

# Campylobacter jejuni Infections: Update on Presentation, Diagnosis, and Management

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**C**ampylobacteriosis is a food- and water-borne zoonotic diarrheal illness caused by bacteria of the genus *Campylobacter*, with most cases caused by *C. jejuni*. *Campylobacter* species have a worldwide distribution, and campylobacteriosis is a leading cause of acute diarrhea and enterocolitis throughout the world. In the United States, approximately 1 million symptomatic *Campylobacter* infections occur each year.<sup>1</sup> The majority of *Campylobacter* infections are acquired via the oral route after handling raw poultry or consuming undercooked poultry.

*Campylobacter* species were first recognized in 1906 by John McFadyean, who described comma-shaped spiral organisms associated with abortions in cattle and sheep. Initially named *Vibrio fetus*, this pathogen was reclassified as *Campylobacter fetus* in 1973.<sup>2,3</sup> Human disease was first described 1959, when organisms were isolated from the blood of children with acute dysentery.<sup>4</sup> *Campylobacter* was first isolated from fecal specimens of patients with acute enteritis in 1972.<sup>5</sup> These initial cases were followed by other sporadic cases worldwide, and community outbreaks due to contaminated water, unpasteurized milk, and community meals were identified.<sup>6-11</sup> In 1978, a large community outbreak associated with the town water system affected 3000 people in Bennington, VT.<sup>8</sup>

Although campylobacteriosis is typically a self-limiting disease in otherwise healthy persons, severe gastrointestinal disease can occur in immunocompromised persons. In addition, postinfectious complications of *Campylobacter* infection, including Guillain-Barré syndrome and reactive arthritis, can occur in both immunocompromised and immunocompetent persons. This article provides an update on the presentation, diagnosis, and management of *Campylobacter* infection and its postinfectious complications.

## EPIDEMIOLOGY

More than 16 *Campylobacter* species have been identified, but most clinically recognized infections in im-

## TAKE HOME POINTS

- Infection with *Campylobacter jejuni* is a common cause of food-borne disease in the United States.
- *C. jejuni* causes self-limiting inflammatory diarrhea in healthy hosts but may be associated with severe and protracted disease in immunocompromised patients.
- Postinfectious sequelae of campylobacteriosis include reactive arthritis, irritable bowel syndrome, and the Guillain-Barré syndrome.
- Clinical judgment should be used when deciding whether to treat with antibiotics. Macrolide antibiotics (azithromycin or erythromycin) are used as first-line therapy for treatment when symptomatic infection with *C. jejuni* is deemed necessary.
- No vaccine against *Campylobacter* is available; strategies to prevent infection include avoiding the ingestion of undercooked meats and poultry and attention to hand hygiene.

munocompetent adults are due to *C. jejuni* and, less frequently, *C. coli*.<sup>12</sup> *Campylobacter*s colonize the colon of farm and domestic animals, including cattle, sheep, goats, pigs, and particularly poultry, which serve as the main source of human infection.<sup>13-15</sup> In microbiologic surveys of raw meat products, broiler chicken appears to be a common source of contamination, with *C. jejuni* detected in 31% to 83% of samples.<sup>15,16</sup>

The incidence of *Campylobacter* infection varies throughout the world but appears to be declining in

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**Table 1.** Selected Risk Factors for *Campylobacter* Infection

| Study                              | Subjects                     | Risk Factor                                      | Odds Ratio (95% CI)        | PAF, % (95% CI)            |
|------------------------------------|------------------------------|--|----------------------------|----------------------------|
| Friedman et al <sup>20</sup>       | 1152 American nontravelers   | Contact with farm animals (persons aged 2–11 yr) | 21 (2.5–178)*              | 2 (0.7–2)                  |
|                                    |                              | Drank raw milk                                   | 4.3 (1.3–12.2)*            | 1.5 (0.4–3)                |
|                                    |                              | Drank untreated water from lake, river, stream   | 3.3 (1.5–7.5)*             | 3 (1–4)                    |
|                                    |                              | Ate chicken prepared in a restaurant             | 2.2 (1.7–2.9)*             | 24 (17–30)                 |
|                                    |                              | Consumption of undercooked poultry               | 2.1 (1.2–3.4)*             | 3 (1–6)                    |
|                                    |                              | Ate meat other than poultry at a restaurant      | 1.7 (1.3–2.2)*             | 21 (13–30)                 |
|                                    |                              | Had contact with animal stool                    | 1.4 (1.02–1.9)*            | 6 (0.9–12)                 |
|                                    |                              | Kapperud et al <sup>21</sup>                     | 212 Norwegian nontravelers | Consumption of any poultry |
| Consumption of undercooked poultry | 6 (0.6–57.7) <sup>†</sup>    |  |                            | ND                         |
| Daily contact with dog             | 5 (1.8–14) <sup>†</sup>      |  |                            | ND                         |
| Eating grilled meat at barbecue    | 3.94 (1.9–8.4) <sup>†</sup>  |  |                            | ND                         |
| Eating homemade minced meat        | 6.6 (0.72–60.9) <sup>†</sup> |  |                            | ND                         |
|                                    |                              |  |                            |                            |

CI = confidence interval; ND = no data; PAF = population attributable factor.

\*Adjusted odds ratio, multivariate.

<sup>†</sup>Unadjusted odds ratio, univariate analysis.

industrialized countries due to improvements in poultry processing. In the United States, the Food Borne Diseases Active Surveillance Networks reported a 30% decline in incidence between 1996 and 2007.<sup>1,17,18</sup> In 2007, 12.79 laboratory-confirmed cases of *Campylobacter* infection occurred per 100,000 persons, second only to *Salmonella* infections (14.92 cases per 100,000 persons) as a bacterial cause of food-borne disease.<sup>1</sup> In the United States, the incidence of *Campylobacter* infection is highest in Alameda and San Francisco counties of California, where incidence reaches 34.4 cases per 100,000 persons and infection accounts for 52% of all infective diarrhea.<sup>19</sup> Sporadic cases occur in 2 peak age-groups, 0 to 4 years and 20 to 39 years, and most cases occur during the spring and summer months.<sup>17</sup> Factors associated with increased risk of sporadic campylobacteriosis are related to poultry consumption, eating outside of the home, international travel, and exposure to animals (Table 1).<sup>20,21</sup>

The epidemiology and clinical manifestations of disease due to *C. jejuni* differs markedly in resource-poor countries. Estimates of incidence are incomplete, but rates are thought to be dramatically higher in such countries than in industrialized nations. Infection occurs without seasonal variability in warmer climates, and *C. jejuni* is often found with other copathogens.<sup>22</sup> Symptomatic disease in these settings appears most often in young children, and isolation of *Campylobacter* organisms in older individuals is inconsistently associated with symptomatic disease.<sup>22,23</sup> *Campylobacter* species account for 8% of diarrhea of bacterial origin in Western Kenya<sup>24</sup> and 14% in Bangladesh.<sup>22</sup>

*Campylobacter* is also an important cause of travelers' diarrhea, second in incidence to enterotoxigenic *Escherichia coli*. In a study of 322 visitors to Jamaica who experienced diarrhea, *C. jejuni* accounted for 6% of cases.<sup>25</sup> *Campylobacter* accounted for 9% of bacterial causes of diarrhea in 328 expatriates to Nepal<sup>26</sup> and 64% in US military troops in Thailand.<sup>27</sup>

Person-to-person transmission of infection is rarely described in adults, but *Campylobacter* species have been reported as a cause of sexually transmitted enteric infection in homosexual men.<sup>28</sup> Case reports describe mother-to-infant perinatal transmission and nosocomial spread in a hospital nursery.<sup>28–31</sup>

## PATHOGENESIS

Campylobacters cause a nonspecific acute inflammatory enteritis involving the colon and small intestine; edema of the infected area as well as an infiltrate composed of neutrophils and mononuclear cells is seen histologically.<sup>32,33</sup> After oral ingestion, the pathogen moves through the intestinal mucus layer via its flagellum and multiplies in the distal ileum and colon. Campylobacters cause diarrhea by damaging the gut epithelial cells either directly by invading the cells or indirectly by initiating an inflammatory response.<sup>34</sup> The infectious dose of *C. jejuni* varies depending on the strain but may be as low as 500 organisms in milk, as shown in a self-infection experiment.<sup>35</sup> In a formal challenge model involving 111 adult volunteers, the infectious dose of *C. jejuni* ranged from 800 to  $2 \times 10^9$  organisms.<sup>36</sup> Rates of infection increased with dose, but

there was no clear relationship between dose and the development of illness, with 10% to 50% of volunteers developing fever and/or diarrhea at these doses.<sup>36</sup>

Less is known about the specific bacterial virulence properties of campylobacters compared with other enteric gram-negative pathogens, such as salmonellae. Completion of the *Campylobacter* genome has shown extensive interstrain variability in several virulence genes, particularly in the organism's capsule, lipooligosaccharides, and flagellum.<sup>37</sup> Specific virulence factors of *Campylobacter* include its motility via a polar flagella, which is important in host colonization and cell invasion; the lipooligosaccharide, which facilitates immune avoidance and is associated with autoimmune disorders (see Guillain-Barré syndrome in Postinfectious Complications); and the capsule, which contributes to serum resistance and facilitates invasion of epithelial cells and colonization. The multifactorial process of host cell invasion also requires the proteins of a flagellar export apparatus system similar to those of type III protein secretion systems as well as a cytolethal distending toxin. Interestingly, host adaptation also appears to play a role in pathogenesis, and chromosomal rearrangements and genetic material exchange occur in vivo.<sup>33,37</sup>

### CLINICAL PRESENTATION

Many individuals with *Campylobacter* infection are thought to be asymptomatic. Rates of asymptomatic infection vary widely by age and region. In a study conducted at 2 large academic hospitals in Baltimore, MD, and New Haven, CT, *Campylobacter* was isolated from 0.9% of healthy individuals of all ages without symptoms of diarrhea but was not found in any healthy adult control subjects in a separate trial conducted in Sweden.<sup>38,39</sup> In symptomatic individuals, onset of clinical disease occurs 1 to 7 days after ingestion of the bacteria. Acute diarrhea is the most common presenting feature, occurring in 98% to 99% of symptomatic patients.<sup>40–42</sup> Classic dysentery may occur with small-volume mucoid stool containing occult or gross blood. However, large-volume fluid losses without dysentery may also occur. In immunocompetent patients, other prominent symptoms include abdominal cramps, nausea, vomiting, fever, headache, and myalgias. Fever and gastrointestinal symptoms, including abdominal cramping and nausea, but without diarrhea, have also been reported (Table 2). Illness in otherwise healthy adults is usually self-limiting and lasts less than 2 weeks. Illness with severe diarrhea, abdominal pain, or high fever are considerations for hospital admission and fluid replacement.<sup>41</sup> Carriage of *Campylobacter* organisms following infection is usually less than 3 weeks even in untreated patients.<sup>14</sup>

**Table 2.** Clinical Presentation of Campylobacteriosis in Immunocompetent Individuals

|                      | Blaser et al <sup>40</sup> | Pitkanen et al <sup>41</sup> | Ponka et al <sup>42</sup> |
|----------------------|----------------------------|------------------------------|---------------------------|
| Location             | Denver, CO                 | Finland                      | Finland                   |
| Subjects             | 124 patients               | 188 inpatients               | 524 outpatients           |
| Features, %          |                            |                              |                           |
| Diarrhea             | 98                         | 99                           | 98                        |
| Blood in stool       | 52                         | 27                           | –                         |
| Mucus in stool       | 35                         | 21                           | –                         |
| Malaise              | 95                         | 92                           | 70                        |
| Abdominal pain       | 88                         | 90                           | 87                        |
| Abdominal tenderness | –                          | 53                           | –                         |
| Fever                | 82                         | 88                           | 78                        |
| Nausea               | 55                         | 65                           | –                         |
| Vomiting             | 35                         | 51                           | –                         |
| Headache             | < 30                       | 55                           | 51                        |
| Myalgia              | < 30                       | 35                           | –                         |
| Arthralgia           | < 30                       | 28                           | 19                        |

Severe gastrointestinal disease, including chronic diarrhea, bacteremia with or without extraintestinal dissemination, and postinfectious syndromes are infrequently seen in healthy patients. Prolonged and severe disease more frequently occurs in individuals with immunodeficiency syndromes, including HIV/AIDS.<sup>43</sup> In a series of 38 patients with HIV and *Campylobacter* infection, most patients presented with acute diarrhea, fever, and abdominal pain; however, 4 (11%) had bacteremia, and 8 (21%) experienced chronic diarrhea.<sup>43</sup> Infrequently, acute extraintestinal complications, prolonged disease, bacteremia, and disseminated disease occur in the elderly and in patients with underlying diseases, including malnutrition, diabetes, malignancy, and alcoholism.<sup>44,45</sup> Rare systemic and extraintestinal complications include meningitis, acute septic arthritis, septic abortion, severe gastrointestinal hemorrhage, cholecystitis, urinary tract infection, abscesses, gram-negative sepsis, toxic megacolon, and endocarditis.<sup>45–48</sup> Extraintestinal manifestations are more common in non-*jejuni* *Campylobacter* species.<sup>44,48</sup>

### POSTINFECTIOUS COMPLICATIONS

Postinfectious complications associated with *Campylobacter* infections include Guillain-Barré syndrome, reactive arthritis, postinfectious irritable bowel syndrome,

**Table 3.** Frequency of Joint Involvement in Postinfectious Reactive Arthritis

| Involved Joint                 | Frequency, % (n = 45) |
|--------------------------------|-----------------------|
| Knees                          | 36                    |
| Proximal interphalangeal, hand | 36                    |
| Metacarpophalangeal            | 33                    |
| Ankles                         | 29                    |
| Shoulder                       | 27                    |
| Metatarsophalangeal            | 24                    |
| Distal interphalangeal         | 24                    |
| Wrist                          | 22                    |

Data from Hannu T et al.<sup>58</sup>

and potentially immunoproliferative small intestinal disease (IPSID). Guillain-Barré syndrome is a rapidly progressive acute flaccid paralysis that results from inflammatory demyelination of peripheral nerves and is the most severe and life-threatening postinfectious sequelae of campylobacteriosis. It is reported in 1 per 1000 to 3000 *Campylobacter* infections.<sup>49</sup> The association of Guillain-Barré syndrome with *Campylobacter* was first reported in a 45-year-old man who presented with bloody stool and developed progressive flaccid paralysis.<sup>50</sup> Approximately 36% to 38% of Guillain-Barré syndrome cases are preceded by symptomatic or asymptomatic *Campylobacter* infection, and cases of Guillain-Barré syndrome associated with this infection appear to be more clinically severe.<sup>51–53</sup>

The development of Guillain-Barré syndrome following *C. jejuni* infection is linked to autoimmune molecular mimicry between terminal sugar molecules shared by human peripheral nerves and *C. jejuni* antigens. As discussed earlier, *C. jejuni* organisms express lipooligosaccharides, and the outer core of lipooligosaccharides of strains associated with Guillain-Barré syndrome contain the same terminal sugars (NeuNAC) found in gangliosides of peripheral nerves. “Molecular mimicry” occurs as antibodies to *C. jejuni* lipooligosaccharides cross-react with the sugars in peripheral nerve gangliosides, resulting in immune reaction against myelin or axons of peripheral nerves and causing demyelination.<sup>54</sup> Investigators have isolated *C. jejuni* strains associated with “classic” Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy and, particularly in patients with *Campylobacter*-associated disease, acute axonal degeneration) and found that these serotypes most frequently develop antibodies to GM1 or GD1a gangliosides. In contrast, *Campylobacter* strains that induce antibodies to GQ1b, GT1a, or GD3 gangliosides are associated with the Miller-Fisher variant of Guillain-

Barré syndrome, which is associated with ataxia, ophthalmoplegia, and nonreactive pupils.<sup>55,56</sup>

Reactive arthritis is a seronegative spondylarthropathy that occurs after approximately 2% to 7% of *Campylobacter* infections.<sup>57,58</sup> Unlike Guillain-Barré syndrome, reactive arthritis appears to be associated with host genetic factors, not the bacterial strain. *Campylobacter* as well as *Salmonella*, *Shigella*, *Yersinia*, and *Chlamydia* are similarly associated with postinfectious reactive arthritis; disease manifestations do not differ based on the associated pathogen.<sup>59</sup> The mechanisms by which these species induce reactive arthritis is poorly understood, but they are thought to result from an autoimmune phenomenon caused by cross-reaction between bacteria antigens and an autologous joint peptide found predominately in genetically predisposed human leukocyte antigen (HLA)-B27–positive patients.<sup>59</sup> Between 65% and 95% of white patients and between 30% and 50% of African American patients with reactive arthritis carry the HLA-B27 allele.<sup>60</sup> Antibiotic treatment of campylobacteriosis does not prevent reactive arthritis; however, patients who subsequently develop reactive arthritis have a longer duration of diarrhea are more likely to have required antibiotic therapy.<sup>61</sup> Both large and small joints can be involved in postinfectious reactive arthritis, as demonstrated in large population studies (Table 3).<sup>58</sup> Twenty-two percent of affected individuals recover within 1 month, but 55% remain symptomatic at 6 months. Occasionally, patients develop full Reiter syndrome, including uveitis.<sup>62</sup>

Persistent gastrointestinal symptoms may occur in some patients after the resolution of acute campylobacteriosis. Postinfectious irritable bowel syndrome occurs following bacterial diarrhea caused by *Campylobacter*, *Shigella*, and *Salmonella*.<sup>63,64</sup> Approximately 9% of patients with campylobacteriosis may develop postinfectious irritable bowel syndrome, particularly after protracted illness, and postinfectious irritable bowel syndrome should also be considered a cause of persistent diarrhea in travelers.<sup>64,65</sup> Although incompletely understood, the mechanisms may involve the inability to downregulate inflammatory markers after persistent inflammation<sup>65</sup> as well as serotonin-mediated effects from enterochromaffin cell hyperplasia.<sup>64</sup>

Finally, a recent report has associated *C. jejuni* infection with a rare form of mucosa-associated lymphoid tissue lymphoma, IPSID/ $\alpha$  chain disease.<sup>66</sup> Patients with early IPSID had previously been known to be antibiotic (tetracycline) responsive.<sup>67</sup> *Campylobacter* DNA was subsequently found in biopsy specimens of an antibiotic-responsive index patient and in 4 of 6 archived specimens from other IPSID cases.<sup>66</sup> The proposed

mechanism of IPSID pathogenesis is via an autoreactive B cell clone that secretes  $\alpha$  chains, possibly stimulated by *C. jejuni*-specific T lymphocytes. Causality has not yet been shown, and since *C. jejuni* is not known to chronically colonize humans, *C. jejuni* may be part of a multifactorial process of IPSID development.<sup>67</sup>

## DIAGNOSIS

*Campylobacter* infection should be suspected in patients with fever and acute diarrhea, particularly those with visible blood and mucus in the stool, including international travelers. Because the clinical presentation is similar to that seen with other common enteric bacterial pathogens such as *Salmonella*, *Shigella*, *Yersinia*, *Clostridium difficile*, and *E. coli* O157:H7, a presumptive diagnosis based on clinical presentation cannot be made. Diagnosis is made by isolating campylobacters from stool samples.

Specimens for culture should have minimal exposure to oxygen and be processed within 24 hours. Campylobacters are gram-negative spiral or S-shaped rods that are nonspore-forming and are highly motile. Gram's staining of diarrheal stool demonstrates curved or spiral-shaped gram-negative rods, and darting motility in darkfield or phase contrast microscopy is seen.<sup>68,69</sup> Definitive diagnosis is based on stool culture in a microaerophilic condition (5%–10% oxygen, 1%–10% carbon dioxide, 85% nitrogen) using selective, blood-based, antibiotic-enriched media, such as Blaser or Skirrow's media. All *Campylobacter* species are oxidase- and catalase-positive and grow at 37°C. *C. jejuni* and *C. coli*, however, grow optimally at 42°C, and this differential growth is used in the clinical microbiology laboratory. *C. jejuni* alone can be distinguished by its ability to hydrolyze hippurate. Campylobacters are slow growing, and incubation of stool cultures is performed for a minimum of 48 hours. These organisms are also generally fragile and can be destroyed by heat, desiccation, acidity, and disinfectants.

## TREATMENT

Most cases of campylobacteriosis are self-limiting in immunocompetent patients without systemic signs of infection, requiring only supportive treatment with adequate hydration. A recent meta-analysis demonstrated that antibiotic treatment was beneficial when begun early, decreasing diarrhea duration by a mean of 1.32 days as well as shortening the microbiologic carriage duration.<sup>70</sup> However, no randomized clinical trial has supported the use of antibiotics, as noted in current guidelines for the management of infectious diarrhea.<sup>71</sup> Two randomized controlled trials have

demonstrated the benefit of antibiotics in the eradication of fecal carriage but did not show a change in the course or duration of illness.<sup>72,73</sup> Since there is no clear standard of care for treatment of immunocompetent individuals, clinical judgment should be used when deciding whether to treat with antibiotics. Prudent use of antibiotics will favor patients with visible blood in the stool, fever, a large number of stools, and/or worsening of symptoms, as with other inflammatory diarrheas.<sup>18,71</sup> Pregnant women and individuals with immunosuppressive medical conditions, including HIV/AIDS, should also receive antibiotics.<sup>12,74</sup> Reasons to withhold antibiotics include the self-limited nature of infection in healthy populations and the rising problem of antibiotic resistance among *Campylobacter* species due to veterinary use.<sup>18</sup>

*C. jejuni* have been historically sensitive to macrolides, tetracyclines, fluoroquinolones, aminoglycosides, imipenem, and chloramphenicol but resistant to trimethoprim.<sup>74</sup> Erythromycin has been the cornerstone of therapy, demonstrating consistent bacteriologic cure of sensitive strains when compared with placebo but with an inconsistent benefit for clinical cure, as discussed above.<sup>72,75</sup> With the introduction of the fluoroquinolones, ciprofloxacin became the mainstay of empiric treatment for acute community-acquired bacterial diarrhea and for travelers' diarrhea.<sup>76,77</sup> However, rapid emergence of fluoroquinolone-resistant *Campylobacter* strains was noted in Europe in the 1980s (0% in 1982 and 11% in 1989), which coincided with the introduction of quinolone use in poultry.<sup>78</sup> In the United States, ciprofloxacin resistance rose from 0% in 1989 to 19% in 2001 and has reached 90% in Thailand.<sup>79–81</sup> Currently, macrolide antibiotics are the preferred treatment for outpatients with *Campylobacter* infection acquired in the United States who require therapy: erythromycin (500 mg twice daily for 5 days) or azithromycin (500 mg orally daily for 3 days).<sup>71,82</sup> Azithromycin should be used for travelers' diarrhea due to *Campylobacter* infection and empirically where quinolone resistance is anticipated.<sup>71</sup> In US military personnel in Thailand, azithromycin was shown to be as effective as ciprofloxacin in shortening symptomatic illness and in microbiologic cure rates.<sup>82</sup> More severe, systemic disease can be treated with a variety of intravenous antibiotics, including cefotaxime, imipenem, ampicillin, and parenteral aminoglycosides, but antimicrobial sensitivities should always be checked.

## PREVENTION

There is no licensed vaccine against *Campylobacter* species that most frequently cause clinical disease (ie,

*C. jejuni* and *C. coli*). Prevention of infection with *Campylobacter* involves attention to handling raw poultry and ingestion of undercooked poultry as well as contaminated water and food. Between 50% and 70% of sporadic infections are attributable to poultry; thorough cleaning of cutting boards, proper cooking (to 170°F–180°F) and hand washing after handling chicken should be encouraged in the home.<sup>36,83,84</sup> International travelers, immunocompromised individuals, and pregnant women should follow general precautions to protect against diarrhea, including the ingestion of clean drinking water, avoidance of unpasteurized milk and undercooked meats, and strict attention to hand hygiene.

## CONCLUSION

Campylobacteriosis is a common cause of diarrhea and enterocolitis worldwide. Although commonly self-limiting, infection can be associated with severe complications, including reactive arthritis and Guillain-Barré syndrome in previously healthy hosts as well as systemic and recurrent disease in immunocompromised patients. The rapid emergence of quinolone resistance has limited antibiotic options for treating symptomatic disease.

HP

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