

## Case Report



# Recurrent *Campylobacter* Bacteremia as the First Manifestation of Hypogammaglobulinemia: a Case Report and Literature Review

Amal A. Gharamti , Nour Moukalled , Ali Taher , and Zeina A. Kanafani

Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

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### Corresponding Author:

**Zeina A. Kanafani, MD, MS, CIC**

Associate Professor of Medicine, American University of Beirut Medical Center, Cairo Street, PO Box 11-0236/11D, Riad El Solh 1107 2020, Beirut, Lebanon.

Tel: +961-1-350000 ext 4747

Fax: +961-1-744489

E-mail: zk10@aub.edu.lb

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### ORCID iDs

Amal A. Gharamti

<https://orcid.org/0000-0002-6175-299X>

Nour Moukalled

<https://orcid.org/0000-0001-6457-7819>

Ali Taher

<https://orcid.org/0000-0001-8515-2238>

Zeina A. Kanafani

<https://orcid.org/0000-0001-8814-1286>

### Conflict of Interest

No conflicts of interest.

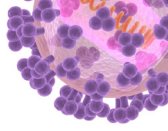
## ABSTRACT

A 30-year-old woman with a past medical history of autoimmune hemolytic anemia presented with fever. Blood cultures grew *Campylobacter*. Her medical history was significant for four prior episodes of *Campylobacter* gastroenteritis and bacteremia. She received ciprofloxacin for the index presentation, then Meropenem de-escalated to doxycycline 6 months later following recurrence of *Campylobacter*. This prompted investigation for an immunodeficiency disorder. She was found to have hypogammaglobulinemia. Her *Campylobacter* infections resolved following the administration of intravenous immunoglobulins every 3 weeks. She did not have recurrence of *Campylobacter* during 5 years of follow-up. A literature search revealed additional four case reports of six hypogammaglobulinemic adult individuals presenting with recurrent *Campylobacter* infections. Three patients were already on intravenous immunoglobulin (IVIG) when *Campylobacter* infection occurred, and two patients achieved clinical cure following therapy with imipenem and IVIG. This case report highlights the importance of suspecting hypogammaglobulinemia in patients with recurrent *Campylobacter* infections, as this is sometimes the first manifestation of the condition.

**Keywords:** *Campylobacter*; Hypogammaglobulinemia; Immunodeficiency; Bacteremia

## INTRODUCTION

*Campylobacter* species (most commonly *C. jejuni* and *C. coli*), Gram-negative non-spore-forming spiral rods of the family *Campylobacteriaceae*, are one of the most common causes of diarrhea worldwide. The incidence of *Campylobacter* infections follows a bimodal distribution, with a peak among infants and children between 1 and 4 years of age and another peak among individuals between 20 and 29 years [1]. Infections typically occur as a result of the ingestion of inadequately cooked poultry products. *C. jejuni* infection can be subclinical or it can present with severe symptoms, including fever, abdominal pain, and diarrhea that can last for more than one week. Although the infection usually resolves without systemic spread [2], in immunocompromised individuals it sometimes seeds to extra-intestinal sites causing bacteremia, hepatitis, cholecystitis, and other focal infections. Antibodies against *Campylobacter* appear in the blood on the fifth day of illness, peak in 2–4 weeks, and then decline, but it is not known how long the immunity persists. In individuals with human immunodeficiency virus



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(HIV) infection or hypogammaglobulinemia, the diarrheal illness may be difficult to eradicate and these individuals often present with recurrent diarrhea and bacteremia [3]. We describe a case of recurrent *Campylobacter* diarrhea and bacteremia due to hypogammaglobulinemia. The patient's written informed consent to publish the case report was obtained.

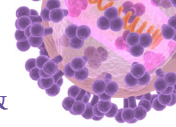
## CASE REPORT

A 30-year-old woman with glucose-6 phosphate dehydrogenase (G6PD) deficiency and autoimmune hemolytic anemia (AIHA) that was refractory to steroids and did not resolve following splenectomy, became transfusion-dependent. She received rituximab for a period of six years, initially with good response, albeit still requiring frequent red blood cell transfusions. She was then diagnosed with ulcerative colitis due to chronic diarrhea and was maintained on prednisone and sulfasalazine, with her course being complicated by aseptic arthritis.

In late September 2012, she presented to the emergency department at the American University of Beirut Medical Center (AUBMC) with fever of 7 days duration reaching 38.5°C, associated with dyspnea on exertion as well as diffuse myalgia and arthralgia. On presentation, she was afebrile, tachycardic (pulse: 125 bpm), and had mild hypotension (blood pressure: 107/74 mm Hg). Laboratory evaluation revealed leukocytosis (white blood cells: 25,200 cells/mm<sup>3</sup>) with 93% polymorphonuclear cells, normocytic anemia (hemoglobin: 7.2 g/dL, mean cell volume: 83 fL), and thrombocytosis (platelets: 1,390,000/mm<sup>3</sup>). All her other initial tests were negative, including routine blood chemistry, liver enzymes, chest X-ray, and computerized tomography scan of her chest, abdomen, and pelvis. Samples were taken for blood and urine cultures and the patient was started empirically on cefepime, which was discontinued on the second day after admission because there was no evidence of an acute bacterial infection. The urine culture and a serum cytomegalovirus polymerase chain reaction test were both negative. Bone marrow aspirate and biopsy showed a markedly hypercellular marrow, decreased erythropoiesis, and an atypical T-cell lymphoid infiltrate suggestive of a response to an infectious or autoimmune process. She remained afebrile and was discharged 3 days later in a stable condition. After 4 days of incubation, the blood culture grew *Campylobacter* spp. The blood culture was repeated and again grew *Campylobacter* spp. which were sensitive to macrolides and quinolones. She was given a 10-day course of ciprofloxacin (500 mg orally 2 times daily), and her condition improved significantly. However, she presented again 6 months later (March 2013) with fever, and was found to have recurrent *Campylobacter* bacteremia, this time with a quinolone-resistant strain. She was treated empirically with meropenem, followed by a 14-day course of doxycycline (100 mg orally 2 times daily).

A review of her medical records revealed that she had a history of recurrent *Campylobacter* infections (febrile gastroenteritis with *Campylobacter* spp. in stool culture in 2008, leg cellulitis and *Campylobacter* bacteremia in 2009, positive stool culture for *Campylobacter* in 2011, and another episode of *Campylobacter* bacteremia in 2011).

Given her history of recurrent *Campylobacter* infections, we suspected that she had an immunodeficiency and requested a test of her immunoglobulin levels. The results revealed significantly low levels of all the immunoglobulin components: immunoglobulin G (IgG): 1.42 g/L (normal: 7.0 – 16.0 g/L), immunoglobulin M (IgM): <0.17 g/L (normal: 0.4 – 2.3 g/L), and immunoglobulin A (IgA): 0.02 g/L (normal: 0.7 – 4.0). She was provisionally diagnosed with common variable immunodeficiency (CVID) and was treated with intravenous



immunoglobulin (IVIG) therapy. She has continued to be provided with IVIG every 3 weeks and has had no recurrence of *Campylobacter* infection during five years of follow-up.

## DISCUSSION

The case patient had an extensive history of autoimmune diseases in addition to recurrent *Campylobacter* colitis and bacteremia. Further investigations revealed that she had low immunoglobulin levels and she was diagnosed with common variable immunodeficiency. According to published studies, recurrent *Campylobacter* disease is usually a sign of immunodeficiency [4, 5]. Our patient's recurrent *C. jejuni* infection was the presenting feature of hypogammaglobulinemia, suggesting that patients with recurrent *Campylobacter* infections should be investigated for hypogammaglobulinemia.

Fernández-Cruz et al. [5] reported a total of 71 episodes of *Campylobacter* bacteremia in 63 patients over a 23-year period. The majority of their patients had an underlying form of immunodeficiency, including liver disease, HIV infection, malignancy, solid organ transplantation, and hypogammaglobulinemia. O'Hara et al. [6] evaluated 41 episodes of *Campylobacter* bacteremia in 41 patients treated at their hospital in London, the United Kingdom, between 1972 and 2013, 20 of which were caused by *C. jejuni*. The focus was the gastrointestinal (GI) tract in 70.7% of the episodes but in other episodes the focus could not be identified. As for clinical signs, fever (temperature >38°C) was noted in all 41 episodes. In contrast to the case series reported by Fernández-Cruz et al. [5], not all patients in this series had an underlying immunosuppressive condition.

Recurrent episodes of *Campylobacter* bacteremia can be caused by reinfection or relapse of an incompletely eradicated initial infection. In one study [7], typing of *Campylobacter* isolates revealed that individuals with hypogammaglobulinemia experience relapse due to colonization with the same organism. Another case report described a patient with recurrent *C. coli* infections due to a latent infection [8]. We believe the same to be true in our patient, although molecular typing was not done.

Fluoroquinolones and macrolides are considered first-line agents for the treatment of *Campylobacter* infections. However, the majority of infections caused by *Campylobacter* spp. are resistant to ciprofloxacin, making this drug an unfavorable first-line agent [9-11]. The first *Campylobacter* isolate cultured from our patient was sensitive to ciprofloxacin but then developed resistance. The development of resistance with ciprofloxacin use in *Campylobacter* infections had been reported previously. Endtz et al. hypothesized that the increasing *Campylobacter* resistance to quinolones in humans first noticed in 1989 in the Netherlands is related to the introduction of enrofloxacin use in poultry in 1987 [12]. In our patient, the *Campylobacter* isolates were consistently susceptible to erythromycin. However, resistance to macrolides does sometimes occur [13].

We searched for relevant publications using MEDLINE and PUBMED databases. We used multiple search terms related to *Campylobacter* bacteremia and hypogammaglobulinemia. **Table 1** summarizes previous case reports published about patients with hypogammaglobulinemia 18 years old and older presenting with recurrent *Campylobacter* bacteremia. Two patients achieved clinical cure with imipenem and IVIG infusions. One patient was cured with 6 weeks of erythromycin. Two patients who developed *Campylobacter*

**Table 1.** Summary of case reports of adult patients with hypogammaglobulinemia presenting with recurrent *Campylobacter* bacteremia

Author (Year)	Age/Sex	Underlying conditions	Definitive Treatment <sup>a</sup>	Recurrence	Comments
LeBar (1985) [18]	24/M	HGG	Tobramycin for each episode	Yes	Patient died of sepsis complicated by disseminated intravascular coagulation
van der Meer (1986) [19]	24/M	XLA on IVIG	Cotrimoxazole and neomycin for 4 weeks, then doxycycline and gentamicin for 3 weeks	Yes	
Kerstens (1992) [7]	26/M	HGG on IVIG	- Erythromycin and gentamicin - Recurrence in two weeks - Cure with imipenem and IVIG	No	
	20/M	HGG	- Initial therapy with erythromycin → Relapse → Response with Ciprofloxacin - 3 years later: Re-infection → Response with Erythromycin for 6 weeks	No	
	24/M	HGG; chronic hepatitis with mild cirrhosis	- 1985: Erythromycin with clinical cure - 1986: Reinfection → Erythromycin with clinical cure - 1990: failure of erythromycin → Clinical cure with Imipenem and IVIG	No	
Kim (2017) [4]	18/M	HGG on IVIG	IV cefazolin and amikacin	Yes	Recurrence despite multiple treatment regimens
Present case (2018)	30/F	AIHA later diagnosed with HGG	- Meropenem then doxycycline for the last episode - Clinical cure with IVIG	No	

<sup>a</sup>Treatment given after cultures grew *Campylobacter*

M, male; HGG, hypogammaglobulinemia; XLA, X-linked agammaglobulinemia; IVIG, intravenous immunoglobulins; IV, intravenous; F, female; AIHA, autoimmune hemolytic anemia.

infections while on IVIG therapy (which mainly serves to replenish IgG) [4] did not respond to multiple lines of antibiotic therapy. This points to the role of immunoglobulins other than IgG in the fight against *Campylobacter*, as will be discussed later.

We suspected that our patient had CVID, an immunodeficiency disorder characterized by defective immunoglobulin production that typically manifests between 20 and 40 years of age, given her history of recurrent *Campylobacter* bacteremia. Although CVID is primarily a B-cell disorder, T-cell abnormalities are common. Patients with CVID are incapable of producing antibodies against foreign antigens but they are more likely to produce autoantibodies. Autoimmune hemolytic anemia is commonly associated with CVID. Since the diagnosis of CVID is usually delayed [14], our patient might have had subclinical CVID that led to autoimmune hemolytic anemia. On the other hand, she had been treated with rituximab, a B-cell depleting monoclonal antibody, which has been associated with prolonged hypogammaglobulinemia [15]. Since hypogammaglobulinemia is associated with multiple disorders requiring treatment with rituximab, it is often difficult to differentiate between primary and secondary etiologies. Our patient had autoimmune manifestations, including AIHA and ulcerative colitis, a history of recurrent infections, almost absent B-cells on bone marrow evaluation with markedly decreased immunoglobulin levels and no evidence of profound T-cell deficiency. Her condition had an adult onset. All these characteristics support the diagnosis of CVID according to the European Society for Immunodeficiencies (ESID) diagnostic criteria [16]. However, her diagnosis remains uncertain because it is not possible to exclude secondary causes of hypogammaglobulinemia, specifically drug-induced hypogammaglobulinemia, because her immunoglobulin levels were not measured prior to initiating therapy with rituximab.

Although patients with CVID and hypogammaglobulinemia receive IVIG regularly, this serves to mainly replenish IgG, and IgA and IgM tend to remain low [4]. IgM has been shown to play an important role in the defense against *Campylobacter*. Borleffs et al. [15] reported the

successful treatment of two patients with hypogammaglobulinemia suffering from persistent *Campylobacter* infections, despite antibiotics and IgG therapy, with an IgM-containing immunoglobulin preparation. On the other hand, there are no studies that suggest increased *Campylobacter* infections in patients with selective IgA deficiency, suggesting that IgA plays a secondary role in the defense against *Campylobacter* [17]. Our patient responded to treatment with regular IVIG infusions.

In conclusion, investigations revealed that the cause of the case patient's recurrent *Campylobacter* infections was hypogammaglobulinemia due to CVID. She has been on maintenance therapy with IVIG for the past 5 years. A review of the literature revealed that recurrent *Campylobacter* infections are a common form of presentation of conditions associated with humoral immunodeficiency.

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