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Intestinal and Extra-Intestinal Manifestations of Campylobacter in the Immunocompromised Host

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Abstract

Purpose of review Describe most recent data on manifestations and treatment of intestinal and extra-intestinal manifestations of Campylobacter among immunocompromised patients.
Recent findings Resistance to fluoroquinolones, macrolides, and tetracycline challenge traditional empiric therapies.
Summary Recurrent Campylobacter enteritis and bacteremia are associated with hypogammaglobinemia, HIV, transplant-associated immunotherapy, and hematologic malignancies. *C. jejuni* and *C. coli* are the most commonly associated Campylobacter species although *C. fetus*, *C. upsaliensis*, *C. lari*, *C. curvus*, and *C. rectus* should be considered as potential causative agents of rare extra-intestinal infections. Successful diagnosis and treatment of these cases may require the recognition of the limits of standard diagnostics and the recent emergence of highly resistant strains of Campylobacter, particularly *C. coli*.

Introduction

Campylobacter, a Gram-negative zoonotic bacterium, is the most common cause of bacterial enteritis in the USA and among the most prevalent causes of enteritis worldwide (1–4). *C. jejuni* and *C. coli* are the species most commonly associated with human disease and colonization (5). The most common clinical presentation, shared by disease caused by both species, in the USA and other industrialized nations includes a self-limiting gastrointestinal infection characterized by diarrhea, abdominal pain, vomiting, and fever, with cases resolving most commonly within 1 week (6, 7). Although it is one of the more common cases of dysentery globally, most cases of Campylobacter enteritis are not dysenteric.

Generally, treatment of Campylobacter intestinal infections includes prescription of a macrolide, namely azithromycin (8, 9). Increasing rates of antimicrobial resistance to fluoroquinolones have caused the Centers for Disease Control to place quinolone-resistant Campylobacter infections at the top of the serious threads list in the 2019 Antibiotic Resistance Threats report (10). Specifically, fluoroquinolone resistance, once rare, has steadily increased over the last 30 years and in 2019 43% of *C. jejuni* and 55% of all *C. coli* isolates in the US were resistant to ciprofloxacin (11). *C. jejuni* resistance to azithromycin in the US is still under 5%, but *C. coli* has rates of azithromycin resistance of 11% in 2020 (11). Rates of resistance are variable globally, and recent international travel markedly increases the risk of highly resistant isolates (12). However, recent rates of macrolide resistance especially of *C. coli* may challenge the administration of azithromycin as the first line of treatment, especially in severe illness and in immunocompromised hosts (13).

Campylobacter incidence has been historically consistently underestimated as estimates were based on bacterial isolation. Given that this microbe is fastidious and the diversity of microbes in the genus contain strains with a heterogeneous optimum nutrient, temperature, and ideal hydrogen and carbon dioxide gas environments for reliable isolation (14). Selective media and high isolation temperatures are techniques aimed at reducing the growth of other bacterial species other than *C. jejuni* and *C. coli*, inhibiting other species of Campylobacter, including ones such as *Campylobacter upsaliensis* and *Campylobacter concisus* that are also recognized human pathogens (15, 16). The use of culture-independent diagnostics such as array cards with gastrointestinal panels across laboratories in the US and Europe and in key epidemiologic studies across the globe provides consistent and growing data as the burden of previously unrecognized disease across epidemiologic settings (17, 18). Campylobacter infection is increasingly recognized for its post-infectious extra-intestinal manifestations as it is the leading cause of Guillan-Barre syndrome, but also is strongly associated with the development of irritable bowel syndrome and post-infectious arthropathy, predominantly of the knees and ankles (19, 20).

Campylobacter epidemiology: sources extend beyond chickens

Campylobacter gastrointestinal infections in the US are most commonly linked to a history of international travel. However, outbreaks of infection continue to occur throughout the country. *Campylobacter jejuni* can be isolated from a variety of animal sources, although the highest prevalence of infection is associated to undercooked poultry and poultry by-products (21). Other common animal sources include cattle, pigs, goats, sheep, ducks, and household companion animals such as dogs. The most recent outbreak of multidrug resistant *Campylobacter jejuni* occurred in the US between January 2016 and January 2018, and involved the infection of 113 individuals from 17 states, with hospitalization rates of 22%. The source of the outbreak was linked to puppies sold through a multi-state pet store chain (16, 22). Other recent Campylobacter outbreaks in US territory have been associated with unpasteurized milk in Utah in 2014 and 2016, and with undercooked chicken livers in the northeastern of the US (21, 23, 24). In general, however, when source attribution is done using molecular methods, it indicates that while poultry is the primary source of infections in most contexts evaluated, ruminants, more frequently cattle are an important secondary zoonotic source of infection at the population level (25).

Although the epidemiology of Campylobacter enteric infections has been extensively described, extra-intestinal Campylobacter infections and disease in immunocompromised patients are rarely discussed and will be the focus of this review.

Intestinal manifestations in the immunocompromised host

Human immunodeficiency virus

A fivefold increase in invasive Campylobacter infection was reported in individuals living with HIV, most of whom had a CD4 of 100 in pre-HAART era, with mortality reaching 30% in this case series (26). Among described cases of *C. jejuni* and *C. coli* infections CD4 counts and viral loads were highly variable with CD4 cell counts and viral load reported ranged between < 150 and 1150 × 10^6 cells/L and between < 40 copies/mL and 886,420 copies/mL (27, 28) but individuals with more profound immunosuppression had higher mortality. Among individuals living with HIV and manifesting *C. fetus* infections, 77.8% had CD4 cell counts that ranged between 270 and 860 × 10^6 cells/L and a viral load of < 40 copies/mL with the exception of one patient with 2000 copies/mL (29).

Cases of *C. upsaliensis* enteritis among people living with HIV have been more frequently reported in the Netherlands and Australia, and were associated with prolonged diarrhea (up to 3 months) with mild to moderate symptomatology (30, 31). Non-selective media is required for isolation, and this may require communication to the laboratory to ensure that isolation procedures do not include the use of selective enrichment media that inhibit the growth of *C. upsaliensis*, including those employing cephalothin.

Evidence of increased incidence in MSM: Campylobacter as a sexually transmitted infection (STI)

Outbreaks of Campylobacter enteric infections among men who have sex with men (MSM) have been well reported in Canada and, more recently, Seattle (27, 28, 32–34) so it is possible that increased rates of gastroenteritis are a result of increased exposure rather than increased susceptibility. This is infrequently recognized, but logical given an infectious dose of as low as 800 organisms (35). In England, potential transmissions of Campylobacter among MSM over a 10-year period have recently been estimated based on an excess number of Campylobacter enteritis cases among men aged 25–49 years old in comparison to female cases (36). In Canada, multiple long-lasting clusters of *C. jejuni* and *C. coli* outbreaks have been reported among MSM between 1999 and 2015. Among the Canadian and US outbreaks, isolates exhibited multiple patterns of multidrug resistance to ciprofloxacin, erythromycin, tetracycline, and gentamicin, and were diagnosed with other concomitant sexually transmitted enteric infections such as *Shigella sonnei*, *S. flexneri*, *Giardia lamblia*, *Entamoeba histolytica*, and rectal *Neisseria gonorrheae* (32, 34). Clinical symptoms were also shared among these multiple outbreaks, including diarrhea and dysentery, fever,

abdominal pain, nausea, and vomiting (32, 34). Generally, treatment included oral administration of an antibiotic, which between 1999 and 2001 varied between the use of ciprofloxacin, azithromycin or erythromycin and tetracycline, but by 2010, the prescription of a macrolide as the first line of treatment predominated and that of the use of amoxicillin/clavulanic acid among isolates that are resistant to fluoroquinolones and ciprofloxacin as was recommended after an outbreak in 2015 (27). Additionally, a cluster of 31 cases of *Campylobacter fetus* gastroenteritis has been described in Quebec, Canada, between 2014 and 2016. Cases were also associated with MSM or patients with high-risk sexual practices (29).

Hypogammaglobulinemias

Primary hypogammaglobulinemias have been frequently associated with recurrent and refractory Campylobacter enteritis. These genetic conditions are associated with defective production of antibodies and those commonly associated with Campylobacter infections include X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), and less frequently Good syndrome (37). More than a dozen cases of recurrent Campylobacter enteritis have been associated with patients with primary hypogammaglobulinemias, while only a single case of secondary hypogammaglobinemia has been reported as a result of the administration of rituximab (a monoclonal anti-CD20 antibody) in a patient with non-Hodgkin lymphoma (37). Importantly, a large great proportion of these cases were accompanied by Campylobacter bacteremia, and as a result, consistent carriage of Campylobacter in the gut is considered the principal reservoir of blood infections (37). A brief discussion about patients with hypogammaglobinemia and Campylobacter bacteremia is provided below. Antibiotic treatment of recurrent infections is required, for which the oral administration of combined ciprofloxacin and azithromycin a reasonable choice in the absence of resistance. Importantly, a case of persistent Campylobacter enteritis in a patient with XLA failed to resolve after the administration of multiple 2-week courses of oral azithromycin and ciprofloxacin as well as a 2-week course of ertapenem. Oral gentamicin (unreported duration) proved successful for the remaining follow-up time (38).

Transplant patients

Campylobacter infections are a known cause of enteritis among transplant patients (39–41). Prolonged asymptomatic shedding is attributed to immunosuppressive therapy has also been noted (42). The majority of well-documented Campylobacter enteric infections among transplant patients are related to renal transplants (43–45). A recent 3-year retrospective revision of pediatric renal transplant patients identified 8 patients with *C. jejuni* enteritis (44). Time from transplantation to symptom was broadly dispersed with an onset that ranged between 0.9 and 16.7 years (median 4.6 years). Clinical symptoms were related to classic Campylobacter enteritis, including diarrhea, dysentery, fever, vomiting, and headaches. Treatment has involved the reduction of immunosuppressive drugs and antibiotic administration for a median number of 7 days (range between 4 and 11 days). Among pediatric transplant patients, treatment with fluoroquinolones was most frequently employed. Susceptibility testing indicated that in 7 out 8 cases, the *C. jejuni* isolate was susceptible to the

antibiotic of choice (44). Among two other cases of Campylobacter enteritis in renal transplant patients, oral azithromycin (unreported duration) (43) and oral ciprofloxacin were employed (45). Recurrence, such as that seen in primary hypogammaglobulineamias, is not reported. Guillain-Barre syndrome (GBS) is a reported complication among kidney transplant patients with a history of enteric disease (46). The association of flaccid paralysis with Campylobacter can be made through the culture of stool (positive in 30%) and antibody tests for GM1and GD1a for classical GBS and GT1a and GQ1b if opthalmoplegia or evidence of brainstem involvement is present (47).

Extra intestinal Campylobacter manifestations

Bacteremia

Estimates from three longitudinal population-based studies indicate that the percentage of Campylobacter bacteremia cases out of all Campylobacter infections ranges between 0.1 and 1% (48–50), and generally, cases are identified as community acquired infections (48, 50). Despite the described serum resistance and the propensity of *C. fetus* to cause bacteremia, the largest case series of 394 cases of Campylobacter bacteremia, *C. jejuni/ coli* cases outnumbered *C. fetus* 10:1. Concurrent gastrointestinal illness occurred in 71% of cases of *C. jejuni/coli* bacteremia and concurrent stool isolation was achieved in 40% of these cases. Concurrent gastrointestinal illness occurred in only 27% of the cases of *C. fetus* bacteremia that was more closely linked to immunodeficiency (41% vs 29% of cases) and endovascular infection (40% v 0.4%) (51, 52). Clearly, there are both host and microbial determinants of Campylobacter sepsis as bacteremic outbreaks of *C. jejuni* have been documented even in healthy individuals despite the common description of all *C. jejuni* and being serum sensitive as compared with *C. fetus* (53).

Host determinants include advancing age and the median age of patients diagnosed with Campylobacter bacteremia ranged between 46 and 56 years. Mortality rates ranged between 3 and 4% within a 28- to 30-day period and 6–8% within 6 months to 1-year after diagnosis (48, 50). Risk factors for Campylobacter bacteremia and associated co-morbidities among patients included being male, being on immunosuppressive drug therapy, having a diagnosed malignancy, cardiovascular disease, chronic obstructive pulmonary disease, a cerebrovascular insult, diabetes mellitus, dementia, and liver disease (48, 50, 54).

Agammaglobulinemia and hypogammaglobulinemia

Among the most frequently reported immunosuppressive conditions associated with Campylobacter bacteremia are both X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID). Clinical symptoms and treatment of bacteremia cases published between 2004 and 2020, associated with both of these immunosuppressive conditions are shown in Table 1. For a summary of previously reported cases, see van den Bruele et al. 2020 (55).

X-linked agammaglobulinemia (XLA) is a genetic condition associated with mutations of the Bruton's tyrosine kinase (BT gene), a tyrosine kinase of the Tec family expressed throughout B cell development. XLA has been associated with Campylobacter bacteremia since 1977 (56). Cases are typically described as

Table 1. Summary of cases of disseminated campylobacteriosis among patients with hypogammaglobinemia in the literature highlight the frequent association with cellulitis and disease recrudescence

Condition	Sex	Age	Clinical presentation	Campylobacter species detected	Antimicrobial resistance	Treatment, route, and duration of administration
CVID	Female	30	Fever, dyspnea, arthralgia	Undetermined	Quinolones (unspecified)	Meropenem (IV) unreported duration; Doxycycline (PO) for 2 weeks
XLA	Male	37	Cellulitis, fever	*C. coli*	Meropenem (MIC >4μg/mL)	Meropenem (IV) for 2 weeks; Tibipenem-privoxil and Fibipenem (PO) for numerous courses lasting between 3 to 10 weeks; Biapenem (IV) for 2 weeks; metronidazol (PO) for 4 weeks; minocycline (PO) for 10 weeks
XLA	Male	18	Persistent diarrhea, weight loss, cellulitis and fever	*C. jejuni*	Ciprofloxacin and Erythromycin (unspecified)	Meropenem (IV) for 3 weeks; Doxycycline (PO) for 3 months
XLA	Male	12	Fever, bilateral ankle edema, supramalleolar ecchymosis, erythematous legs and pain	*C. jejuni* subsp. *jejuni*	Quinolones (unspecified)	Meropenem (IV), for 10 days Clarithromycin (IV) for 10 days; Clarithromycin (PO) for 3 weeks
XLA	Male	15	Fever, anorexia	*C. jejuni*	Erythromycin (MIC	>= 256 mg/L)
(53)						
XLA	Male	33	Fever, cellulits	*C. coli*	Not reported	Meropenem (IV), Ciprofloxacin (IV), Minocycline (IV) and Azythromycin (PO) for at least 6 weeks; Kanamycin (PO) for 10 weeks
XLA	Male	35	Fever, ankle edema, pain	*C. coli*	Erythromycin (unspecified)	Meropenem (IV) unreported duration and minocycline (PO) for 2 weeks
XLA	Male	22	Cellulitis	*C. coli*	Macrolides (unspecified)	Imipenem-cilastatin (IV) for 4 days and amikacin (IV) for 4 days; Panipenem/betamipron (IV) for 5 weeks; Kanamycin (PO) unreported duration

Table 1. (Continued)

Condition	Outcome	Campylobacter detection in gastrointestinal tract	Other characteristics	Reference
Condition	Outcome	Campylobacter detection in gastrointestinal tract	Other characteristics	Reference
CVID	Resolved after 5 years	Yes	Glucose-6 phosphate dehydrogenase (G6PD) deficiency and autoimmune hemolytic anemia (AIHA). Rituximab for 6 years. Recurrent Campylobacter infections (enteritis, cellulitis)	(60)
XLA	Multiple relapses for 1 year	Yes		(55)
XLA	Repased 5 times up to 10 months later	Yes		(62)
XLA	Resolved after 1 year	No	History of *C. jejuni* subsp. *jejuni* bacteremia and enteritis 1 year prior to the reported bacteremia episode	(56)
XLA	Relapse after 10 months	Yes		(53)
XLA	Relapse at day 7, resolved after 8 months post kanamycin admin	Yes		(57)
XLA	Relapse at month 10, 16, and 18, resolved after 1 year	Yes		(59)
XLA	Resolved after multiple relapses over 3 years	Yes		(58)

young male patients presenting with fever and cellulitis, generally of the lower extremities. Empirical treatment for cellulitis is initiated until Campylobacter bacteremia is diagnosed, for which the intravenous administration of carbapenems is the most common choice of treatment (55, 57–62). Common variable immunodeficiency (CVID) cases associated with Campylobacter bacteremia are less frequently reported than XLA patients despite the higher prevalence of CVID. Both clinical symptoms and treatment options resemble those associated with XLA and Campylobacter bacteremia cases (62).

The reduced concentration of serum IgM is considered the most probable link between cases of hypogammaglobinemia and Campylobacter bacteremia. It is hypothesized that IgM plays a significant role in initiating and promoting pathogen opsonization and this may explain the different in excess risk in XLA relative to CVID as IgM is preserved in most cases of CVID. As a result, the patient's humoral response is unable to tackle the presence of the pathogen. It is worth noting that the lack of specific intestinal IgA in the intestinal mucosa was not associated with an increase in Campylobacter infections (63, 64).

Hematologic malignancies

Hematological malignancies are a principal risk factor for Campylobacter bacteremia (65). *C. jejuni*, *C. coli*, and *C. fetus* bacteremia cases have been associated with haematologic malignancies such as acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), multiple myeloma, and myelodysplastic syndrome (65–70). Treatment in patients with ALL included amoxicillin/clavulanic acid and trimethoprim-sulfamethoxazole for 2 weeks, as well as clarithromycin for 10 days (67). Repeated *C. fetus* subsp. *fetus* of presumed reptile origin was observed in a patient with ALL with fever, chronic cough, and a history of pneumocystis pneumonia. Intravenous imipenem-cilastatin (unspecified duration) is followed by intravenous levofloxacin and metronidazole (unspecified duration) at relapse and oral levofloxacin for 10 days at discharge (68). Treatment of two fatal Campylobacter bacteremia cases in patients with NHL and myelodysplastic syndrome included intravenous carbapenems and aminoglycosides (69, 70).

Disentangling the risk factor for increased rates of disease is difficult and likely variable. Patients may have low levels of functional immunoglobulins because of their underlying malignancy, as a result of cytotoxic or immunotherapies, particularly those that include relatively non-selective kinase inhibitors (71).

Hepatic insufficiency

Cirrhosis, active hepatitis B and C, and hepatocellular carcinoma have all been identified as risk factors for bloodstream infections with Campylobacter species (65).

Meningitis

Campylobacter associated meningitis is a rare extra intestinal Campylobacter infection (72). Reports of *C. jejuni*, *C. coli*, and *C. fetus* associated meningitis in adults have been associated with immunocompromised patients with malignancies such as metastatic lung adenocarcinoma (73, 74). Additionally, cases

with chronic alcoholism, diabetes mellitus, immunosuppressive medication, and patients who had undergone splenectomies have been reported (74–78), as well as cases of immunocompetent patients associated with the ingestion of raw poultry liver, unpasteurized cheese, and khat chewing (79–82). Preferred therapy reported is with carbapenems (73–75, 77, 79, 81). Importantly, *C. fetus* can be involved in hospital-based outbreaks among neonates (83, 84).

Endocarditis

Endocarditis has been more frequently associated with *C. fetus* subsp. *fetus* among male patients with pre-existing valvular pathologies including prosthetic valve surgery (85–89). The ability of *C. fetus* subsp. *fetus* to form biofilms has been recently established and is considered an important virulence factor for endocarditis among patients with prosthetic valves (86). The choice of antibiotic treatment has varied, including intravenous administration of ampicillin for 6 weeks with concurrent administration of gentamicin for 2 weeks (85), and intravenous administration of meropenem for 6 weeks (88).

Osteomyelitis

Reported osteomyelitis cases due to Campylobacter infections have been generally associated with concurrent cases of bacteremia (90, 91). Treatments have included intravenous administration of meropenem for 6 weeks (91), and ciprofloxacin for 6 weeks (90). Various reports of Campylobacter spondylodiscitis have been reported, with *C. fetus* being the most commonly isolated Campylobacter species (79, 92–95), followed by *C. jejuni* and *C. coli* (96, 97). Cases are not exclusive to immunocompromised patients, although they have been reported among people living with HIV (93).

Intracranial infections

Cases of central skull-base osteomyelitis and other intracranial infections due to *Campylobacter rectus* have been reported (98–101). *C. rectus* is generally found within the oral microbiota associated with periodontal disease and should be considered an opportunistic infection among immunocompromised patients (101). Antibiotic chemotherapy reported has included intravenous administration of meropenem for 12 weeks, and subsequent oral intake of doxycycline for 3 months (99). A second case of intravenous administration of meropenem and metronidazole with additional oral antibiotics upon discharge (unreported duration) has been reported (98). A third reported case included intravenous administration of ertapenem administration (100).

Pulmonary infections

Pulmonary infections associated with Campylobacter infections are rare. Empyema cases have been associated with oral Campylobacters including *Campylobacter rectus* (102–104), *Campylobacter curvus* (105), and *Campylobacter concisus* (106) among patients with and without diagnosed immunodeficiency. Treatment of empyema cases with atypical Campylobacter infections is hindered by the lack of data reporting susceptibility profiles. Antibiotic therapy of *C. rectus* cases has included intravenous carbapenems and amoxicillin-clavulanate (unreported duration) (102), as well as intravenous ampicillin-sulbactam and oral third-generation quinolones (104). Intravenous

ampicillin-sulbactam followed by oral continuation for 5 weeks was successful in a *C. curvus* empyema case (105).

Conclusion

Campylobacter should be considered as a potential diagnosis among immunocompromised patients with recurrent diarrhea. These same patients with recurrent Campylobacter enteritis are at risk of Campylobacter extra-intestinal manifestations such as bacteremia which is not infrequently associated with cellulitis in the lower extremities and frequently associated with relapsing disease despite appropriate therapy. Although *C. jejuni*, *C. coli*, and *C. fetus* are commonly associated with cases of bacteremia, other Campylobacter species such as *C. curvus* and *C. rectus* commonly associated with periodontal disease should be considered as differential diagnosis in uncommon extra-intestinal manifestations of Campylobacter infections. For mild cases of disease, amoxicillin-clavulanate is a reasonable choice whereas moderate to severe illness, particularly in the immunocompromised host warrants empiric therapy with a carbapenem with or without an aminoglycoside pending antibiotic resistance profiling. Relapse of infection is well documented in immunocompromised hosts and clinicians should counsel patients of the significant risk of recrudescence even with the prompt institution of appropriate antimicrobial therapy.

Compliance with Ethical Standards

Conflict of Interest
Dr. Schiaffino has nothing to disclose. Dr. Kosek has nothing to disclose.

Human/Animal Studies Statement
This article does not contain any studies with human or animal subjects performed by any of the authors.

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