Campylobacter jejuni Infections: Update on Emerging Issues and Trends

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Infection with *Campylobacter jejuni* is one of the most common causes of gastroenteritis worldwide; it occurs more frequently than do infections caused by *Salmonella* species, *Shigella* species, or *Escherichia coli* O157:H7. In developed countries, the incidence of *Campylobacter jejuni* infections peaks during infancy and again during early adulthood. Most infections are acquired by the consumption and handling of poultry. A typical case is characterized by diarrhea, fever, and abdominal cramps. Obtaining cultures of the organism from stool samples remains the best way to diagnose this infection. An alarming recent trend is the rapid emergence of antimicrobial agent–resistant *Campylobacter* strains all over the world. Use of antibiotics in animals used for food has accelerated this trend. It is fortunate that complications of *C. jejuni* infections are rare, and most patients do not require antibiotics. Guillain-Barré syndrome is now recognized as a post-infectious complication of *C. jejuni* infection, but its incidence is <1 per 1000 infections. Careful food preparation and cooking practices may prevent some *Campylobacter* infections.

Campylobacter jejuni infection is one of the most commonly identified bacterial causes of acute gastroenteritis worldwide. In developing countries, *Campylobacter* species are an important cause of childhood morbidity caused by diarrheal illness. They are among the most common causes of diarrhea in travelers from developed nations. Remarkably, in many studies in the United States and other industrialized countries, *Campylobacter* infections were found to cause diarrheal disease >2–7 times as frequently as infections with *Salmonella* species, *Shigella* species, or *Escherichia coli* O157:H7 [1, 2]. Although 14 species of *Campylobacter* have been identified, in the United States >99% of reported infections with *Campylobacter* are with *C. jejuni* [3]. Therefore, this paper will be limited to a discussion of *C. jejuni.*

HISTORY

Despite their widespread occurrence, *Campylobacter* species were not understood as a cause of diarrhea in humans until 1957 [4], and their impact in terms of sheer numbers of human infections emerged only in the past 20 years. The first recognized *Campylobacter* infections were reported in the early part of the 20th century and occurred in farm animals. The infections were attributed to *Vibrio fetus* (now known to be *Campylobacter fetus*) and were realized by veterinarians to be a cause of septic abortions in sheep and cattle. In 1947, *V. fetus* was reported to be the cause of septic abortion in a woman, and during the next 3 decades, the organism was believed to be a rare, opportunistic, invasive pathogen that occurred principally in debilitated hosts.

In 1973, the new genus *Campylobacter* was proposed [5]. Finally, the development and increasingly widespread use of selective media for isolation of *Campylobacter* from stool samples in the 1970s led to the recognition in the early 1980s of the importance of these infections as a cause of human gastrointestinal illness. By the mid-to-late 1980s, it had been determined that *Campylobacter* species are one of the most common bacterial causes of diarrhea worldwide.

MICROBIOLOGY

Campylobacter species are gram-negative bacilli that have a curved or spiral shape (hence their initial classification as vibrios). Recently, the complete genome sequence of *C. jejuni* was

Received 4 August 2000; revised 4 December 2000; electronically published 28 March 2001.

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Clinical Infectious Diseases 2001;32:1201–6

1058-4838/2001/3208-0012$03.00

characterized. Of note was the finding of hypervariable regions that might be important in the survival of the organism [6]. *Campylobacter* species are motile by means of unipolar or bipolar flagellae. The organisms grow quite slowly; 72–96 h are required for primary isolation from stool samples, and isolation from blood can take even longer. They grow best at 42°C. Because most *Campylobacter* species are resistant to cephalothin (an agent to which most other stool flora are susceptible), the usual method for isolation from stool samples is use of a medium that contains cephalothin. Because some *Campylobacter* species, especially non-*jejuni Campylobacter* species, are susceptible to cephalothin, the filter method and antibiotic-free media should be used if initial results of cultures are negative and the suspicion of *Campylobacter* infection is high. This method involves first filtering the stool onto an antibiotic-free medium through 0.45–0.65-μm filters; the filters will block the passage of most stool flora but will permit the passage of smaller bacteria such as *Campylobacter* species [7].

CLINICAL CHARACTERISTICS OF *CAMPYLOBACTER* GASTROENTERITIS

Most typically, infection with *C. jejuni* results in an acute, self-limited gastrointestinal illness characterized by diarrhea, fever, and abdominal cramps. Clinically, *Campylobacter* infection is indistinguishable from acute gastrointestinal infections produced by other bacterial pathogens, such as *Salmonella, Shigella,* and *Yersinia* species. In most patients, the diarrhea is either loose and watery or grossly bloody; 8–10 bowel movements per day occur at the peak of illness [2]. In some patients, the diarrhea is minimal and abdominal cramps and pain are the predominant features; this can lead to a mistaken diagnosis of acute abdomen and unnecessary laparotomy. Fever is reported by >90% of patients and can be low-grade or >40°C and persist for up to 1 week. By that time, the illness has usually resolved, even in the absence of specific antibiotic treatment. Occasionally, however, patients can develop a longer, relapsing diarrheal illness that lasts several weeks [8]. Although *Campylobacter* is rarely identified in the stools of healthy persons, depending upon the population studied, as many as 50% of persons who are infected during outbreaks are asymptomatic [9].

Fecal leukocytes and RBCs are detected in the stools of 75% of infected persons [10]. The peripheral WBC count may be mildly elevated. Other laboratory studies, including liver function, electrolytes, and hematocrit levels, are normal. Because diffuse colonic inflammation may be seen on sigmoidoscopic examination, *Campylobacter* enteritis may be confused with early inflammatory bowel disease. Diagnosis of *Campylobacter* enteritis is confirmed by obtaining cultures of the organism from stool samples. Some laboratories have begun performing PCR analysis on stool samples for *Campylobacter,* but this is not yet a standard practice. Species-specific assays, such as PCR-enzyme-linked immunosorbent assays to detect *Campylobacter* antigens in stool samples, have been developed and also may become useful in the diagnosis of *Campylobacter* infections [11].

COMPLICATIONS OF *CAMPYLOBACTER* INFECTIONS

Local complications of *Campylobacter* infections occur as a result of direct spread from the gastrointestinal tract and can include cholecystitis, pancreatitis, peritonitis, and massive gastrointestinal hemorrhage. Extraintestinal manifestations of *Campylobacter* infection are quite rare and may include meningitis, endocarditis, septic arthritis, osteomyelitis, and neonatal sepsis. Bacteremia is detected in <1% of patients with *Campylobacter* enteritis and is most likely to occur in patients who are immunocompromised or among the very young or very old [12]. Transient bacteremia in immunocompetent hosts with *C. jejuni* enteritis may be more common but not detected because most strains are rapidly cleared by the killing action of normal human serum and because blood cultures are not routinely performed for patients with acute gastrointestinal illness. Serious systemic illness caused by *Campylobacter* infection rarely occurs but can lead to sepsis and death. The case-fatality rate for *Campylobacter* infection is 0.05 per 1000 infections.

The most important postinfectious complication of *C. jejuni* infection is the Guillain-Barré syndrome (GBS). GBS is an acute demyelinating disease of the peripheral nervous system that affects 1–2 persons per 100,000 population in the United States each year. Although *C. jejuni* infections are a common trigger of GBS (probably preceding 30% of GBS cases), the risk of developing GBS after *C. jejuni* infection is actually quite small (<1 case of GBS per 1000 *C. jejuni* infections) [13]. The risk of developing GBS is increased after infection with certain *Campylobacter* serotypes. In the United States, Penner type O:19 is most commonly associated with GBS [14]; in South Africa, Penner type O:41 is the serotype most frequently associated with GBS.

GBS that occurs after *C. jejuni* infection is usually a more severe disease, associated with extensive axonal injury, a greater likelihood of the need for mechanical ventilation, and increased risk of irreversible neurological damage. In contrast, the severity of *C. jejuni* infection is not associated with an increased risk of the development of GBS. Indeed, many GBS-associated *C. jejuni* infections are asymptomatic [15]. Because the neurological symptoms of GBS that follow *C. jejuni* infection typically occur 1–3 weeks after the onset of diarrheal illness, humoral immunopathogenic mechanisms are likely involved. Molecular mimicry between peripheral nerve glycolipids or myelin proteins and structures on the lipopolysaccharides of some *Cam-*

pylobacter strains likely plays a role in the pathogenesis of *Campylobacter*-induced GBS [16].

Persons with the HLA-B27 histocompatibility antigen are prone to the development of reactive arthritis several weeks after infection with *Campylobacter* [17]. Other postinfectious complications of infection include uveitis, hemolytic anemia, hemolytic uremic syndrome, carditis, and encephalopathy.

EPIDEMIOLOGY

Incidence. In the United States, *Campylobacter* infections became reportable illnesses in many states in the early 1980s; however, from the outset, the reporting systems routinely underestimated the impact of these infections. In the early years of *Campylobacter* surveillance, many hospital microbiology laboratories did not seek *Campylobacter* when they performed stool cultures for other enteric pathogens. Later studies confirmed that when diarrheal stool samples were cultured for *Campylobacter* every time they cultured for *Salmonella* or *Shigella, Campylobacter* was identified 2–7 times more frequently than was *Salmonella* or *Shigella.* Even currently, estimates have shown that only 1 in 38 cases of detected *Campylobacter* infection is reported [18].

Accurate estimates of the true incidence of *Campylobacter* infections in the United States and other industrialized nations depend upon many data sources. In 1996, the Emerging Infections Program Foodborne Diseases Active Surveillance Network (Foodnet) of the Centers for Disease Control and Prevention (CDC) began the collection of data on 9 foodborne illnesses in selected United States cities. In the first year, *Campylobacter* was detected more frequently than was any other pathogen—more frequently than *Salmonella* and *Shigella* combined. However, from 1996 through 1999, the incidence of *Campylobacter* infection decreased 26%, although the organism remained the most commonly identified enteric pathogen [19] (table 1).The decreased rates were attributed to disease prevention efforts that had been implemented in food service establishments, meat and poultry processing plants, and egg production farms [19]. Currently, the CDC estimates that 2.4 million cases of *Campylobacter* infection occur in the United States each year, involving almost 1% of the entire population [3].

Demographic data. The age and sex distributions of *Campylobacter* infections are unique among bacterial enteric pathogens. In industrialized nations, 2 age-peaks occur: the first is at <1 year of age, and a second surge occurs during young adulthood, at 15–44 years of age. Furthermore, there is a preponderance of males among infected persons, which begins during early childhood and persists until old age [3]. The reasons for these age and sex distributions remain unknown. Since the beginning of national reporting on *Campylobacter* in the early 1980s, the infections have demonstrated a marked seasonal distribution, with a surge that begins in May and peaks in August [3].

Table 1. Rates of selected enteric bacterial infections detected by the Foodborne Active Surveillance Network of the Centers for Disease Control and Prevention (United States, 1996–1999).

	No. of infections per 100,000 population			
Causative organism	1996	1997	1998	1999
Campylobacter species	23.5	25.2	21.4	17.3
Salmonella species	14.5	13.6	12.3	14.8
Shigella species	8.9	7.9	8.5	5.0
Escherichia coli O:157:H7	2.7	2.3	2.8	2.1
Yersinia species	1.0	0.9	1.0	0.8

NOTE. Active surveillance was done in Maryland, Oregon, selected counties in California, Connecticut, and Georgia. Table is modified from [16].

Sources and transmission of infection. The single most important route of *Campylobacter* infections in the United States and other industrialized nations remains the consumption and handling of chicken. In studies in many parts of the United States, Europe, and Australia, 50%–70% of all *Campylobacter* infections have been attributed to consumption of chicken [20–22]. Perhaps this should not be surprising in light of the frequency with which poultry products are consumed and the nearly universal contamination of chicken carcasses with *Campylobacter* [23]. Indeed, it has been estimated that just 1 drop of chicken juice may contain 500 infectious organisms [24]. Even with strict attention to good handwashing and cleaning of cutting boards, it is easy to see how simple errors in the handling of food might result in cross-contamination in the kitchen and, therefore, human illness. Because heat kills viable *Campylobacter* species, thorough cooking of chicken should be emphasized as an important food-safety measure.

Other foods and activities also have been implicated as sources of *Campylobacter* infection. Although outbreaks of infection account for a small fraction of *Campylobacter* infections in humans (most infections are sporadic), consumption of unpasteurized milk is the most frequently reported cause of outbreaks of infection [3]. Other sources of sporadic infection include sausages or red meat (especially in Scandinavian countries), contaminated water, contact with pets (especially birds and cats), and international travel [25–27].

Because the infectious dose of *Campylobacter* is quite high in comparison with that of *Shigella* or *Giardia* (800–10^6 ingested organisms are needed to produce illness in 10%–50% of persons) [28], person-to-person transmission is unusual. Outbreaks of *Campylobacter* infection in day care centers or mental

institutions are almost unheard of. Although the reported incidence of *Campylobacter* infection among homosexual men is almost 40 times greater than in the general population [29], recent analysis shows the rate is not higher than among heterosexual men of a similar age [3].

Campylobacter *in developing countries.* The epidemiology of *Campylobacter* infections is quite different in developing countries than in the industrialized world. In tropical developing countries, *Campylobacter* infections are hyperendemic among young children, especially those aged <2 years. Asymptomatic infections occur commonly in both children and adults, whereas, in developed countries, asymptomatic *Campylobacter* infections are unusual. In addition, in developing countries, outbreaks of infection are uncommon and the illness lacks the marked seasonal nature observed in industrialized nations. Nevertheless, in both developed and developing countries, *Campylobacter* remains one of the most common bacterial causes of diarrhea.

TREATMENT AND RESISTANCE

Maintenance of hydration and electrolyte balance, not antibiotic treatment, is the cornerstone of treatment for *Campylobacter* enteritis. Indeed, most patients with *Campylobacter* infection have a self-limited illness and do not require antibiotics at all. Nevertheless, there are specific clinical circumstances in which antibiotics should be used. These include high fevers, bloody stools, prolonged illness (symptoms that last >1 week), pregnancy, infection with HIV, and other immunocompromised states.

The decision to use antibiotics should be made judiciously. In the United States, the most common cause of bloody diarrhea is not *Campylobacter* but *E. coli* O157:H7 infection [1]. Recent studies suggest that administration of antibiotics to children with *E. coli* O157:H7 infection actually increases the risk of the hemolytic uremic syndrome (HUS) [30], a recognized sequela of this infection. Therefore, young children with bloody diarrhea (and others who might be at risk of infection with *E. coli* O157:H7 and HUS) should not be treated with antibiotics unless it is absolutely necessary or until this infection is ruled out.

Until a few years ago, if antimicrobial therapy was indicated for *Campylobacter* infection, fluoroquinolones were considered the drugs of choice. This approach was the simplest for physicians and patients alike because the symptoms of *Campylobacter* enteritis (fever, abdominal cramps, and diarrhea) are clinically indistinguishable from those of bacterial gastroenteritis caused by other organisms, such as *Salmonella* or *Shigella* species. Because these other pathogens were also generally susceptible to fluoroquinolones, empirical treatment with these drugs could be used without waiting for the results of stool cultures. Fluoroquinolones were especially apt to be used for the treatment of traveler's diarrhea.

However, in the past few years, a rapidly increasing proportion of *Campylobacter* strains all over the world have been found to be fluoroquinolone-resistant (table 2). Primary resistance to quinolone therapy in humans was first noted in the early 1990s in Asia and in European countries such as Sweden, The Netherlands, Finland, and Spain. Not surprisingly, this coincided with initiation of the administration of the fluoroquinolone, enrofloxacin, to food animals in those countries [31]. A similar increase in rates of resistance to fluoroquinolones in *Campylobacter* isolates from humans was observed in the United Kingdom after the approval of the use of fluoroquinolones in veterinary animals there as well [32].

In the United States, the licensure of sarafloxacin in 1995 and enrofloxacin in 1996 for use in poultry flocks contributed to an increase in the number of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in Minnesota [33]. In that state, fluoroquinolone resistance among *Campylobacter* isolates from humans increased from 1.3% in 1992 to 10.2% in 1998. The impact of the use of fluoroquinolones in food animals upon human health was the subject of a recent World Health Organization meeting [34]. In addition to more prudent use of these agents in people, international controls on the use of antibiotics in food animals may become necessary to curtail the development of additional resistance among foodborne bacterial pathogens.

Erythromycin has once again come to be considered the optimal drug for treatment of *Campylobacter* infections. Despite decades of use, the rate of resistance of *Campylobacter* to erythromycin remains quite low. Other advantages of erythromycin include its low cost, safety, ease of administration, and narrow spectrum of activity. Unlike the fluoroquinolones and tetracyclines, erythromycin may be administered safely to children and pregnant women and is less likely than many agents to exert an inhibitory effect on other fecal flora. Erythromycin stearate is acid-resistant, stable, and incompletely absorbed. Therefore, in addition to its systemic effects, it may be capable of exerting a contact effect throughout the bowel [35]. The

Table 2. Percentage of *Campylobacter* isolates (from humans) with primary resistance to fluoroquinolones.

Reference, country	Year(s)	Isolates studied, *n*	Resistant to fluoroquinolones, %
[36] Sweden	1992–1995	586	19
[37] India	1994	75	3
[38] Thailand	1995	57	84
[39] Spain	1997–1998	641	72
[33] United States	1998	833	10
[32] United Kingdom	1998	495	18
[40] The Netherlands	1999	1315	29

recommended dosage for adults is 500 mg administered orally 2 times per day for 5 days. For children, the recommended dosage is 40 mg per kg per day in 2 divided doses for 5 days.

The newer macrolides, azithromycin and clarithromycin, are also effective against *C. jejuni* infections, but they are more expensive than erythromycin and provide no clinical advantage. *Campylobacter* species also are generally susceptible to aminoglycosides, chloramphenicol, clindamycin, nitrofurans, and imipenem. High rates of resistance make tetracycline, amoxicillin, ampicillin, metronidazole, and cephalosporins poor choices for the treatment of infections with *C. jejuni*. All *Campylobacter* species are inherently resistant to vancomycin, rifampin, and trimethoprim.

PREVENTION

Because most *Campylobacter* infections are acquired by consuming or handling poultry, the ideal way to control the number of human infections would be to limit contamination of poultry flocks. However, the near-universal contamination of poultry with *Campylobacter* and the heavy bacterial burden in these flocks [24] make elimination of *Campylobacter* in chickens impractical, if not impossible. Current mass processing and distribution of chicken may amplify the bacterial load; perhaps future investigations will lead to the creation of a system that will produce chickens that are only lightly colonized with *Campylobacter*. New strategies will likely include limiting animals' consumption of antibiotics, disinfection of their food and water, treatment of their manure, and isolation of the contagiously ill. Perhaps the irradiation of foods of animal origin will one day become sufficiently acceptable to the public to make this a feasible method of control of the bacterial contamination of foods.

Observing careful food-preparation habits in the kitchen is also important in the prevention of infections. Chicken should be adequately cooked—not charred on the outside and left pink near the bone. Use of a meat thermometer may help to ensure that temperatures adequate to kill *Campylobacter* species organisms are achieved. Cutting boards and utensils used in handling uncooked poultry or other meats should be washed with hot soapy water before being used for preparation of salads or other foods that are eaten raw.

Although person-to-person transmission of *C. jejuni* infection is unusual, persons with any acute diarrheal illness should avoid preparation and handling of food until their illness resolves. Of course, as part of good general hygiene, all persons should wash their hands after using the bathroom, especially if they have diarrhea. Similarly, all people, but especially those who handle pets or other animals, should wash their hands before eating. Prevention of many outbreaks of *C. jejuni* infection could be accomplished with avoidance of the consumption of unpasteurized milk; this should be emphasized to pregnant women, the elderly, immunocompromised persons, or other persons in whom *C. jejuni* infection may have serious consequences. Persons who travel to developing countries and campers should be cautioned against drinking untreated water. Routine use of antibiotic prophylaxis to prevent *Campylobacter* infections is not recommended.

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