 month later)	6 <sup>th</sup> admission (10 months later)
Antibiotics	Cefazolin	10 days		6 days	14 days	7 days	
	Amoxicillin /clavulanate		8 days				
	Meropenem					21 days	
	Amikacin	10 days	8 days				
	Arbekacin			6 days	14 days	28 days	
	Roxithromycin	15 days		10 days			
	Clarithromycin				10 days	7 days	
	Doxycycline					21 days	3 months
Symptoms	Fever	(+)	(+)	(-)	(-)	(+)	(+)
	Diarrhea	(+/-)	(+)	(+)	(+)	(+)	(+)
	Cellulitis	(+)	(-)	(+)	(+)	(+)	(-)
	Blood culture	(+)	(+)	(+)	(-)	(+)	(-)
	Stool culture	(-)	(-)	(-)	(+)	(-)	(+)

Figure 1. The clinical course of recurrent *Campylobacter jejuni* infection.

agammaglobulinemia had never been performed. On admission, a chest radiography showed a pneumonic consolidation on the left lower lobe. Blood tests revealed a white blood cell (WBC) count of 7120/mm<sup>3</sup> (neutrophils, 80.8%; lymphocytes, 12.4%; and monocytes, 6.6%), hemoglobin level of 8.4g/dL, and a platelet count of 22,000/mm<sup>3</sup>. Blood chemistry tests showed no abnormalities. The last IVIG was administered 1 week before this admission, and the serum IgG level was 418 mg/dL on admission. He was diagnosed with pneumonia and cellulitis of the left leg based on his presenting symptoms and X-ray findings. Intravenous cefazolin and amikacin were administered for cellulitis of the leg, and oral roxithromycin was administered for pneumonia. He developed a fever on hospital day (HD) 2, which resolved on HD 5. Diarrhea occurred only on HD 3. The stool culture grew no pathogens, and occult blood and WBC were negative. *C. jejuni* was identified on the blood culture that was performed on admission; however, the blood culture performed on HD 4 was negative for *C. jejuni*. Antibiotic susceptibility tests for the identified *C. jejuni* were not performed. The patient was discharged from the hospital after intravenous antibiotic therapy for 10 days, and oral roxithromycin was administered for a total of 15 days. Serum immunoglobulin levels on discharge were as follows: IgG, 352 mg/dL; IgA, <1.0 mg/dL; IgM, <1.0 mg/dL; and IgE, <1.0 mg/dL. Lymphocyte subset tests on discharge showed the following results: CD3+ cells, 97.2%; CD4+ cells, 59.6%; CD8+ cells, 34.3%; CD19+ cells, <0.1%; and CD3–56+ cells, 2.4%. The patient developed diarrhea 2 weeks after discharge and this persisted. Two months after discharge, he was readmitted with continued weight loss and poor oral intake due to oral mucositis. Blood culture on admission grew *C. jejuni*, and he was discharged from the hospital after intravenous amoxicillin/clavulanate, amikacin, and acyclovir therapy for 8 days. One month later, he was readmitted due to persistent diarrhea and left shin cellulitis that had recurred. Blood culture on admission again grew *C. jejuni*, and he received oral roxithromycin for 10 days. Although *C. jejuni* was reported as a cause of cellulitis in patients with hypogammaglobulinemia, we could not ignore the fact that Gram-positive cocci are the most common cause of cellulitis.

Therefore, the patient also received intravenous cefazolin and arbekacin therapy for 6 days. After that time, diarrhea waxed and waned. Two months later, the left shin cellulitis recurred. Stool culture grew *C. jejuni*, although blood was sterile. Intravenous cefazolin and arbekacin was given for 14 days along with oral clarithromycin for 10 days. He was readmitted with fever and left shin cellulitis 1 month later. Intravenous cefazolin and amikacin, and oral clarithromycin therapy was begun as recurrent *C. jejuni* infection was suspected. Blood cultures were negative on admission; however, a repeat blood culture on HD 5 was positive for *C. jejuni*. On HD 8, the antibiotic susceptibility test revealed resistance against ciprofloxacin and erythromycin and susceptibility to tetracycline. Intravenous cefazolin and oral clarithromycin were switched to intravenous meropenem and oral doxycycline. The patient's fever disappeared on HD 9, and a repeat blood culture on HD 10 was negative. Stool culture revealed no pathogens, and the diarrhea resolved on HD 27. After the administration of meropenem and doxycycline for 3 weeks and amikacin for 4 weeks, the patient was discharged from the hospital. Oral doxycycline therapy was continued for an additional 3 months after discharge. Ten months after the completion of the doxycycline therapy, the patient again experienced fever and diarrhea. The stool culture was positive for *C. jejuni*; but blood cultures were negative. The patient received doxycycline, with resolution of his symptoms before the report of the antibiotic susceptibility test; therefore, doxycycline was continued for 10 days, even though the report showed resistance to tetracycline. Figure 1 shows the clinical course of recurrent *C. jejuni* infection in our patient.

### 3. Discussion

There are numerous reports about *Campylobacter* bacteremia in patients with chronic illnesses, such as chronic hepatitis, liver cirrhosis, diabetes, chronic lung diseases and cardiovascular disorders, HIV-infected patients, and immunocompromised patients.<sup>[7–12]</sup> In the past, it was believed that *C. fetus* was the cause of most systemic campylobacteriosis. Recent studies show,

however, that both bacteremia and enterocolitis are caused mainly by *C. jejuni*.<sup>[8–13]</sup> Bacteremia due to *Campylobacter* spp. is very rarely, comprising only 0.2% to 0.4% of all *Campylobacter* infections.<sup>[10,12]</sup> Also, recurrent bacteremia occurs in 2% to 5% of all bacteremia cases.<sup>[11–13]</sup>

Most cases of recurrent *Campylobacter* bacteremia were reported in patients with hypogammaglobulinemia.<sup>[4–6,13]</sup> In accordance with these findings, humoral immunity seems to play a role in immunity against and eradication of *Campylobacter* spp.<sup>[5]</sup> Secretory IgA in the intestinal mucosa may act as an important local immune defense; however, there was no significant increase in *Campylobacter* infections in patients with selective IgA deficiency.<sup>[2]</sup> Therefore, other immune mechanisms against *Campylobacter* spp. should be considered. Serum IgM is thought to be important because it promotes complement-mediated phagocytosis by increasing opsonization of pathogens.<sup>[2]</sup> Consequently, lack of IgA in the intestinal mucosa and IgM in the serum makes hypogammaglobulinemia patients more susceptible to *Campylobacter* infections, and prevents the eradication of colonized *Campylobacter* spp.<sup>[2]</sup> Although hypogammaglobulinemia patients receive IVIG regularly, IVIG consist mainly of IgG. Our patient's serum IgM and IgA levels could not be detected. It appears that the patient could not eradicate *C. jejuni* after the primary infection, and the colonized *C. jejuni* caused prolonged diarrhea and recurrent bacteremia.

Previously, *C. jejuni* was reported to be susceptible to macrolides and fluoroquinolones, and azithromycin was the recommended drug of choice.<sup>[1]</sup> However, *Campylobacter* strains isolated from patients with bacteremia showed resistance rates of 26% to 70% for fluoroquinolones and 6% to 79% for erythromycin. Resistance rates were 1% to 8% for amoxicillin/clavulanate, 0% to 6% for gentamicin, and 0% for carbapenems.<sup>[9–11,13,14]</sup> Therefore, amoxicillin/clavulanate, carbapenems, or aminoglycosides are recommended for patients with *Campylobacter* bacteremia.<sup>[9–11,13,14]</sup> Previously, recurrence of *C. jejuni* bacteremia was reported in spite of amoxicillin/clavulanate, erythromycin, or gentamicin therapy.<sup>[5,15,16]</sup> However, bacteremia did not recur with prolonged antibiotic therapy (e.g., imipenem for 2–6 weeks, ciprofloxacin for 6 weeks, or doxycycline for 4 months).<sup>[5,15,16]</sup> One patient showed persistent positive stool cultures for *C. jejuni* following imipenem therapy that was eradicated by ciprofloxacin and maternal plasma infusion therapy.<sup>[17]</sup> Other examples include erythromycin given for 6 weeks to eradicate *Campylobacter*s,<sup>[5]</sup> clarithromycin given for 3 weeks in a patient with *C. jejuni* bacteremia,<sup>[18]</sup> and oral kanamycin in patients with recurrent *C. coli* bacteremia.<sup>[6,19]</sup> Our patient received aminoglycosides at the time of each admission. First-generation cephalosporins, which almost all *C. jejuni* strains are resistant to,<sup>[11,20]</sup> were concomitantly administered, and the duration of antibiotic therapy in each bacteremia episode was less than 2 weeks. Therefore, *C. jejuni* could not be eradicated from our patient. Antibiotic susceptibility tests for *Campylobacter* spp. are not routinely performed in our hospital, and therefore, the susceptibility test was performed with the authors' requirement, at the fifth recurrence of bacteremia. The strain isolated from our patient was susceptible to tetracycline, and the patient did not experience recurrent fever and diarrhea after 3 months of doxycycline therapy. However, his symptoms recurred 10 months after the completion of doxycycline therapy, and the isolated strain became resistant to tetracycline. In the future, if the patient experiences repeated episode of *C. jejuni* infection, oral aminoglycosides should be considered to eradicate intestinal colonization.

In conclusion, recurrent *Campylobacter* infections can occur in immunocompromised patients, especially in patients with a humoral immune deficiency. Further studies to establish appropriate antibiotic therapy for eradicating colonized *Campylobacter* spp. and preventing recurrent infections should be conducted.

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