0031-3998/03/5501-0003
PEDIATRIC RESEARCH

Vol. 55, No. 1, 2004
Printed in U.S.A.

REVIEW

Enteric *Campylobacter*: Purging Its Secrets?

ELLEN CRUSHELL, SINEAD HARTY, FARHANA SHARIF, AND BILLY BOURKE

Children's Research Centre, Our Lady's Hospital for Sick Children, Department of Pediatrics, Conway Institute of Biomolecular and Biomedical Research and Dublin Molecular Medicine Center, Univeristy College Dublin, Dublin 12, Ireland.

ABSTRACT

Campylobacterial infections are the most common cause of bacterial enterocolitis in humans. Among children, especially in developing countries, *Campylobacter* infections can cause severe life-threatening diarrheal disease. Although usually associated with a benign outcome in the developed world, the burden of illness posed by *Campylobacter* infections is enormous, and serious neurologic sequelae also can occur. For a variety of reasons our understanding of the molecular and cellular pathogenesis of *Campylobacter* infection has lagged far behind that of other enteric pathogens. However, recent completion of the genome sequence of *Campylobacter jejuni* promises to open up the *Campylobacter* research field with the prospect of developing novel therapeutic and preventive strategies. **(*Pediatr Res* 55: 3–12, 2004)**

Abbreviations
GBS, Guillain-Barré syndrome
CDT, cytolethal distending toxin

After its successful isolation from stool in the 1970s, *Campylobacter jejuni* rapidly has become the most commonly recognized cause of bacterial gastroenteritis in humans. Fastidious culture requirements (1) and difficulties with early attempts at genetic modification have hampered progress in understanding this organism compared with other enteric pathogens such as *Escherichia coli* and *Salmonella* species. Currently, however, there is a renaissance of interest in *Campylobacter*. In particular, the 1.64 million nucleotides of the *C. jejuni* genome have been sequenced, providing an impetus for further research into this pathogen and its unique virulence and survival properties (2). Although *C. jejuni* is the best-studied member of the *Campylobacter* genus, there exists a number of other *Campylobacter* species of relevance to human disease. This review focuses on the current state of our understanding of human enteric campylobacters, with particular emphasis on the recent progress in molecular genetic and pathogenesis research in this area.

MICROBIOLOGY

Campylobacter (Greek "curved rod") organisms are Gram-negative, spiral, flagellated rods that have a characteristic rapid darting motility on microscopy. Campylobacters have fastidious culture requirements, and the routine culture of these organisms from stool has been developed relatively recently (1). Campylobacters are strictly microaerophilic, requiring 5 to 10% ambient oxygen, and do not grow in air. Some *Campylobacter* species including *C. jejuni* take up a coccal shape when exposed to atmospheric oxygen.

The family *Campylobacteraceae* (including *Campylobacter* and *Arcobacter*) continues to evolve. Fourteen *Campylobacter* species have been validated, and novel members continue to appear (3). *C. fetus,* the type species of the genus, is a common cause of abortion and infectious infertility among sheep and cattle, while rarely causing disease in humans. Traditionally, *C. jejuni* and *C. coli* are recognized as human enteropathogens. In addition, *C. upsaliensis* is now increasingly accepted as causing diarrheal disease, particularly in children (4–6).

HISTORIC PERSPECTIVES

Campylobacters are probably unique among enteric pathogens as almost a century elapsed between the first reports of the organism and the development of routine techniques for the culture of *Campylobacter* from stools. The earliest record of this organism dates back to 1886 when Escherich (7) described organisms resembling campylobacters ("vibrionen") in the intestinal contents from 16 of 17 children who had died of diarrheal disease. Thereafter, there appeared a number of arti-

Received January 17, 2003; accepted August 8, 2003.
Correspondence: Billy Bourke, M.D., FRCPI, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland; e-mail: billy.bourke@ucd.ie
DOI: 10.1203/01.PDR.0000099794.06260.71

cles in German describing "nonculturable" spiral bacteria in dysenteric disease (8). The first successful culture of *Campylobacter* was from ovine abortuses by McFadyean and Stockman in 1913 (9). In 1938 Levy (10) isolated *Campylobacter*-like organisms from the blood of 13 patients affected during a large milkborne outbreak of diarrheal disease in the United States. *Campylobacter* subsequently was cultured from the blood of three pregnant women in France in 1947 (11). King (12, 13) labeled these spiral bacteria "related vibrios" (because of their apparent similarity to *Vibrio cholera*) and described them in great detail. King recognized that the organism likely was more important as a cause of diarrhea of unknown etiology than previously was recognized.

Early isolates of *Campylobacter* were from blood and other normally sterile sites. Stool cultures were unsuccessful because of overgrowth of coliforms. As culture methods were refined, attempts to isolate the organism succeeded, and recognition of the importance of *C. jejuni* in diarrheal disease led rapidly to the introduction of routine methods for its isolation from stool (1, 14–16).

EPIDEMIOLOGY

In the United States, it is estimated that 2.4 million cases of campylobacteriosis occur annually. Although accounting for only 5% of estimated food-related deaths, campylobacters are responsible for approximately 17% of hospitalizations resulting from foodborne infections (17). The global economic burden of *Campylobacter* infections and *Campylobacter*-induced GBS is substantial. In the United States alone it has been estimated that human *Campylobacter* illnesses cost up to $8 billion annually (18). This figure likely represents an underestimate, as it does not include other indirect costs such as physical and psychological liability associated with *Campylobacter*-induced GBS.

In view of potential under-reporting, attempts have been made to estimate the true incidence of intestinal infections (19). In a recent community- and general practice–based study in the United Kingdom, it was found that for every isolate of *Campylobacter* reported to the National Surveillance Scheme, 7.6 were unreported. By extrapolating, it was estimated that the total number of cases of *C. jejuni* in 1999 in the United Kingdom was 450,000. This figure agrees closely with other community-based studies in both the United Kingdom and United States that estimate a population-based incidence of approximately 1% (20, 21).

The incidence of *Campylobacter* infection among children is age related with a higher incidence among younger children in the developing world whereas in industrialized countries the incidence is highest in older children. In a study of American children *Campylobacter* was isolated in 4.8% and 8.3% of diarrheal stools in those aged 1–4 y and 10–19 y, respectively (21). In developing countries, *Campylobacter* infection is hyperendemic owing to poor sanitation and close contact with animals in the home (22–24). In these countries, *C. jejuni* infection is very common in early childhood, with five to 10 separate infections commonly occurring in the first 2 y of life (25–27). For example, in a report from Tanzania, 22% of stool samples from children aged <18 mo with diarrhea grew *Campylobacter* (23), whereas in an Egyptian cohort, children younger than 3 y had an incidence of 0.6 episodes of *Campylobacter* diarrhea per year (28). By late childhood, however, few symptomatic infections occur, a decline that correlates with the appearance of specific serum IgA antibodies to *C. jejuni* (29).

Although *Campylobacter* enteritis generally is considered a benign self-limiting disease, there is significant morbidity and mortality, even in developed countries. A recent report from the U.S. Centers for Disease Control and Prevention estimates *Campylobacter* infection causes 124 deaths annually in the United States (17). Mortality rates in developing countries are much higher; 13% of *Campylobacter* enteritis in Egyptian children younger than 3 y is characterized by severe dehydration (28). The mortality risk from infection is highest at the extremes of age and in those with an underlying disease process.

TRAVELERS' DIARRHEA

Campylobacters are a leading cause of travelers' diarrhea (30, 31). For example, Petruccelli *et al.* (32) found *Campylobacter* in 41% of stools from military personnel with travelers' diarrhea. The prevalence of *Campylobacter*-associated travelers' diarrhea shows seasonal variation. For example, Mattila *et al.* (33) implicated *C. jejuni* in 30% of diarrheal episodes among Finnish travelers to Morocco during winter, whereas 7% of cases were ascribed to this organism during autumn. Similarly, *C. jejuni* enteritis among American students in Mexico is commoner in winter (34). The clinical symptoms of *C. jejuni* appear to be determined by the country of origin of the traveler, suggesting that the expression of the illness may relate to prior exposure and immunity rather than to local strains of the bacteria (35).

RESERVOIRS AND TRANSMISSION OF INFECTION

Campylobacter enterocolitis is considered to be a zoonosis. Enteric campylobacters are regarded as normal flora in many mammals and birds. The ability of these bacteria to grow at 42°C likely reflects their adaptation to the avian gut. *Campylobacter* appears to permanently colonize the gastrointestinal tract of birds with few noticeable ill effects and only occasionally is diarrhea observed with *Campylobacter* infection in young animals (36). Shedding of campylobacters by birds [very high *Campylobacter* carriage rates have been reported among geese and ducks (37, 38), among others] causes contamination of waterways, and, as campylobacters can survive in water for weeks, open waters may then act as a source of infection for domestic animals.

Although waterborne and milkborne outbreaks of human *C. jejuni* infection may occur (39–42), *Campylobacter* infections in humans are usually sporadic. Raw milk and poultry are the main sources of *Campylobacter* entering the food chain. Up to 6% of bulked raw milk samples in the United Kingdom yield campylobacters (43). Cross-contamination of milk occurs from feces during milking or from *Campylobacter* mastitis (44, 45), and failed pasteurization also has been associated with out-

breaks of infection (41, 46, 47). Studies have shown very high rates of *Campylobacter* contamination among supermarket chickens (48). Liver and offal from other species also may harbor *Campylobacter,* whereas contamination of red meat is much less frequent (49, 50). Although traditional cooking methods kill *Campylobacter,* these organisms may survive fondue and barbecue cooking (51).

Direct transmission from animals accounts for a minority of human infections occurring mainly among people who work in close contact with animals or their products (52). *Campylobacter* carriage is common among asymptomatic dogs and cats. However, prevalence rates are very variable, being highest among immature animals (up to 50% in some studies) that are strays or living in kennels and lowest (<2%) among adult animals living in households. Animal-to-human transmission of *C. jejuni* has been validated by the finding of genotypically identical strains in a household pet and an infant with sepsis (53). Zoonotic infection with *Campylobacter* usually occurs in young children who have had close contact with puppies or kittens with diarrhea. Having a household pet with diarrhea and daily contact with a dog has been estimated to increase substantially the risk of becoming ill with *Campylobacter* compared with unexposed controls (54). In addition, dogs and cats may be important sources of infection with *Campylobacter* species other than *C. jejuni* (51), for example, *C. upsaliensis* is particularly common among these household animals (55–57).

It appears that the risk of direct transmission of *Campylobacter* from person-to-person is low, and secondary cases in outbreaks are not common. However, infants born to mothers who are excreting campylobacters are at risk of infection at the time of birth, usually resulting in self-limiting neonatal enteritis associated with bloody diarrhea (58, 59). There also have been outbreaks of campylobacteriosis in neonatal units; vehicles including communally used rectal thermometers and asymptomatic person-to-person spread have been implicated (60, 61).

PATHOGENESIS

Campylobacter *in the postgenomic era.* Adhesion, invasion, toxin production, and subversion of host cell processes are themes common to the virulence machinery of many enteric prokaryotic pathogens (Table 1). Our understanding of the roles of these virulence processes in *Campylobacter* pathogenesis is relatively poorly developed compared with other enteric pathogens. Potential reasons underlying this relative paucity of understanding of *Campylobacter* pathogenesis include initial difficulties at molecular genetic manipulations, interstrain variability in virulence, and lack of an effective animal model of human enteric infection. However, there now appears to be a renewal of interest in *Campylobacter* infections, resulting in novel and important insights into basic research on these organisms and the attraction of new investigators to the field.

In a landmark paper, Parkhill *et al.* (2) recently described the completion of the *C. jejuni* NCTC11168 genome sequence. It would be difficult to overemphasise the importance of the completion and deposition in the public domain of this 1.6-megabase sequence. In the first instance, availability of the genome has provided immediate clarification of a number of previously unresolved questions and contentious issues surrounding *Campylobacter* research. For example, there are no pilus structures encoded on the chromosome, and the only toxin genes identifiable are the *cdt* genes (2). In addition, a number of unexpected findings from the completed *C. jejuni* sequence have prompted research endeavors in novel directions. In particular, the identification of a substantial number of homopolymeric tracts indicates the potential importance of slipped-strand mispairing and consequent phase variation to the virulence and survival of this organism (62).

Table 1. *Campylobacter* virulence factors

Host factors
Cytoskeletal rearrangement
Microtubules
Microfilaments
Tyrosine phosphorylation
IL-8 induction
Apoptosis
Bacterial factors
Motility/chemotaxis
Adhesion
PEB1
CadF
JlpA
MOMP
LOS
CPS
Flagellin
Invasion
Flagellum
pVIR (type IV secretion apparatus)
Cytolethal distending toxin
Secreted effector proteins (CIA proteins)

See text for discussion of individual virulence factors.

MOMP, major outer membrane protein; LOS, lipooligosaccharide; CPS, capsular polysaccharide.

Flagella. The flagella of *C. jejuni* are composed of proteins, *FlaA* and *FlaB*, encoded by two genes sharing a high degree of sequence homology (63). Disruptions in *FlaA*, in particular, reduce motility and markedly reduce the ability of the organism to colonize the gastrointestinal tract (63). However, flagella are also important for invasion of (and to a lesser extent adherence to) host cells, as aflagellate organisms show markedly reduced internalization into host cells *in vitro* (63).

Invasion. *C. jejuni* has been shown within human colonic epithelial cells taken both from infected humans and macaque monkeys (64). In addition, the invasiveness of this organism has been studied in a variety of cell lines, in particular human intestine-derived Caco-2 and INT 407 cells (64, 65). Although some isolates of *C. jejuni,* such as the well characterized 81–176 strain, are highly invasive in these experimental models, many isolates show low levels of host cell entry *in vitro* (65). It has been suggested that campylobacters may not efficiently enter the host cell via the apical membrane, and recent evidence supports the contention that *C. jejuni* preferentially enters polarized epithelial cells via the basolateral membrane (66). In support of this model, there exists evidence both for paracellular passage (66) and M-cell transcytosis (64, 65) of *C. jejuni.*

Many invasive pathogens subvert host cytoskeletal structures as part of the pathogenic process. The highly invasive *C. jejuni* 81–176 demonstrates microtubule-dependent invasion, and also appears to rely on microtubule motors for uptake and intracellular motility (62, 67) (Fig. 1). Nonetheless, most strains of *C. jejuni* demonstrate microfilament-dependent or

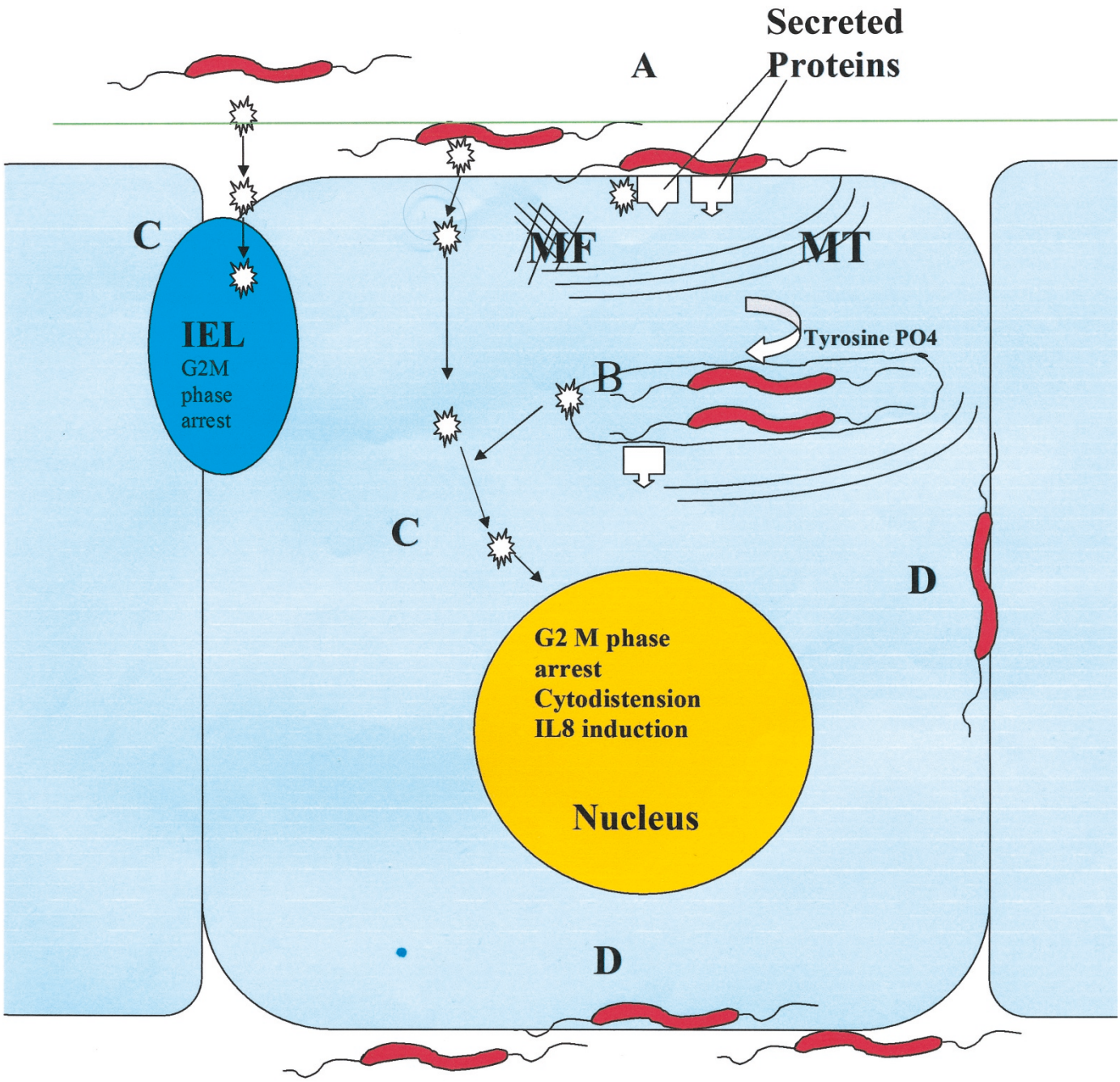

Figure 1. A speculative model of *C. jejuni* interaction with host intestinal epithelial cells is presented. *A,* after access to, and motility within, the mucus layer, *C. jejuni* organisms attach to the apical surface of host intestinal cells. Current evidence suggests that the attachment process is mediated via a number of adhesin-receptor interactions. Putative adhesins include major outer membrane protein (*MOMP*), lipooligosacharride, capsular polysacharride, CadF, JlpA, and PEB1 (see text). *C. jejuni* is one of only a handful of bacteria that appear to subvert host microtubule structures to gain entry to and move within host cells. Bacterial secreted proteins may be involved in recruiting host cell structures, including microtubules (*MT*), microtubule motors (*e.g.* dynein), and microfilaments (*MF*), as well as inducing host cell protein tyrosine phosphorylation or activation of trimeric G proteins to effect bacterial entry to the cell and possible subsequent intracytoplasmic motility. *B,* bacteria appear to survive and replicate, at least to some extent, within intracytoplasmic vacuoles. How bacteria achieve access to adjacent cells is unknown. *C,* CDT has DNase activity (mediated by CdtB). It may act directly on enterocytes to induce host cell cycle arrest, distension, and proinflammatory cytokine induction. Alternatively (or in addition), CDT may act on immune cells, such as intraepithelial lymphocytes (*IEL*), to cause cell cycle arrest. Whether CDT accesses cells after release from bacteria before cell contact, at the time of attachment, or after internalization is unknown. *D,* there also exist data to support paracellular migration of bacteria, possibly through disrupted tight junctions, or M-cell transcytosis with access of bacteria to the basolateral mebrane of the enterocytes (66). MT, microtubules; MF, microfilaments; IEL, intraepithelial lymphocytes. ☼, cytolethal distending toxin (B subunit) 🗩, secreted effector proteins including CiaB.

microfilament/microtubule-dependent invasiveness (68). Little is known of the invasiveness of other enteric campylobacters. However, a recent report implicates both of these cytoskeletal structures during cellular uptake of *C. upsaliensis* (69).

Adhesion. A variety of putative *C. jejuni* adhesions have been identified. These include PEB1 (a homolog of Gram-negative ABC transport systems) (70), CadF (a fibronectin-binding protein) (71), major outer membrane protein (72), and lipooligosaccharide (73). Recently, a novel surface-exposed lipoprotein specific to *C. jejuni* has been implicated in host cell adherence (74). As with other aspects of *Campylobacter* virulence, determining the precise contribution of these potential virulence factors to human disease has been frustrated by the lack of a suitable and widely accessible animal model of infection. However, from available data, it would appear that adherence of *C. jejuni* to host cells is a multistep process, involving both specific and nonspecific adhesin-receptor interactions. Intriguingly, the *C. jejuni* genome sequence has identified the presence in this organism of capsular polysaccharide biosynthesis genes. This heretofore unrecognized structure is common among *C. jejuni* strains, and appears to form the basis of the Penner serotyping system for this species (75). Recent publications also suggest a role for this polysaccharide structure in virulence (75, 76), and the presence of hypervariable genes within the locus with the potential for phase variation (77) is notable in this respect.

Toxin production. Historically, a variety of toxic activities have been attributed to *C. jejuni*. This subject has been extensively reviewed elsewhere (78). However, CDT is the only verified *Campylobacter* toxin identified to date, a situation unlikely to change unless one or more of the open reading frames of unknown function encoded on the genomic sequence (or on an extrachromasomal element) are shown to encode a toxin-inducing protein. Work on CDT from campylobacters and other organisms recently has led to a rapid advancement in our understanding of the cellular effects of these proteins *in vitro* (75–85). It is now clear that CdtB is the active moiety of the Cdt ABC complex. The *cdtB* gene product has DNase activity (86). It appears that CdtA and CdtC interact with CdtB to form a tripartite CDT holotoxin necessary for the delivery of the enzymatically active subunit, CdtB (86). Affected epithelial cells undergo cytodistension and cell cycle arrest in G_2/M phase (79, 84). Cell cycle arrest also occurs in T lymphocytes exposed to CDT-mediating sonicates from *C. upsaliensis* (83). It is not yet clear what role CDT plays in infection *in vivo*. However, it may contribute more to immune-modulation and invasiveness (81) than directly to inducing diarrhea.

Secreted proteins and chemokine induction. Subversion of host cell processes by targeting bacterial products to host cytoplasm during the infection process is an increasingly recognized prokaryotic virulence mechanism. Using confocal microscopy, Konkel *et al.* (87) have identified a *C. jejuni* protein, CiaB, that appears to enter host cells during the invasion process. Isogenic *ciaB*-negative mutants were shown to be deficient in secretion of a number of bacterial proteins. The genome of *C. jejuni* 11168 encodes a flagellar export system. However, there is no evidence for the presence of a typical type III secretory apparatus—the so-called molecular syringe—implicated in delivering bacterial proteins to the host cell in other infections. Recently, homologs of a type IV secretory apparatus have been identified on a large plasmid (pVir) in *C. jejuni* 81–176 (88). Type IV systems, for example the *cag* pathogenicity island of *H. pylori,* also are used by bacterial pathogens to inject substrates into the cytosol of target cells. *C. jejuni* pVir is a 37-kb plasmid that has been shown to harbor 54 predicted open reading frames (89). Mutations in some of the plasmid-encoded genes reduced invasion compared with the parental strain *in vitro*. However, transfer of the plasmid to the sequenced strain, NCTC 11168, did not increase the relatively low invasiveness of this isolate. Clearly, with only 10% of 58 fresh clinical *C. jejuni* isolates harboring the plasmid-encoded *VirB11* gene (88), pVir is not responsible for all *C. jejuni*-induced pathogenic effects.

C. jejuni enterocolitis involves activation of the local immune response. IL-8 is a potent chemokine involved in, among other things, neutrophil attraction. IL-8 can be induced by *C. jejuni* (85). Current evidence implicates both direct interaction of *C. jejuni* with host cells and CDT elaboration in the induction of IL-8 (82, 85). It appears that uptake of bacteria into host cells is required for high levels of IL-8 induction *in vitro*.

It is apparent that there has been a rapid expansion in our understanding of *C. jejuni* pathogenesis (Fig. 1). Recently, successful and efficient transposon mutagenesis (90, 91) has breached one of the early barriers to the explication of *C. jejuni* molecular pathogenesis. Together with the genomic sequence, which will provide the cornerstone for powerful novel techniques such as microarray and protein expression methodologies, these developments herald a renaissance period for *Campylobacter* research that can be expected to continue for some time.

CLINICAL MANIFESTATIONS

Gastrointestinal. The clinical presentation of patients with *C. jejuni* infection differs between developing and industrialized countries. Variations in bacterial virulence or host immune response each may play a role in these different phenotypic expressions of disease (35). In the developing world, infection can be asymptomatic or there may be mild noninflammatory diarrhea, predominantly affecting young children (23, 27). In the industrialized world, the commonest illness caused by *C. jejuni* infection is a self-limiting gastrointestinal illness. Affected individuals experience varying degrees of diarrhea, which may range from a few loose stools to profuse watery diarrhea causing dehydration. Often, although probably not as frequently as previously thought (42), the stools are bloody and may contain mucus or pus. The diarrhea is accompanied by crampy abdominal pain that usually begins within 1–5 d of exposure (42). Systemic upset is common with fever [and febrile convulsions in vulnerable children (92)], malaise, and headache. These symptoms sometimes precede the onset of abdominal symptoms. Vomiting also may occur. Symptoms usually resolve within a week. The convalescent excretion of the organism lasts a mean of 16 d. Infants excrete the organisms for longer than older children (mean, 14 d in infants *versus* 8 d in 1- to 5-y-olds) (27). Carriage may be prolonged

with 4% of untreated children continuing to excrete the organism for 6 wk (93). Relapse occurs in up to 20% of patients, but symptoms are usually milder than in the original illness.

Recent evidence suggests a much higher incidence of irritable bowel syndrome among patients after an episode of *Campylobacter* enteritis than in patients without an antecedent history of enteric infection (94). *Campylobacter* also occasionally has been implicated as the cause of nonenteric gastrointestinal disease, as illustrated in Table 2. However, most of these complications are very uncommon or have been reported in adults with a contributing underlying disease process. Infection with enteric campylobacters, other than *C. jejuni* (*C. coli* and *C. upsaliensis*), results in a similar disease spectrum to that caused by *C. jejuni*. However, watery diarrhea appears to be more commonly associated with *C. upsaliensis* infection than is inflammatory diarrhea (4, 95).

Host response. After ingestion of campylobacters, colonization of the mucous blanket and adhesion to the intestinal cell surface occurs. The normal absorptive function of the intestinal cell is disrupted directly by cell invasion and toxin production and indirectly after the initiation of an inflammatory response. The clinical presentation is dependent on many factors, including possible variations in virulence among *C. jejuni* bacteria (96) and also the extent and nature of the host response, which will determine the degree to which the intestinal epithelium is damaged and the amount of fluid secreted. The host response appears to be largely determined by immunity acquired through prior infection. Infection of adult volunteers with *C. jejuni* produced an inflammatory illness with a serum antibody response (97). When these volunteers were rechallenged with the same strain, they were protected from illness but not from colonization (97). In developing countries recurrent early infections with *Campylobacter* strains leads to progressive immunity (with an age-related rise in specific immunoglobulins), which results in successively milder symptoms with each infection (26, 29, 30).

Table 2. *Spectrum of disease caused by* Campylobacter *spp.*

Gastrointestinal
Enteritis
Toxic megacolon and perforation
Hepatitis
Pancreatitis
Cholecystitis
Gastric ulceration
Peritonitis
Splenic rupture
Rheumatologic
Reactive arthritis
Reiters syndrome
Septic arthritis
Vertebral osteomyelitis
Henoch-Schönlein purpura
Neurologic
Guillain-Barré syndrome
Meningitis
Meningoencephalitis
Skin
Cellulitis
Skin eruption
Abscess
Lung
Empyema
Pneumonia
Intravascular
Bacteremia
Septic shock
Endocarditis
Thrombophlebitis
Hemolytic uremic syndrome
Aneurysm

Immunocompromised hosts. Immunocompromised patients may have a severe, prolonged, or relapsing illness with extraintestinal manifestations, and accompanying bacteremia is more frequent (98–100). In patients with immunoglobulin deficiencies, the organism can take years to eradicate (101), indicating that the humoral immune response is important in combating these infections. The incidence of *Campylobacter* infection is 40–100 times greater in persons with AIDS than in the background population (102), and non-*C. jejuni* species are found in this group (103). In a study from Spain the incidence of *Campylobacter* bacteremia among AIDS patients was 0.8% (99). Bacteremia was associated with low $CD4^+$ lymphocyte counts and normal neutrophil counts. In patients with advanced HIV or AIDS, bacteremia is persistent or recurrent, despite appropriate antimicrobial treatment. Occurrence of *Campylobacter* infections in AIDS patients may herald a marked deterioration in immune status and limited patient survival (102).

Extraintestinal diseases and GBS. *C. jejuni* causes abortion and premature birth in humans. Maternal *C. jejuni* bacteremia is associated with fetoplacental involvement, resulting in premature labor, perinatal sepsis, and neonatal meningitis. Fetal and neonatal mortality rate may be as high as 80%, particularly if infection occurs before the third trimester of pregnancy (104, 105). Other extraintestinal manifestations (Table 2) are rare.

Longer-term sequelae of *C. jejuni* include reactive arthritis, commonly affecting the knee and other peripheral joints, and Reiters syndrome, comprising the triad of asymmetric arthritis, urethritis, and ophthalmitis in HLA B-27–positive patients (106). GBS, an acute progressive neuropathy characterized by paralysis, pain, muscular weakness, and distal sensory loss, is a more sinister complication of *Campylobacter* enteritis. With the marked reduction in incidence of poliomyelitis, GBS is now the leading cause of acute flaccid paralysis in the world and is thought to occur in 1 in 1000 cases of *C. jejuni* enteritis (107). *C. jejuni* is the most common antecedent of GBS (108–110); serologic and culture evidence indicates that 30 to 40% of patients with GBS have had infection with *C. jejuni* between 10 d and 2 wk before the onset of neurologic symptoms. A seasonal epidemic form of GBS termed acute motor axonal neuropathy is observed mainly in northern China and is particularly associated with evidence of antecedent *C. jejuni* infection (111, 112).

A detailed review of the immunopathogenesis of GBS is beyond the scope of this review. The reader is referred to a recent extensive review by Hadden and Gregson (113). However, current evidence suggests that both host and bacterial factors contribute to the development of GBS after *C. jejuni* infection. Several observations point to microorganism-related

factors. In Japan 52 to 77% of patients with *C. jejuni*-associated GBS were shown to have Penner serotype O:19, an unusual strain among enteritis isolates (accounting for approximately 3% of *C. jejuni* enteritis) (114–116). In South Africa, 9 (53%) of 17 children admitted to an intensive care unit with GBS had evidence of *C. jejuni* infection and all isolates were Penner serotype 0:41. This particular serotype was isolated from only 12 (including the nine GBS isolates) of 7119 isolates (<0.002%) of *C. jejuni* in that laboratory during the same time period, thus supporting a causal relationship between rare variants of this organism and GBS (117, 118). Interestingly, these findings have not been reproduced in U.K. studies, implying that the GBS-inducing properties of *C. jejuni* may not be solely related to Penner serotype (110).

Miller-Fisher syndrome, a variant of GBS characterized by ophthalmoplegia, ataxia, and areflexia, also is associated with *C. jejuni*. During the acute phase of this illness, IgG antibodies to GQ1b ganglioside (a ganglioside found abundantly in ocular motor nerves) are present in 90% of Miller-Fisher syndrome patients, implicating antigenic mimicry between *C. jejuni* and myelin sheath epitopes in the pathogenesis of this less common neuropathy (119).

Management. As *C. jejuni* infection usually is self-limited, in most cases there is no rationale for antimicrobial treatment. Management is usually supportive with administration of fluid and electrolyte therapy, when necessary. There is evidence to suggest that erythromycin or azithromycin given early in the course of the infection shortens the duration of illness and prevents relapse (93). With these treatments, the organism usually is eradicated from the stool within 2 or 3 d. The recommended duration of treatment is 5 to 7 d. Bacteremic strains of *Campylobacter* are usually sensitive to aminoglycosides, meropenem, and imipenem. Antimicrobial treatment should be considered in children with immunodeficiencies, in severe cases with much bloody diarrhea, and when the infection is ongoing after 1 wk (120).

Antibiotic resistance among *C. jejuni* has become a serious worldwide problem. Ciprofloxacin has been commonly used to treat *Campylobacter* infections. However, fluoroquinolones have become less effective as resistance has increased dramatically (121). Quinolone resistance is thought to have emerged because of the widespread use of this class of antibiotics on poultry farms in Europe and the United States (122, 123). The link to animal agriculture was first demonstrated in Holland by Endtz *et al.* (122), where the prevalence of quinolone resistance rates among isolates from poultry products increased from 0 to 14% between 1982 and 1989, coinciding with the increasing use of fluoroquinolones in veterinary medicine. During the same time frame, resistant human isolates increased from 0 to 11%. Similarly, Smith *et al.* (123) demonstrated a significant increase in quinolone resistance among human *Campylobacter* isolates between 1996 and 1998 that was temporally associated with the licensure of fluoroquinolones for use in poultry in the United States. Conversely, quinolone resistance is not a problem in Australia, where these antibiotics have been prohibited from use in food-producing animals. In contrast, erythromycin resistance rates remain low among human isolates (<5%) (124–126), and erythromycin is the antibiotic of choice for the treatment of *Campylobacter* gastroenteritis (123, 124). To date, ciprofloxacin has been commonly used for traveler's diarrhea, although Sanders *et al.* (127) found *in vitro* resistance to quinolones in 96% of *Campylobacter* isolates from U.S. military personnel in Thailand, thereby highlighting the problem with empiric treatment in areas with high quinolone resistance rates.

For patients with GBS, referral to a tertiary center may be necessary, as a proportion of patients will need ventilatory assistance and plasmapheresis. Multiple stool samples (or rectal swabs) at the time of presentation are necessary if antecedent *C. jejuni* is to be detected (114). Serologic studies may also be necessary as the median onset of neuropathic symptoms is 9 d after the onset of diarrhea (110). Treatment studies have shown that both plasma exchange (128) and i.v. immunoglobulin (129, 130) significantly reduce the duration of GBS.

PREVENTION

As the primary source of *Campylobacter* infection in humans is foodstuffs, particularly poultry, prevention should be aimed at reducing the infection level among poultry houses. Biosecurity measures on poultry farms have improved, with increased usage of disinfectant foot dips and hygiene barriers at the entrances to poultry houses. However, once *Campylobacter* infection enters a poultry house, all birds become carriers very quickly (131).

The high levels of campylobacters on chicken carcasses can be reduced effectively by irradiation; however, there is public resistance to this method of disinfection. In the kitchen, cross-contamination of *Campylobacter* from chicken carcasses occurs rapidly and widely (49). Hot water and detergent have been shown to remove *Campylobacter* from kitchen surfaces (132). In addition, the use of chlorine-based disinfectant significantly reduces kitchen surface contamination rates with *Campylobacter* when compared with hot water and detergent or no cleaning (133). Adequate cooking of poultry meat is essential, and fondue and barbecuing may not be sufficient to kill the campylobacters. Public education programs are important in the prevention of infection acquired through poor hygiene and food preparation techniques. However, a recent insightful commentary on the area clearly points to substantial deficits in our understanding of the risk to human health posed by domestic *Campylobacter* contamination levels (49).

Human milk contains secretory IgA antibodies to a *Campylobacter* antigen and breastfed infants are less likely to develop *Campylobacter*-associated diarrhea than their nonbreast-fed counterparts (92). The development of a vaccine against *Campylobacter* has been hindered because until recently there was a lack of understanding of the basic virulence mechanisms and antigenic complexity of these organisms and also because of the theoretical risk of triggering GBS. Nonetheless, an oral, killed, whole-cell vaccine has been shown to be safe and effective in animal studies (134).

CONCLUSIONS

Campylobacters are major causes of human disease worldwide. A new era of *Campylobacter* research has been heralded

by the recent completion of the genomic sequence of *C. jejuni,* and substantial progress now has been made in our understanding of how these organisms mediate disease in humans. Transcriptomics, proteomics, and efficient mass mutagenesis techniques are set to rapidly expand our knowledge of the molecular and cellular microbiology of *Campylobacter* infection. There is a pressing need for the development of easily accessible, reproducible, and biologically relevant models of enteric and neurologic diseases caused by these organisms so that we may devise effective therapeutic and preventive strategies against human *Campylobacter* infection and its consequences.

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