Zoonosis Update

Human campylobacteriosis: a challenge for the veterinary profession

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Historical Aspects and Current Problems

The first description of a bacterium belonging to the genus *Campylobacter* is attributed to Theodore Escherich at the end of the 19th century.1 At the beginning of the 20th century, infections with *Campylobacter* spp., described as a related *Vibrio*, were recognized to cause abortions in sheep. Only after a suitable isolation medium was developed in the 1970s were 2 closely related pathogens, *C. jejuni* and *C. coli*, recognized to be common human enteric pathogens.2 In humans, *C. jejuni* causes approximately 90% of confirmed enteric *Campylobacter* infections.3,4

In a 1999 report,1 the national Centers for Disease Control and Prevention estimates that there are 2.5 million human cases of campylobacteriosis in the United States per year. Although there has been a decline of approximately 27% in the incidence of campylobacteriosis in FoodNet surveillance sites between 1996 and 2001, *Campylobacter* spp remain among the most common bacterial causes of foodborne infection.5 Postinfectious sequelae of infection include Guillain-Barré syndrome (GBS) and reactive arthritis. Challenges for the veterinary profession include implementation of pathogen reduction measures across the food chain and prevention of foodborne and zoonotic infections and infections caused by fluoroquinolone-resistant *Campylobacter* strains. This report provides an outline of the illness in humans, risk factors for human infection, *Campylobacter* ecology, and potential control points to prevent human infections.

Human Illness

Although *C. jejuni* and *C. coli* can exist as commensals of domestic poultry and livestock, they are considered human pathogens. In humans, the clinical spectrum of *Campylobacter* enteritis ranges from loose feces to dysentery. Self-limiting acute enteritis is the most common syndrome. Prodromal symptoms are common and include headache, low fever, and myalgia lasting from a few hours to a few days. Symptoms of acute infection often begin with abdominal cramps followed by diarrhea and high fever, peaking during the first days of illness.3 *Campylobacter jejuni*-specific serum antibodies confer immunity to symptomatic infection; however, the duration of protective immunity is not known.5,6

Complications of Infection

An estimated 100 people die of *C. jejuni* infections each year in the United States. These fatal infections occur most often in infants, the elderly, or immunosuppressed individuals.3 Bacteremia is most often detected in patients with underlying disease5 and is a potentially fatal complication of HIV/AIDS.7 Chronic diarrhea is also a complication of HIV-associated campylobacteriosis. The HIV-positive individuals who develop campylobacteriosis have shorter survival times and higher rates of bacteremia and hospitalization than HIV-positive individuals without campylobacteriosis.6

Sequelae of Infection

Guillain-Barré syndrome—With several thousand cases occurring each year, GBS is the most common cause of acute flaccid paralysis in the United States.5 Guillain-Barré syndrome is an acute immune-mediated disorder of the peripheral nervous system. Leg weakness is often the presenting sign, followed by ascending paralysis. After 1 year, 70% of patients make complete neurologic recovery, 22% partially recover, 8% remain unable to walk, and 2% remain bedridden or require ventilation. Most cases of GBS are believed to follow an infectious disease, and approximately 40% of those are thought to follow *Campylobacter* infection. Guillain-Barré syndrome is estimated to occur in 1 in every 1,000 patients infected with *Campylobacter*. Although a diverse group of strains is associated with GBS,14 the syndrome is strongly linked to a few strains of *C. jejuni* (eg, heat-stable or Penner serotype HS:19 and HS:41).15-16 *Campylobacter* strains contain sialic acid linkages to lipooligosaccharides resembling sialic acid moietyes on the gangliosides of peripheral nerve tissues.17 Patients with GBS develop antibodies against these gangliosides, resulting in autoimmune targeting of peripheral nerve sites. Complement-mediated damage8 and blockage of neurotransmission9 are suspected to affect GBS pathogenesis.

Many individuals are exposed to *C. jejuni* strains that mimic gangliosides, and only a few develop GBS; therefore, host factors are suspected to contribute to GBS. In

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1 study, Campylobacter-related GBS was associated with major histocompatibility antigen, HLA-DQBI*03; however, this association was not replicated in another well-designed study. Proposed treatments for GBS have not been fully evaluated in clinical trials but include treatment with corticosteroids, immunoglobulin, and plasmapheresis.

Reactive arthritis—Reactive arthritis, or Reiter’s syndrome, may also be a sterile sequela to acute gastrointestinal campylobacteriosis. The frequency of reactive arthritis as a sequela of campylobacteriosis has not been well described in the United States, but in Finland, 45 of 609 (7%) patients with laboratory-confirmed campylobacteriosis developed reactive arthritis. Arthritis was oligo- or polyarticular and in most cases mild. In the Finnish study, 37 of the 43 (82%) patients had C. jejuni infections, and 8 (18%) had C. coli infections. None of the patients with reactive arthritis were children. In a Danish study, patients with joint pain had more severe gastrointestinal symptoms and longer duration of diarrhea than those without joint pain. Anti-Campylobacter antibody titers were similar in both patient groups. Antimicrobial treatment did not prevent reactive arthritis.

Fluoroquinolone resistance—The FDA has proposed to ban the use of fluoroquinolones in poultry in response to the emergence of fluoroquinolone-resistant Campylobacter strains as a cause of human infections in the United States. The FDA partially attributed this trend to veterinary use of fluoroquinolones, concluding that use of fluoroquinolones in poultry compromises the clinical utility of fluoroquinolones in humans. An FDA risk assessment estimated that each year, thousands of people who are being treated with a fluoroquinolone are infected with fluoroquinolone-resistant Campylobacter strains after consuming or handling chicken, which may result in a prolonged duration of illness. Fluoroquinolone-resistant Campylobacter strains were not detected in the United States in 1986, the year when this class of antimicrobials was first introduced for human use in the United States. Resistance rates increased to 5% in the next few years. The proportion of Campylobacter isolates from humans who exhibited resistance to fluoroquinolones increased more rapidly after 1995, when fluoroquinolones were first approved by the FDA for the treatment of avian colibacillosis in poultry flocks. Since 1997, 14 to 18% of Campylobacter strains isolated from humans in the United States have been resistant to ciprofloxacin. A study by the Minnesota Department of Health suggested that the epidemiology of infection with fluoroquinolone-resistant Campylobacter strains shifted beginning in 1995 with the emergence of a domestic reservoir of fluoroquinolone-resistant C. jejuni. In Minnesota, the molecular subtypes of fluoroquinolone-resistant C. jejuni strains isolated from humans who had not traveled outside the United States matched the molecular subtypes of fluoroquinolone-resistant C. jejuni isolated from locally purchased retail poultry products. An increase in the frequency of infections with fluoroquinolone-resistant strains was also observed in the National Antimicrobial Resistance Monitoring System (NARMS). Case-control studies conducted by NARMS revealed that chicken consumption is an important risk factor for infection with domestically acquired fluoroquinolone-resistant strains. Infections with such strains were also associated with longer duration of diarrhea and increased likelihood of hospitalization.

Engberg et al documented the emergence of fluoroquinolone-resistant Campylobacter strains as a cause of human infection in 10 developed nations during the 1990s in relation to the approval of this class of antimicrobial drugs for use in veterinary practice. Most fluoroquinolone resistance is caused by spontaneous point mutations in the DNA gyrase A subunit region that alters the fluoroquinolone-binding site. Strains with this mutation have elevated minimum inhibitory concentrations. This trait confers selective advantage to the bacteria in the presence of fluoroquinolones.

Risk Factors for Human Illness

Poultry consumption—The initial epidemiologic studies of sporadic campylobacteriosis conducted in the United States and western Europe revealed robust associations with the handling and consumption of poultry and particularly the consumption of undercooked poultry. More recent epidemiologic studies in the United States, United Kingdom, and New Zealand confirmed the association between human campylobacteriosis and poultry consumption and added an additional nuance: an association between Campylobacter infection and eating commercially prepared poultry. These associations are not unexpected given data that most chicken in stores is contaminated with C. jejuni. Molecular subtyping studies demonstrate partial correspondence between poultry and human isolates. In Quebec, for example, 20% of genotypes from humans and poultry had matching pulsed-field gel electrophoresis patterns.

Consumption of other commercially prepared foods—As noted, case-control studies in the United States and nations of the British Commonwealth have revealed that eating chicken in restaurants is associated with increased risk of infection. On occasion, other foods prepared in restaurants or commercial kitchens (eg, tuna salad, sweet potatoes, and lettuce) have been implicated in outbreaks of campylobacteriosis. Cross-contamination during food preparation is typically suspected to be a contributory factor in such outbreaks, and studies clearly show that C. jejuni can survive on food contact surfaces and thereby cross-contaminate other foods.

Other food items—In addition to poultry, several types of meat have been epidemiologically implicated as sources of Campylobacter spp in developed nations. Some of these implicated food items include pork loins, barbecued foods, and liver pâté.

Unpasteurized milk—Drinking unpasteurized milk is a primary risk factor for outbreaks of campylobacteriosis.
sis. Between 1981 and 1990, 20 outbreaks of enteritis were reported in the United States. They occurred among children who drank unpasteurized milk on school field trips or other youth activities. Unlike sporadic Campylobacter infections, which peak during the summer and are also associated with exposures such as eating chicken, eating at restaurants, and international travel, milk-associated outbreaks have a bimodal seasonality, with peaks during the spring and fall corresponding to the peak seasons for youth activities such as school field trips. Despite regulatory efforts to address this hazard, unpasteurized milk-associated outbreaks continue to occur. Recently, molecular typing studies have linked outbreak-associated infectious strains with unpasteurized milk from implicated dairies.

Water—One of the first case-control studies of campylobacteriosis, which was conducted in Colorado, found an association between campylobacteriosis and the consumption of untreated surface water. More recently, a study conducted in England found that people with C. coli infection were more likely to report drinking bottled water than those with C. jejuni infection. In industrialized nations, waterborne outbreaks of campylobacteriosis typically involve lapses in community water sanitation.52,53

Zoonotic transmission—Case-control studies identify contact with pet dogs and cats, and especially juvenile or diarrheic pets, as risk factors for Campylobacter infection, accounting for perhaps 5% of campylobacteriosis in humans. The hazard of zoonotic transmission may be greatest for young children, an age group with high rates of infection. In 1 case report, a 3-week-old girl in a household with a recently acquired Labrador Retriever puppy developed C. jejuni bacteremia. Amplified fragment-length polymorphism analysis confirmed that the human and canine isolates were genetically similar. In an Australian case-control study, children < 3 years of age who lived in a home with a pet puppy had a 17-fold increase in risk of campylobacteriosis, compared with children with no puppy. Higher risk of campylobacteriosis in young children was also associated with ownership of pet chickens. Occupational risk factors for campylobacteriosis include farm residence, poultry occupation, and daily contact with chickens.

Foreign travel—Foreign travel is a commonly reported risk factor for campylobacteriosis. In Sweden, where Campylobacter contamination of poultry meat is uncommon, international travel has traditionally accounted for approximately 75% of human Campylobacter infections. In the United States, it is estimated that between 20 and 25% of Campylobacter infections are acquired during international travel. Campylobacteriosis was the most frequently reported enteric bacterial infection in Austrian tourists returning from southern Europe and Asia. In England, travel to South Africa was associated with C. coli infection.

Antimicrobial usage—In a Hawaiian case-control study, use of antimicrobials in the month prior to onset of illness was associated with campylobacteriosis, a unique finding in studies to date. One hypothesis for the observation is that antimicrobial usage lowers the infectious dose of drug-resistant C. jejuni strains. Another potential explanation is that the use of antimicrobials may alter colonic flora, resulting in decreased resistance to infection even with antimicrobial-susceptible C. jejuni strains.

Campylobacter Ecology
Survival in the environment—Campylobacter jejuni is adapted to the intestinal tract of warm-blooded animals and does not normally replicate outside this environmental niche. In humans, the infectious dose is reported to be < 1,000 Campylobacter organisms. Other adaptations to an intestinal niche include a single polar flagellum and corkscrew shape (Fig 1). These traits facilitate motility in the viscous intestinal mucus. Requirements for growth in the laboratory also reflect this narrow ecological niche: a microaerophilic nitrogen atmosphere with low oxygen (5 to 7%) and high carbon dioxide tension (7 to 13%). Optimal replication of C. jejuni occurs under conditions similar to those in the lower intestinal tract of mammals (eg, 37°C and pH 4.9). The bacterium is also sensitive to desiccation and osmotic stress (eg, NaCl concentrations > 2%).

The bacterium gradually dies outside the host intestinal tract. In 1 study, 58 of 83 (68%) C. jejuni strains could not be isolated from water after 3 weeks; however, a few strains were detected in unstirred water after 60 days. Environmental factors may facilitate Campylobacter survival under adverse conditions. Survival times are longer in nutrient-rich water than in deionized water. Similarly, biofilms are reported to facilitate the survival of C. jejuni in broiler houses. Some researchers postulate that campylobacters can survive in water in a viable but noncultivable form; however, the role of this dormant stage in the Campylobacter life cycle is controversial.

Animal Sources
Poultry—Although not all poultry flocks become colonized during the production cycle, C. jejuni is...
introduced into many broiler flocks during the production cycle. Horizontal transmission appears to play an important role in the natural history of *C. jejuni* in poultry operations. Risk factors for flock colonization include seasonality, caretakers who work with other animals, and drinking-water sanitation. Associations are also reported with type of air-handling system and degree of beetle infestation. Infections spread rapidly within flocks after introduction. Colonization typically occurs by 3 to 4 weeks of age. Although most campylobacters do not survive in in clean and disinfected houses, certain strains appear to persist in successive broiler flock rotations. Recent studies suggest that the crop is among the most frequently infected organs of broilers entering processing plants, with overall crop carriage rates on the order of 60%, similar to the frequency of contamination reported on broiler carcasses after processing.

**Cattle, sheep, and swine—Campylobacter species** often inhabit the bovine intestinal tract, particularly of calves. In a Swedish study, the overall prevalence of *C. jejuni* in calves during the first 3 months of life on large cow-calf farms was 39%. In a Danish study, 20 of 24 cattle herds were infected, and young animals had a higher prevalence than older animals. In 40% of infected herds, all *C. jejuni* isolates had the identical serotype and pulsed-field gel electrophoresis type. In a California study, prevalence of *Campylobacter* infection in a multiple-herd study of adult beef cattle was 5%. The number of adult cows on the farm was positively associated with the proportion that tested positive.

In a study of sheep raised around Lancaster, England, *C. jejuni* accounted for 90% of all campylobacters isolated from fecal specimens. Three hundred thirty of 360 (92%) sheep were intestinal carriers of campylobacters at the processing plant. Among pastured sheep, the lowest incidence of fecal shedding was seen in lowland pastured sheep (94 of 390 [24%]), and the highest rate of fecal shedding was seen in salt marsh pastured sheep (122 of 240 [51%]). The highest incidence of shedding (30 of 30 [100%] fecal specimens) coincided with spring lambing, movement of ewes onto pasture after weaning, and fall weaning. The lowest incidence (0 of 30 [0%]) occurred between November and March among sheep fed on hay or silage.

*Campylobacter coli* is the predominant *Campylobacter* sp of swine. In a study of fecal specimens from healthy Belgian swine, 61 of 65 (94%) *Campylobacter* isolates were *C. coli*. A Dutch study suggests that strict breeding management (eg, the use of high-efficiency particulate air filters and isolation of sows) can eliminate most *C. coli* in swine operations by breaking the chain of transmission from sows to piglets. These findings related to strict controls and may not be applicable to commercial swine industries.

**Wildlife**—The evidence that wildlife is an important reservoir for human *Campylobacter* infections is equivocal. To be a substantial source of human infection, feces from wildlife would need to enter the human food or water supply. Although some wild birds are colonized with *Campylobacter*, a Danish study of *C. jejuni* isolates indicated that the serotype distribution in wildlife was different from the distributions in broilers and humans. *Campylobacter jejuni* contamination rates in wild bird-associated specimens vary markedly—between 0 and 50% in a US study. The finding of *Campylobacter* in wildlife may also indicate contact with food animals. In a study from Japan, 3 of 13 *C. jejuni* isolates from sparrows were resistant to quinolone, suggesting that these sparrows acquired campylobacters from food animal populations.

**Food and Water Sources**

Retail meat and poultry—Surveillance programs to monitor retail foodborne hazards have been implemented in the United States. In 2002, FoodNet sites in the United States began routine retail food surveys to compare genotypic antimicrobial resistance patterns of campylobacters from human and food isolates. Ongoing surveillance will provide data for managing risks by type of retail meat and poultry product. In metropolitan Washington, DC, for example, 130 of 184 (71%) packages of chicken sold at retail outlets contained *C. jejuni* or *C. coli*, followed by 4% of 172 turkey packages and <2% of pork and beef packages. Another US study of more than 2,000 lamb carcasses from 6 large processing plants showed that <1% were contaminated with *C. jejuni* or *C. coli*. In an English study of nearly 500 retail specimens, chicken meat had the highest contamination rate (83%); however, the majority of lamb liver (73%), pork liver (72%), and beef liver (54%) was also contaminated. In that study, as expected, *C. jejuni* was the predominant *Campylobacter* sp isolated from chicken meat (77%), and *C. coli* was the predominant species isolated from pork liver (42%).

**Milk and water**—Surveys of bulk tank milk specimens indicate that unpasteurized milk is a source of *C. jejuni*. In a study conducted in Minnesota and South Dakota, approximately 10% of unpasteurized milk specimens from dairy bulk tanks was contaminated with *C. jejuni*. Surface waters are often contaminated with campylobacters. In a Norwegian study of 32 of 60 water specimens from the Bo River contained campylobacters; *C. coli* was detected more often than *C. jejuni*. In that study, fecal coliforms were not a reliable indicator of low-level *Campylobacter* contamination.

**Disease Prevention**

**On-farm controls**—Efforts to reduce pathogen loads at the farm increase the likelihood that pathogen reduction steps at processing plants and in the kitchen will increase the safety of foods of animal origin. Investigations to reduce broiler intestinal colonization have been most actively pursued in Western Europe. In 1 study, biosecurity measures reduced *Campylobacter* colonization rates in flocks by half. Reduction in colonization was associated with use of disinfectant footbaths, daily water disinfection, and the location of ventilation units in the poultry production room. In another study, cleaning and disinf-
fection, change of footwear at the entrance to broiler houses, and control of vermin were associated with substantially lower rates of Campylobacter colonization in broiler flocks.

Several studies have focused on interventions during broiler flock depopulation. In one study, lactic acid treatment of drinking water during the 8-hour preslaughter feed withdrawal period reduced carcass contamination by 15%. Other studies indicated that colonization rates increased when flocks were depopulated in batches rather than all at once. Transport crates brought to the farm at the time of depopulation also appear to expose birds to campylobacters.

Competitive exclusion products have also been proposed to reduce colonization levels. Various products containing defined poultry isolates of Campylobacter jejuni, Lactobacillus, and undefined cultures are reported to reduce colonization under experimental conditions. Diet may also alter intestinal carbohydrates that affect the colonization potential of campylobacters.

**Processing controls**—Carcass processing is a promising site for pathogen reduction efforts. The microbial quality of broiler carcasses has been associated with the abattoir where processing occurred. Treatment of wash water is a potential processing control to reduce contamination, and the microbial quality of poultry wash water is thought to contribute to higher contamination rates of poultry than red meat. In one study, the use of electrolyzed water for washing poultry carcasses resulted in a 3-log reduction of Campylobacter jejuni counts on chicken. In another study, washing poultry skin in 10% oleic acid significantly reduced the number of campylobacters that remained attached to poultry skin. Campylobacters are also sensitive to active chlorine. Chlorination of carcass wash water, an important component of the HACCP programs in processing plants, may have contributed to the decline in human campylobacteriosis in the United States since the mid-1990s.

Postprocessing interventions have also been investigated. Compared with refrigeration, freezing poultry carcasses to −20°C reduced Campylobacter counts by 2 logs. Electron beam irradiation of poultry would virtually eliminate campylobacters from poultry products; however, some consumers report that the color and texture of chicken fillets are altered by irradiation. It if these food-quality issues can be successfully resolved, irradiation of poultry products may become among the most important technologies for the prevention of foodborne campylobacteriosis in the United States.

**Food handling**—Veterinarians who specialize in food safety address hazards in the food chain from the farm to the consumer, including the promotion of safe food-handling practices. Surveys conducted in the United States indicate that safe food-handling skills could be improved in several demographic groups, including males and young adults. In addition, food handling is the last control point in the farm-to-table food safety continuum for preventing foodborne campylobacteriosis. One useful source of safe food-handling information is the Partnership for Food Safety Education Web site (www.fightbac.org). Studies indicate that restaurants and home kitchens are venues for the transmission of Campylobacter jejuni to humans.

Recommendations for kitchen sanitation emphasize cleaning and disinfection of food contact surfaces, hands, and utensils following contact with raw meat and poultry. In addition, raw meat and poultry should be stored separately from foods that will be served without subsequent cooking. Meat thermometers are recommended to measure the internal temperature of meat and poultry. Poultry should be heated to an internal temperature of 82°C (180°F) to kill campylobacters. Veterinarians are also in a unique position to discourage the public from selling or buying unpasteurized milk.

**Zoonosis prevention**—Handwashing after animal contact is a prudent step to prevent zoonotic transmission of campylobacters in household and occupational settings. Additional sanitary precautions are recommended with juvenile or diarrheic pets. It is particularly important to ensure that children wash their hands after animal contact. Working together, veterinarians and other health care providers can formulate a plan of hygienic precautions that will permit most immunocompromised patients to safely enjoy animal companionship.

**Conclusion**

It is humbling that a bacterium as sensitive to physiologic stress as Campylobacter jejuni remains a common cause of foodborne infection in the new millennium. Well-defined hazards for the transmission of campylobacters exist in the environment and food chain (Fig 2). Because no single intervention will eliminate all of these hazards, a combination of prevention efforts is needed related to animal contact—on farms, in processing plants, and in kitchens. When considering options for pathogen reduction, it is important to balance cost and effectiveness; however, cost should not be an excuse for inaction. If the veterinary profession takes an active leadership role, it is uniquely poised to contribute to reduction in the burden of human campylobacteriosis.


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