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Perspectives

Campylobacter jejuni—An Emerging Foodborne Pathogen

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Campylobacter jejuni is the most commonly reported bacterial cause of foodborne infection in the United States. Adding to the human and economic costs are chronic sequelae associated with C. jejuni infection—Guillain-Barré syndrome and reactive arthritis. In addition, an increasing proportion of human infections caused by C. jejuni are resistant to antimicrobial therapy. Mishandling of raw poultry and consumption of undercooked poultry are the major risk factors for human campylobacteriosis. Efforts to prevent human illness are needed throughout each link in the food chain.

History

Awareness of the public health implications of Campylobacter infections has evolved over more than a century (1). In 1886, Escherich observed organisms resembling campylobacters in stool samples of children with diarrhea. In 1913, McFaydean and Stockman identified campylobacters (called related Vibrio) in fetal tissues of aborted sheep (1). In 1957, King described the isolation of related Vibrio from blood samples of children with diarrhea, and in 1972, clinical microbiologists in Belgium first isolated campylobacters from stool samples of patients with diarrhea (1). The development of selective growth media in the 1970s permitted more laboratories to test stool specimens for Campylobacter. Soon Campylobacter spp. were established as common human pathogens. Campylobacter jejuni infections are now the leading cause of bacterial gastroenteritis reported in the United States (2). In 1996, 46% of laboratory-confirmed cases of bacterial gastroenteritis reported in the Centers for Disease Control and Prevention/U.S. Department of Agriculture/Food and Drug Administration Collaborating Sites Foodborne Disease Active Surveillance Network were caused by Campylobacter jejuni. Campylobacteriosis was followed in prevalence by salmonellosis (28%), shigellosis (17%), and Escherichia coli O157 infection (5%) (Figure 1).

Disease Prevalence

In the United States, an estimated 2.1 to 2.4 million cases of human campylobacteriosis (illnesses ranging from loose stools to dysentery) occur each year (2). Commonly reported symptoms of patients with laboratory-confirmed infections (a small subset of all cases) include diarrhea, fever, and abdominal cramping. In one study, approximately half of the patients with laboratory-confirmed campylobacteriosis reported a history of bloody diarrhea (3). Less frequently,

Figure 1. Cases of Campylobacter and other foodborne infections by month of specimen collection; Centers for Disease Control and Prevention/U.S. Department of Agriculture/Food and Drug Administration Collaborating Sites Foodborne Disease Active Surveillance Network, 1996.

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C. jejuni infections produce bacteremia, septic arthritis, and other extraintestinal symptoms (4). The incidence of campylobacteriosis in HIV-infected patients is higher than in the general population. For example, in Los Angeles County between 1983 and 1987, the reported incidence of campylobacteriosis in patients with AIDS was 519 cases per 100,000 population, 39 times higher than the rate in the general population (5). Common complications of campylobacteriosis in HIV-infected patients are recurrent infection and infection with antimicrobial-resistant strains (6). Deaths from C. jejuni infection are rare and occur primarily in infants, the elderly, and patients with underlying illnesses (2).

Sequela to Infection

Guillain-Barré syndrome (GBS), a demyelinating disorder resulting in acute neuromuscular paralysis, is a serious sequela of Campylobacter infection (7). An estimated one case of GBS occurs for every 1,000 cases of campylobacteriosis (7). Up to 40% of patients with the syndrome have evidence of recent Campylobacter infection (7). Approximately 20% of patients with GBS are left with some disability, and approximately 5% die despite advances in respiratory care. Campylobacteriosis is also associated with Reiter syndrome, a reactive arthropathy. In approximately 1% of patients with campylobacteriosis, the sterile postinfection process occurs 7 to 10 days after onset of diarrhea (8). Multiple joints can be affected, particularly the knee joint. Pain and incapacitation can last for months or become chronic.

Both GBS and Reiter syndrome are thought to be autoimmune responses stimulated by infection. Many patients with Reiter syndrome carry the HLA B27 antigenic marker (8). The pathogenesis of GBS (9) and Reiter syndrome is not completely understood.

Treatment of C. jejuni Infections

Supportive measures, particularly fluid and electrolyte replacement, are the principal therapies for most patients with campylobacteriosis (10). Severely dehydrated patients should receive rapid volume expansion with intravenous fluids. For most other patients, oral rehydration is indicated. Although Campylobacter infections are usually self limiting, antibiotic therapy may be prudent for patients who have high fever, bloody diarrhea, or more than eight stools in 24 hours; immunosuppressed patients, patients with bloodstream infections, and those whose symptoms worsen or persist for more than 1 week from the time of diagnosis. When indicated, antimicrobial therapy soon after the onset of symptoms can reduce the median duration of illness from approximately 10 days to 5 days. When treatment is delayed (e.g., until C. jejuni infection is confirmed by a medical laboratory), therapy may not be successful (10). Ease of administration, lack of serious toxicity, and high degree of efficacy make erythromycin the drug of choice for C. jejuni infection; however, other antimicrobial agents, particularly the quinolones and newer macrolides including azithromycin, are also used.

Antimicrobial Resistance

The increasing rate of human infections caused by antimicrobial-resistant strains of C. jejuni makes clinical management of cases of campylobacteriosis more difficult (11,12). Antimicrobial resistance can prolong illness and compromise treatment of patients with bacteremia. The rate of antimicrobial-resistant enteric infections is highest in the developing world, where the use of antimicrobial drugs in humans and animals is relatively unrestricted. A 1994 study found that most clinical isolates of C. jejuni from U.S. troops in Thailand were resistant to ciprofloxacin. Additionally, nearly one third of isolates from U.S. troops located in Hat Yai were resistant to azithromycin (11). In the industrialized world, the emergence of fluoroquinolone-resistant strains of C. jejuni illustrates the need for prudent antimicrobial use in food-animal production (12). Experimental evidence demonstrates that fluoroquinolone-susceptible C. jejuni readily become drug-resistant in chickens when these drugs are administered (13). After fluoroquinolone use in poultry was approved in Europe, resistant C. jejuni strains emerged rapidly in humans during the early 1990s (12). Similarly, within 2 years of the 1995 approval of fluoroquinolone use for poultry in the United States, the number of domestically acquired human cases of ciprofloxacin-resistant campylobacteriosis doubled in Minnesota (14). In a 1997 study conducted in Minnesota, 12 (20%) of 60 C. jejuni isolates obtained from chicken purchased in grocery stores were ciprofloxacin-resistant (14).
Pathogenesis

The pathogenesis of *C. jejuni* infection involves both host- and pathogen-specific factors. The health and age of the host (2) and *C. jejuni*-specific humoral immunity from previous exposure (15) influence clinical outcome after infection. In a volunteer study, *C. jejuni* infection occurred after ingestion of as few as 800 organisms (16). Rates of infection increased with the ingested dose. Rates of illness appeared to increase when inocula were ingested in a suspension buffered to reduce gastric acidity (16).

Many pathogen-specific virulence determinants may contribute to the pathogenesis of *C. jejuni* infection, but none has a proven role (17). Suspected determinants of pathogenicity include chemotaxis, motility, and flagella, which are required for attachment and colonization of the gut epithelium (Figure 2) (17). Once colonization occurs, other possible virulence determinants are iron acquisition, host cell invasion, toxin production, inflammation and active secretion, and epithelial disruption with leakage of serosal fluid (17).

Survival in the Environment

Survival of *C. jejuni* outside the gut is poor, and replication does not occur readily (17). *C. jejuni* grows best at 37°C to 42°C (18), the approximate body temperature of the chicken (41°C to 42°C). *C. jejuni* grows best in a low oxygen or microaerophilic environment, such as an atmosphere of 5% O₂, 10% CO₂, and 85% N₂. The organism is sensitive to freezing, drying, acidic conditions (pH ≤ 5.0), and salinity.

Sample Collection and Transport

If possible, stool specimens should be chilled (not frozen) and submitted to a laboratory within 24 hours of collection. Storing specimens in deep, airtight containers minimizes exposure to oxygen and desiccation. If a specimen cannot be processed within 24 hours or is likely to contain small numbers of organisms, a rectal swab placed in a specimen transport medium (e.g., Cary-Blair) should be used. Individual laboratories can provide guidance on specimen handling procedures (18).

Numerous procedures are available for recovering *C. jejuni* from clinical specimens (18). Direct plating is cost-effective for testing large numbers of specimens; however, testing sensitivity may be reduced. Preenrichment (raising the temperature from 36°C to 42°C over several hours), filtration, or both are used in some laboratories to improve recovery of stressed *C. jejuni* organisms from specimens (e.g., stored foods or swabs exposed to oxygen) (19). Isolation can be facilitated by using selective media containing antimicrobial agents, oxygen quenching agents, or a low oxygen atmosphere, thus decreasing the number of colonies that must be screened (18,19).

Subtyping of Isolates

No standard subtyping technique has been established for *C. jejuni*. Soon after the organism was described, two serologic methods were developed, the heat-stable or somatic O antigen (20) and the heat-labile antigen schemes (21). These typing schemes are labor intensive, and their use is limited almost exclusively to reference laboratories. Many different DNA-based subtyping schemes have been developed, including pulsed-field gel electrophoresis (PFGE) and randomly amplified polymorphic DNA (RAPD) analysis (22). Various typing schemes have been developed on the basis of the sequence of flaA, encoding flagellin (23); however, recent evidence suggests that this locus may not be representative of the entire genome (24).

Transmission to Humans

Most cases of human campylobacteriosis are sporadic. Outbreaks have different epidemio-
logic characteristics from sporadic infections (2). Many outbreaks occur during the spring and autumn (2). Consumption of raw milk was implicated as the source of infection in 30 of the 80 outbreaks of human campylobacteriosis reported to CDC between 1973 and 1992. Outbreaks caused by drinking raw milk often involve farm visits (e.g., school field trips) during the temperate seasons. In contrast, sporadic Campylobacter isolates peak during the summer months (Figure 1). A series of case-control studies identified some risk factors for sporadic campylobacteriosis, particularly handling raw poultry (25,26) and eating undercooked poultry (27-31) (Table). Other risk factors accounting for a smaller proportion of sporadic illnesses include drinking untreated water (29); traveling abroad (25); eating barbequed pork (28) or sausage (27); drinking raw milk (29, 32) or milk from bird-pecked bottles (33); and contact with dogs (27) and cats (29,31), particularly juvenile pets or pets with diarrhea (25,34). Person-to-person transmission is uncommon (25,32). Overlap is reported between serotypes of C. jejuni found in humans, poultry, and cattle, indicating that foods of animal origin may play a major role in transmitting C. jejuni to humans (35).

In the United States, infants have the highest age-specific Campylobacter isolation rate, approximately 14 per 100,000 person years. As children get older, isolation rates decline to approximately 4 per 100,000 person years for young adolescents. A notable feature of the epidemiology of human campylobacteriosis is the high isolation rate among young adults, approximately 8 per 100,000 person years. Among middle-aged and older adults, the isolation rate is < 3 per 100,000 person years (2). The peak isolation rate in neonates and infants is attributed in part to susceptibility on first exposure and to the low threshold for seeking medical care for infants (2). The high rate of infection during early adulthood, which is pronounced among men, is thought to reflect poor food-handling practices in a population that, until recently, relied on others to prepare meals (2).

### Reservoirs

The ecology of C. jejuni involves wildlife reservoirs, particularly wild birds. Species that carry C. jejuni include migratory birds—cranes, ducks, geese (36), and seagulls (37). The organism is also found in other wild and domestic bird species, as well as in rodents (38). Insects can carry the organism on their exoskeleton (39).

### Table. Epidemiologic studies of laboratory-confirmed cases of sporadic campylobacteriosis

<table>
<thead>
<tr>
<th>Number</th>
<th>Cases</th>
<th>Controls</th>
<th>Date</th>
<th>Population</th>
<th>Location</th>
<th>Foods associated with illness</th>
<th>Animal contacts</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>103</td>
<td></td>
<td>1989-1990</td>
<td>Residents of three counties</td>
<td>Norway</td>
<td>Poultry, sausage</td>
<td>Dogs</td>
<td>27</td>
</tr>
<tr>
<td>218</td>
<td>526</td>
<td></td>
<td>1982-1983</td>
<td>HMO patients</td>
<td>Washington State</td>
<td>Undercooked chicken</td>
<td>Animals with diarrhea</td>
<td>30,34</td>
</tr>
<tr>
<td>29</td>
<td>42</td>
<td></td>
<td>1990</td>
<td>Residents of Manchester</td>
<td>England</td>
<td>Bottled milk*</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>45</td>
<td>45</td>
<td></td>
<td>1983-1984</td>
<td>University students</td>
<td>Georgia</td>
<td>Chicken</td>
<td>Cats</td>
<td>31</td>
</tr>
<tr>
<td>53</td>
<td>106</td>
<td></td>
<td>1982-1983</td>
<td>Rural children</td>
<td>Iowa</td>
<td>Raw milk</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>40</td>
<td>80</td>
<td></td>
<td>1981</td>
<td>Residents of Denver, Ft. Collins</td>
<td>Colorado</td>
<td>Untreated water, raw milk, undercooked chicken</td>
<td>Cats</td>
<td>29</td>
</tr>
<tr>
<td>54</td>
<td>54</td>
<td></td>
<td>1982</td>
<td>Residents of Rotterdam</td>
<td>Netherlands</td>
<td>Chicken, pork, barbequed foods</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td></td>
<td>1982</td>
<td>Residents of Larimer County</td>
<td>Colorado</td>
<td>Preparing chicken</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>55</td>
<td>14</td>
<td></td>
<td>1980</td>
<td>Residents of Göteborg</td>
<td>Sweden</td>
<td>Preparing chicken</td>
<td>Kitten, dog with diarrhea</td>
<td>25</td>
</tr>
</tbody>
</table>

*aBottle tops pecked by wild birds.*
The intestines of poultry are easily colonized with \textit{C. jejuni}. Day-old chicks can be colonized with as few as 35 organisms (40). Most chickens in commercial operations are colonized by 4 weeks (41,42). Vertical transmission (i.e., from breeder flocks to progeny) has been suggested in one study but is not widely accepted (43). Reservoirs in the poultry environment include beetles (39), unchlorinated drinking water (44), and farm workers (41,42,45). Feeds are an unlikely source of campylobacters since they are dry and campylobacters are sensitive to drying.

\textit{C. jejuni} is a commensal organism of the intestinal tract of cattle (46). Young animals are more often colonized than older animals, and feedlot cattle are more likely than grazing animals to carry campylobacters (47). In one study, colonization of dairy herds was associated with drinking unchlorinated water (48).

Campylobacters are found in natural water sources throughout the year. The presence of campylobacters is not clearly correlated with indicator organisms for fecal contamination (e.g., \textit{E. coli})(49). In temperate regions, organism recovery rates are highest during the cold season (49,50). Survival in cold water is important in the life cycle of campylobacters. In one study, serotypes found in water were similar to those found in humans (50). When stressed, campylobacters enter a “viable but nonculturable state,” characterized by uptake of amino acids and maintenance of an intact outer membrane but inability to grow on selective media; such organisms, however, can be transmitted to animals (51). Additionally, unchlorinated drinking water can introduce campylobacters into the farm environment (44,48).

\textbf{Campylobacter in the Food Supply}

\textit{C. jejuni} is found in many foods of animal origin. Surveys of raw agricultural products support epidemiologic evidence implicating poultry, meat, and raw milk as sources of human infection. Most retail chicken is contaminated with \textit{C. jejuni}; one study reported an isolation rate of 98% for retail chicken meat (52). \textit{C. jejuni} counts often exceed $10^8$ per 100 g. Skin and giblets have particularly high levels of contamination. In one study, 12% of raw milk samples from dairy farms in eastern Tennessee were contaminated with \textit{C. jejuni} (53). Raw milk is presumed to be contaminated by bovine feces; however, direct contamination of milk as a consequence of mastitis also occurs (54). Campylobacters are also found in red meat. In one study, \textit{C. jejuni} was present in 5% of raw ground beef and in 40% of veal specimens (55).

\textbf{Control of Campylobacter Infection}

\textbf{On the Farm}

Control of \textit{Campylobacter} contamination on the farm may reduce contamination of carcasses, poultry, and red meat products at the retail level (27). Epidemiologic studies indicate that strict hygiene reduces intestinal carriage in food-producing animals (41,42,45). In field studies, poultry flocks that drank chlorinated water had lower intestinal colonization rates than poultry that drank unchlorinated water (42,44). Experimentally, treatment of chicks with commensal bacteria (56) and immunization of older birds (57) reduced \textit{C. jejuni} colonization. Because intestinal colonization with campylobacters readily occurs in poultry flocks, even strict measures may not eliminate intestinal carriage by food-producing animals (39,41).

\textbf{At Processing}

Slaughter and processing provide opportunities for reducing \textit{C. jejuni} counts on food-animal carcasses. Bacterial counts on carcasses can increase during slaughter and processing steps. In one study, up to a 1,000-fold increase in bacterial counts on carcasses was reported during transportation to slaughter (58). In studies of chickens (59) and turkeys (60) at slaughter, bacterial counts increased by approximately 10- to 100-fold during defeathering and reached the highest level after evisceration. However, bacterial counts on carcasses decline during other slaughter and processing steps. In one study, forced-air chilling of swine carcasses caused a 100-fold reduction in carcass contamination (61). In Texas turkey plants, scalding reduced carcass counts to near or below detectable levels (60). Adding sodium chloride or trisodium phosphate to the chiller water in the presence of an electrical current reduced \textit{C. jejuni} contamination of chiller water by $2\log_{10}$ units (62). In a slaughter plant in England, use of chlorinated sprays and maintenance of clean working surfaces resulted in a 10- to 100-fold decrease in carcass.
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contamination (63). In another study, lactic acid spraying of swine carcasses reduced counts by at least 50% to often undetectable levels (64). A radiation dose of 2.5 KGy reduced C. jejuni levels on retail poultry by 10 log_{10} units (65).

Conclusions

C. jejuni, first identified as a human diarrheal pathogen in 1973, is the most frequently diagnosed bacterial cause of human gastroenteritis in the United States. Sequelae including GBS and reactive arthritis are increasingly recognized, adding to the human and economic cost of illness from human campylobacteriosis. The emergence of fluoroquinolone-resistant infections in Europe and the United States, temporally associated with the approval of fluoroquinolone use in veterinary medicine, is also a public health concern. The consumption of undercooked poultry and cross-contamination of other foods with drippings from raw poultry are leading risk factors for human campylobacteriosis. Reinforcing hygienic practices at each link in the food chain—from producer to consumer—is critical in preventing the disease.

Dr. Altekruse is a Public Health Service Epidemiology Fellow with the Food and Drug Administration, Center for Veterinary Medicine. His current research interest is antimicrobial-resistant foodborne pathogens.


