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Campylobacter and *Arcobacter* 16

The *Campylobacteraceae* family consists of three genera, *Campylobacter*, *Arcobacter*, and *Helicobacter*. The members of the genus *Campylobacter* and *Arcobacter* were initially recognized as commensals in birds and domestic mammals and had veterinary importance causing abortion in animals. However, in recent years, these pathogens are increasingly implicated in foodborne outbreaks and are considered significant zoonotic pathogens. *Campylobacter* causes enteritis, bacteremia, endocarditis, and periodontal diseases in humans and animals, and the infection often leads to chronic sequelae, such as Miller Fisher syndrome, reactive arthritis, and Guillain–Barré syndrome in humans. *Arcobacter* has been identified relatively recently to cause diarrhea in humans and abortion in animals. *Helicobacter pylori* is a human pathogen, which can be carried asymptomatically in humans for decades. In 1982, two Australian physicians, Barry J. Marshall and J. Robin Warren, discovered *Helicobacter* in the human stomach to be related to the genus *Campylobacter*. Later, they reclassified the organism as *Helicobacter pylori* and demonstrated it to be responsible for gastritis and peptic ulcer. Both scientists won the Nobel Prize in Physiology and Medicine in 2005. Characteristics of three genera are summarized in Table 16.1.

Campylobacter

Introduction

Campylobacter means "curved rod" in Greek, and the bacterium was discovered in the late nineteenth century (1886) by Theodor Escherich, a German–Austrian pediatrician. He isolated the bacterium from an infant who died of cholera, and he called the disease "cholera infantum." Later in 1913, McFayden and Stockman identified an organism from an aborted sheep and called it *Vibrio fetus*, which is renamed as *Campylobacter fetus*. Since then *Campylobacter* is considered a significant animal pathogen. In 1972, Dekyser and Butzler in Belgium isolated a *Campylobacter* strain from the blood and feces of a woman who suffered from hemorrhagic enteritis. The development of selective growth media in the 1970s permitted more laboratories to test stool specimens for the presence of *Campylobacter*. Soon *Campylobacter* spp. were established as common human pathogens. In the last 40 years, *Campylobacter* has been recognized as a leading pathogen causing diseases in both animals and humans and considered a zoonotic pathogen. Human campylobacteriosis disease may vary from mild, noninflammatory,

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Table 16.1 Classification of the *Campylobacteraceae* family based on biochemical properties

Characteristics	*Arcobacter*	*Campylobacter*	*Helicobacter*
Aerobic growth at 25 °C	+	−	−
Catalase	+	+ (*C. concisus* and *C. upsaliensis* are negative)	+
Oxidase	+	+	+
Urease	−	− (*C. lari* is positive)	− (*H. pylori* is positive)

Adapted from Lehner et al. (2005). Int. J. Food Microbiol. 102, 127–135

self-limiting diarrhea to severe, inflammatory, bloody diarrhea lasting for several weeks. In some cases, the disease may progress to the development of immunoreactive arthritis and peripheral neuropathies, such as Guillain–Barrè syndrome and Miller Fisher syndrome.

Campylobacter is involved in 400–500 million illnesses annually worldwide. In developing countries, *Campylobacter* infection is often limited to the children and culminates into watery diarrhea. In industrialized countries, *Campylobacter* is the most reported bacterium associated with an acute inflammatory enteric infection. *Campylobacter jejuni* infection is now the leading cause of bacterial gastroenteritis reported in the USA. The Centers for Disease Control and Prevention (CDC) reports that between 1999 and 2008, *Campylobacter* was responsible for 4936 outbreaks in the USA. It is now estimated that the *Campylobacter*-related infection is the highest among all the foodborne bacterial infections in the USA with an estimated 1.9 million cases per year, and many of these cases are associated with consumption of chicken products. Approximately 95% of these human infections are caused by *C. jejuni* or *C. coli*. Immunocompromised individuals are at the highest risk of infection, and the infection is 40–100% more common in the AIDS (acquired immunodeficiency syndrome) patients than in the immunocompetent individuals.

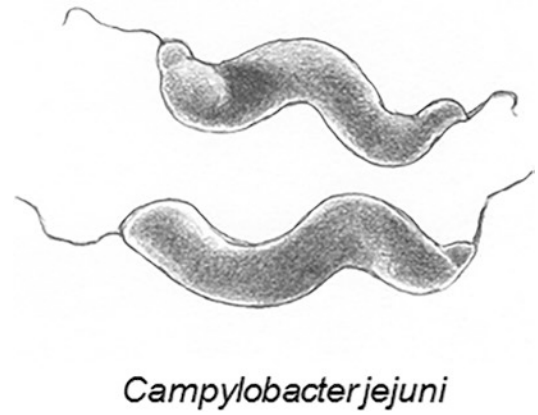

Fig. 16.1 *Campylobacter jejuni* cells with characteristic curved shape and polar flagella

Biology

Campylobacter species are Gram-negative, non-spore-forming, curved, S-shaped, or spiral–helical rods with approximately 0.5–5.0 μm in length (Fig. 16.1). Bacteria also express capsules, which primarily consist of 6-methyl-D-glycero-α-L-glucoheptose, β-D-glucuronic acid modified with 2-amino-2-deoxyglycerol, β-D-Gal*f*NAc, and β-D-ribose. The capsule and the outer membrane also contain lipooligosaccharides (LOS) which are composed of a core oligosaccharide and lipid A. Most *Campylobacter* species display a single polar flagellum at one end or both ends and exhibit corkscrew-like motility, except *Campylobacter gracilis*, which is nonmotile. Flagella are also important virulence factor. In older cultures, the bacterium may actually appear as spherical or coccoid bodies, which correspond to a dormant, viable but nonculturable (VBNC) state. These highly successful foodborne pathogens are actually quite fastidious and have a stringent set of growth requirements. *Campylobacter* is microaerophilic that requires oxygen concentrations of 3–5% and carbon dioxide of 3–10% and have a respiratory type of metabolism. However, several species, including *C. concisus*, *C. curvus*, *C. rectus*, *C. mucosalis*, *C. showae*, and *C. gracilis*, require hydrogen or formate as an electron donor for microaerobic growth. Some *Campylobacter* spp. such as *C. coli*, *C. jejuni*,

C. upsaliensis, and *C. lari* are thermophiles and grow at 37–42 °C and optimally at 42 °C and will not grow below 30 °C. The non-thermophilic *Campylobacter* spp. include *C. concisus*, *C. curvus*, and *C. fetus*. Growth is further limited by the osmotic stress (2% NaCl concentration), desiccation, and pH less than 4.9. *Campylobacter* utilizes amino acids instead of carbohydrates for energy and is resistant to bile. The genome of *C. jejuni* is relatively small, 1.6–1.9 Mbp, indicating the presence of fewer genes compared to other bacterial pathogens, thus reflecting its requirement for complex growth media. Some strains of *C. jejuni* carry a plasmid, pVir, which encodes genes for type IV secretion system (T4SS), and the effector proteins may have a role in the host cell invasion and pathogenicity.

Classification

The *Campylobacteraceae* family belongs to the order *Campylobacterales*, the class *Epsilonproteobacteria*, and the phylum *Proteobacteria*. The *Campylobacteraceae* family consists of three genera: *Campylobacter*, *Arcobacter*, and *Helicobacter*. The genus *Campylobacter* contains 26 species and 9 subspecies. Of these 12 species are considered pathogenic including *C. jejuni*, *C. coli*, *C. fetus*, *C. upsaliensis*, *C. concisus*, *C. curvus*, and *C. lari*. Infection by these pathogens may lead to gastroenteritis; however, *C. jejuni* has also been implicated in systemic infection. *C. jejuni* is the most recognized *Campylobacter* that is involved in the 95% of the outbreaks and sporadic illnesses. A typing system based on the heat-labile antigenic factors has identified 100 serotypes of *C. jejuni*, *C. coli*, and *C. lari*, whereas the heat-stable LPS O-antigen typing system classifies these pathogens into 60 serotypes. Biochemical properties are used routinely in the laboratory for classification of *Campylobacter* species (Table 16.2).

Sources

Mammals and birds are the main reservoirs, but *Campylobacter* can be found in rabbits, birds, sheep, horses, cows, pigs, poultry, and even domestic pets. This organism is also found in vegetables, shellfish, and water. Poultry is the natural host, and poultry products serve as the major source of *Campylobacter* contributing about 80% of the human campylobacteriosis cases. However, outbreak investigations have also implicated unpasteurized milk, food handler, and contaminated surface water as infection sources. *Campylobacter* spp. colonize in the caeca of broiler chicken with an average of 10^6–10^7 cfu g^{-1} of cecal content, and *C. jejuni* and *C. coli* are reported to be the predominant species.

Table 16.2 Classification of *Campylobacter* species based on their biochemical properties

Characteristic	*C. jejuni*	*C. jejuni* subsp. *doylei*	*C. coli*	*C. lari*	*C. fetus* subsp. *fetus*	*C. upsaliensis*
Growth at 25 °C	−	±	−	−	+	−
Growth at 35–37 °C	+	+	+	+	+	+
Growth at 42 °C	+	±	+	+	+	+
Nitrate reduction	+	−	+	+	+	+
H_2S, lead acetate strip	+	+	+	+	+	+
Catalase	+	+	+	+	+	−
Oxidase	+	+	+	+	+	+
Motility (wet mount)	+	+	+	+	+	+
Hippurate hydrolysis	+	+	−	−	−	−
Nalidixic acid	S	S	S	R	R	S
Cephalothin	R	R	R	R	S	S

Adapted from FDA/CFSAN – BAM – *Campylobacter* (http://www.cfsan.fda.gov/~ebam/bam-7.html)
+ positive, − negative, *S* sensitive, *R* resistance

Antibiotic Resistance

The emergence of antibiotic resistance in thermophilic campylobacters especially in *C. jejuni* and *C. coli* is becoming a major concern worldwide, because of their resistance to fluoroquinolones and macrolide. Antibiotic resistance is also prevalent among the poultry isolates of campylobacters; thus, the US Food and Drug Administration (FDA) has banned the use of fluoroquinolones as growth-promoting supplement in poultry production. *Campylobacter* species generally cause self-limiting diarrhea; thus, antibiotic treatment is usually not necessary. However, antibiotic is needed for severe cases with prolonged or systemic infection. Campylobacters are zoonotic pathogens; thus, their transmission to humans will raise a serious concern since the most popular antibiotics would be ineffective against Campylobacteriosis.

Virulence Factors and Mechanism of Pathogenesis

The infective dose is thought to be 500–10,000 *Campylobacter* cells, and the dosage often correlates with the intensity of the attack. Immunocompromised individuals are at the higher risk of infection. The incubation period for *Campylobacter* spp. is 1–7 days, but 24–48 h is most common. Following ingestion, *Campylobacter* reaches the lower gastrointestinal tract and invades the epithelial cells in the distal ileum and colon, resulting in cell damage and severe inflammation (Fig. 16.2). For bacterial colonization and invasion, chemotaxis and motility and quorum sensing are critical. For survival and growth, iron acquisition, oxidative stress defense, and resistance to bile salts are required. Tissue damage and inflammatory response are mediated by bacterial toxins. *Campylobacter* adhesion, invasion and toxin-induced cell damage and inflammation involving macrophage, neutrophil and dendritic cell recruitment, NF-κB activation, and IL-8 secretion are depicted in Fig. 16.2.

Intestinal Colonization

Motility

Bacterial motility requires flagella and a chemosensing system to respond to the gastrointestinal environment. Hence, the flagellum is an important virulence factor, which is involved in the bacterium motility toward the epithelial cell surface, adhesion and colonization, and invasion of host epithelial cells. The helical shape of one or two polar flagella contributes to the corkscrew propulsive movement in the viscous mucus. Flagellum also possesses the type III protein secretion (T3SS) responsible for transport of proteins necessary for bacterial host interaction. Flagellum consists of a woven structure of the flagellin proteins consisting of a hook–basal body and the extracellular filament. The hook–basal body is composed of proteins that include FliF, the T3SS proteins (FlhA, FlhB, FliO, FliP, FliQ, FliR), motor switch proteins (FliG, FliM, FliN, FliY), motor components (MotA and MotB), and minor hook components (FlgI, FlgH, FlgE, FliK, FliM, FliM). The extracellular filament is composed of FlaA and FlaB proteins. The mutation in key genes such as *flaA*, *flaB*, and *flhA* and *flhB* prevents the production of FlaA or FlaB, ultimately halting motility, invasion, and pathogenesis.

Chemotaxis

Chemotaxis is a physiological response of the motile bacterium to move toward chemoattractants using chemosensors. The chemosensors are two components: histidine kinase-dependent signal transduction system composed of chemotaxis proteins, CheA, CheB, CheR, CheW, CheY, and CheZ, and methyl-accepting chemotaxis proteins (MCPs). The chemosensing proteins regulate flagellar proteins thus control directional movement of the bacterium. *Campylobacter* movement toward mucins and glycoproteins on the mucosal surface help bacterial colonization in the gut. Other chemoattractants include α-ketoglutarate, aspartate, asparagine, cysteine, glutamate, pyruvate, serine, formate, malate, lactate, succinate, and so forth.

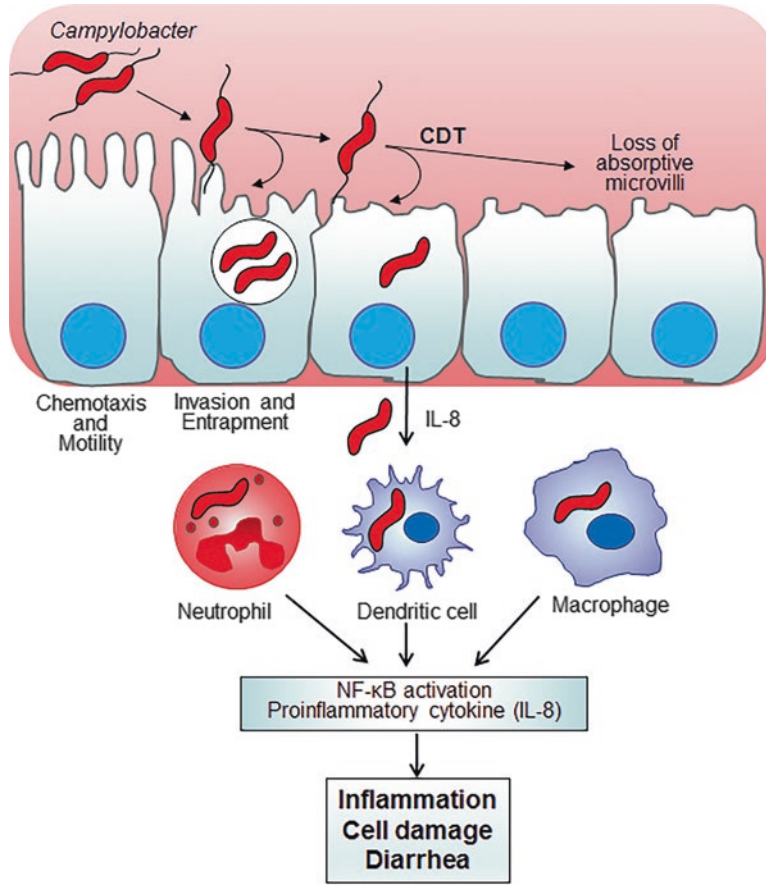

Fig. 16.2 Mechanism of *Campylobacter jejuni*-induced epithelial cell damage in the intestine. Steps in pathogenesis include (1) chemotaxis and motility; (2) adhesion, invasion, and growth inside the vacuole; and (3) production of cytolethal distending toxin (CDT). Cell damage and inflammation lead to fluid loss and diarrhea

Adhesion

Several C*ampylobacter* adhesion proteins have been identified that contribute to bacterial adhesion. *Campylobacter* uses CadF protein (37 kDa) that binds to fibronectin, a 220 kDa glycoprotein commonly found in locations of cell-to-cell contact on epithelial cells in the gastrointestinal tract. This interaction triggers a signaling cascade that leads to the activation of the GTPases Rac1 and Cdc42, which promote *Campylobacter* cell internalization through actin-mediated induced phagocytosis.

Campylobacter also uses periplasmic binding protein (Peb1; 21 kDa protein), *Campylobacter* adhesion protein A (CapA), fibronectin-like protein A (FlipA), and a lipoprotein, JlpA (42.3 kDa) for adhesion. JlpA binds to the eukaryotic Hsp90 (90 kDa) and induces signal transduction in the host cell. *Campylobacter* also adheres to the host cell H-2 antigen for colonization. The lipopolysaccharide (LPS) and lipooligosaccharide (LOS) also contribute to bacterial adhesion and serum resistance (Fig. 16.2).

Campylobacter heat-shock proteins, GroESL, DnaJ, DnaK, and ClpB, aid in bacterial thermotolerance and survival in the bird intestine since the gut temperature is about 42 °C. Among the heat-shock proteins, only DnaJ was shown to directly contribute to bacterial colonization.

Invasion

The flagellum is believed to play an important role during the host cell invasion by facilitating secretion of nonflagellar proteins through its T3SS channel. The FlaC and CiaB (*Campylobacter* invasion antigen B; 73 kDa) proteins are delivered through T3SS to the host cell cytoplasm and are required for adhesion and

invasion. Other invasion and intracellular survival factors are CiaC, CiaI, invasion-associated protein A (IamA), and HtrA, a chaperone protein. Bacterial binding to the host cells triggers host cell cytoskeletal rearrangements through activation of microfilaments and microtubules that allow bacterial internalization possibly by two mechanisms: zipper and trigger mechanisms (Fig. 16.3). In the zipper mechanism, high-affinity binding of bacterial surface adhesins to their receptors initiates signaling event leading to the cytoskeleton-mediated zippering of the host cell plasma membrane around the bacterium. The bacterium is subsequently internalized into a vacuole. In the trigger mechanism, the bacterium injects effector proteins through T3SS and initiates a signaling event to activate small Rho GTPases and cytoskeletal reorganization to induce membrane ruffling. The bacterium is subsequently internalized into the vacuole. *Campylobacter* is unable to escape the membrane-bound vacuole and replicates at least one cycle inside. Survival inside the vacuole is facilitated by the production of superoxide dismutase (SOD) to inactivate oxygen radical and the catalase to protect against oxidative stress from the host. Some studies have reported escape of the bacterium from the vacuole.

Toxin

Campylobacter produces several toxins, but the cytolethal distending toxin (CDT) is the main toxin and is encoded by a three-gene operon (*cdtABC*). CDT consists of three similar-sized molecular weight toxins, CdtA (30 kDa), CdtB (29 kDa), and CdtC (21 kDa). Hence, it is called

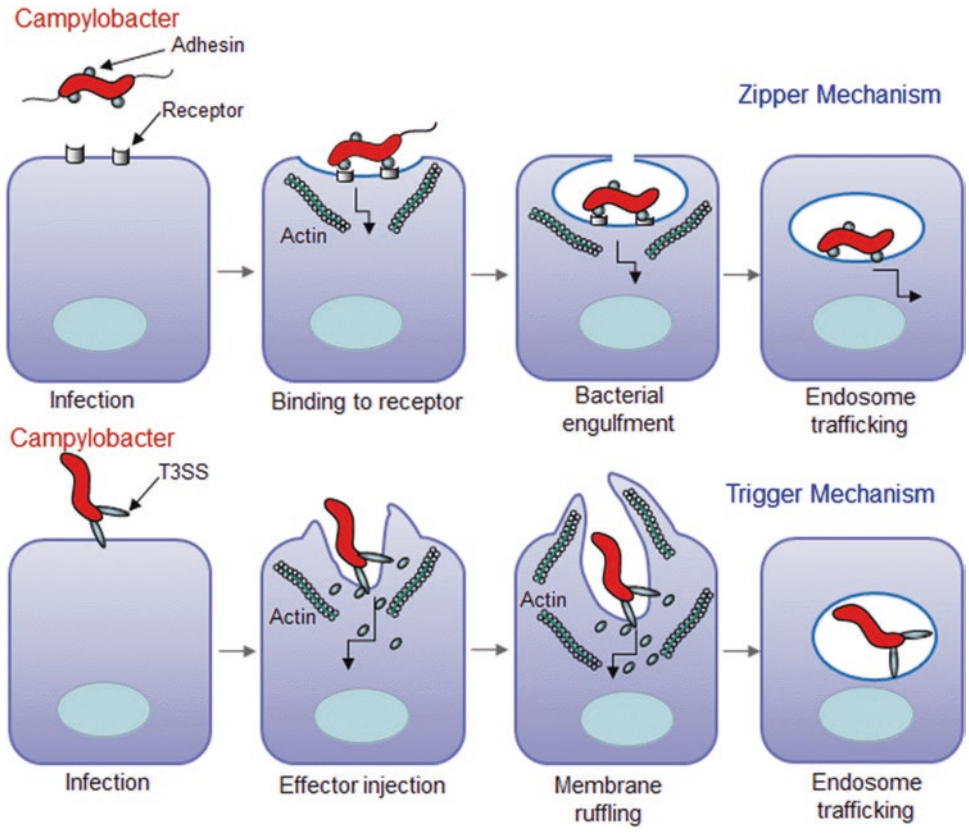

Fig. 16.3 *Campylobacter jejuni* invasion strategy: zipper mechanism and trigger mechanism (Adapted from Tegtmeyer et al. (2012). Microbial Food Safety. pp.13–31: Springer)

a tripartite "AB_2" toxin, in which CdtB is the active toxic unit with enzymatic activity, while the CdtA and CdtC constitute the "B_2" subunit, which is responsible for binding to the cell receptor and internalization of the active CdtB. CdtB has a nuclease activity that triggers DNA damage resulting in cell cycle arrest, especially in the G2/M phase of mitosis affecting cell division. CDT also causes cell distention over 72 h and detachment in target cells such as HeLa, Vero, Caco-2, and CHO cell lines. CDT is thought to disturb the maturation of crypt cells into functional villous epithelial cells; thus, it temporarily ceases the absorptive function and induces diarrhea. CDT is heat-labile (70 °C for 30 min) and trypsin-sensitive. Other toxins produced by *Campylobacter* are cholera-like enterotoxin that activates cAMP, a Shiga-like toxin that inhibits protein synthesis, pore-forming hemolysin, and hepatotoxin.

Iron Acquisition

The ability of *Campylobacter* to acquire iron from the host transferrin in serum and lactoferrin from mucus is important for their survival and pathogenesis. The bacterium does not produce any siderophores of its own but uses siderophores, ferrichrome, and enterochelin produced by other bacteria to acquire iron. However, *Campylobacter* expresses the iron-uptake receptor, enterobactin FeEnt, encoded by *cfrA* and *cfrB* genes. Fur (ferric uptake regulator) and PerR (peroxide stress regulator) are two proteins that regulate gene products necessary for iron acquisition.

Regulation of Virulence Genes

Thermotolerance and colonization in the gut are regulated by a two-component regulatory system consisting of a histidine kinase (HPK) sensor and a response regulator (RR). The RR is phosphorylated by HPK and regulates the expression of CheY, RacR, and other proteins that are responsible for colonization and thermotolerance at 37–42 °C. Furthermore, the FlgS/FlgR two-component signal transduction system regulates the *flaA* regulon, responsible for flagella synthesis in *C. jejuni*. As mentioned before, the iron acquisition is regulated by Fur and PerR proteins.

Symptoms

Gastrointestinal Disease

Campylobacter infects children and young adults, and the symptoms appear within 24–72 h following ingestion. The symptoms are acute enterocolitis characterized by severe abdominal cramp mimicking appendicitis, nausea, general malaise, fever, muscle ache, headache, and acute watery to bloody diarrhea lasting for 3–4 days. The symptoms usually begin within 24–72 h following ingestion, but may take longer to develop when infected with a low dosage of the bacterium. Majority cases are self-limiting; however, *C. jejuni* infection can be severe and may even lead to death in patients with immunocompromised conditions: AIDS, cancer, and liver diseases.

Campylobacter infection is also associated with other gastrointestinal conditions, such as inflammatory bowel disease (IBD), Barrett's esophagus (BE), colorectal cancer, and cholecystitis. In the esophageal disease, BE, flow-back of stomach acid or the bile can cause mucosal damage thus increases the risk of BE onset. *Campylobacter* (often *C. concisus*) can colonize the damaged mucosa and exaggerates esophageal reflux. Cholecystitis refers to inflammation of the gallbladder, which can be induced by *Campylobacter*. When the cystic duct is blocked by the gallstones, bile accumulates within the gallbladder resulting in cholecystitis.

Extraintestinal Diseases

Campylobacter infection is also involved in extra-gastrointestinal diseases, such as Guillain–Barré syndrome (GBS), Miller Fisher syndrome (MFS), and reactive arthritis. *Campylobacter* infection can cause other inflammatory conditions such as appendicitis, endocarditis, peritonitis (inflammation of peritoneum), brain abscess and meningitis, and bacteremia.

Guillain–Barré Syndrome

Guillain–Barré syndrome (GBS) is one of the common consequences of *Campylobacter* infection, especially by *C. jejuni*. GBS is a neurologic condition characterized by a progressive weakness and flaccid paralysis in the limbs and can also affect respiratory muscles. GBS was first described in 1916 by the French neurologists Guillain, Barré, and Strohl. *Campylobacter* possesses lipooligosaccharide (LOS) in its capsule. The LOS molecule is composed of a core oligosaccharide and lipid A and helps bacteria to evade the immune system and promotes host cell adhesion and invasion. During the infection, sialylation of the LOS occurs, and the sialylated LOS mimics the ganglioside structure of the myelin sheath on nerve cells. During campylobacter infection, the immune system develops an antibody against sialylated LOS, and the LOS-reactive antibodies cause demyelination of nerve, block nerve impulses, and culminate into progressive weakness in limbs and the respiratory muscles, resulting in paralysis.

Miller Fisher Syndrome

Charles Miller Fisher discovered a clinical variant of GBS, which is characterized by an acute onset of ophthalmoparesis (ophthalmoplegia), areflexia (hyporeflexia), and ataxia. In this case, the antibody to ganglioside GQ1b is developed after exposure to the LOS from certain bacterial pathogens, including *C. jejuni*. Such molecular mimicry leads to the development of Miller Fisher syndrome (MFS) characterized by oculomotor weakness and the vision problem.

Reactive Arthritis

Reactive arthritis develops in about 4 weeks after gastrointestinal or genitourinary infections, in which bacterial antigens disseminate into the synovial fluids in the joints, such as knees and ankles, as well as the eyes and the genital, urinary, and gastrointestinal systems. Enteric pathogens, *Campylobacter*, *Salmonella*, *Shigella*, *Vibrio*, and *Yersinia* infections, and urinary tract infective agent, *Chlamydia trachomatis*, often cause reactive arthritis. Antibody–antigen reaction due to molecular mimicry may be involved in the process. Symptoms include inflammation of joints which may vary from mild mono- or oligo-arthralgia to a severely disabling polyarthritis. Symptoms are seen a month after the infection and resolve within a year but may persist for up to 5 years. Reactive arthritis is generally associated with patients who are positive for HLA-B27 (human leukocyte antigen B27) and are susceptible to the autoimmune diseases.

Arcobacter

Biology

The genus *Arcobacter* is closely related to the genus *Campylobacter*; however, the members of the genus *Arcobacter* are aerotolerant and are able to grow at temperature below 30 °C. *Arcobacter* (means "arc-shaped" in Latin) is a Gram-negative helical rod (1–3 μm × 0.2–0.4 μm) and sometimes may produce unusually long cells (>20 μm). These bacteria express single polar flagellum and display typical corkscrew motility. *Arcobacter* is microaerophilic, grows at a pH range of 6.8–8.0, and has a temperature range of 15–37 °C but not at 42 °C. *Arcobacter* spp. grow well in brain heart infusion (BHI) agar containing 0.6% yeast extract and 10% blood.

There are 18 recognized species in the genus *Arcobacter*, of which *Arcobacter butzleri*, *A. cryaerophilus*, and *A. skirrowii* are recognized human and animal pathogens. *Arcobacter butzleri* and *A. cryaerophilus* are responsible for gastroenteritis in humans and occasional bacteremia and peritonitis. *A. skirrowii* has also been routinely isolated from the patients with diarrhea, despite a lack of evidence for its direct involvement in enteritis. An *Arcobacter*-related outbreak was first reported in 1983 in Italy affecting children in a primary school caused by *A. butzleri*. Ten children showed the symptoms of abdominal cramp without causing any diarrhea.

Arcobacter has been isolated from food, drinking water, animals, humans, and aborted animal fetuses. The bacterium has been isolated from poultry carcasses; however, it is not considered a natural reservoir.

Pathogenesis

The pathogenic mechanism of *Arcobacter* is not fully elucidated, but the genome sequence revealed the presence of several key virulence genes, which contribute to the pathogenesis: *cadF*, *ciaB*, *pldA*, *tlyA*, *hecA*, and *irgA*. Bacterial flagella and chemotaxis are important in cell motility and chemotaxis and involved in adhesion to the host epithelial cells. Bacterial adhesion to the intestinal cells is attributed to the presence of CadF encoded by *cadF*, which is involved in adhesion to the host fibronectin protein. CadF interaction also triggers bacterial internalization by the host epithelial cells. CiaB (*ciaB*) homologous to *Campylobacter* species is involved in the invasion. The *pldA* gene encodes phospholipase A, and the *tlyA* encoding a hemolysin have hemolytic activities. The *hecA* gene encodes an adhesin protein, hemagglutinin (20 kDa), a glycoprotein, which possibly interacts with a glycan receptor containing D-galactose for bacterial adhesion. The *irgA* gene encodes an iron-regulated outer membrane protein. Some species produce cytotoxin, enterotoxin, or vacuolizing toxins responsible for cell rounding and vacuole formation. Evidence for the production of cytolethal distending toxin (CDT) by *Arcobacter* species is inclusive. *Arcobacter* induces a strong inflammatory response similar to campylobacter and induces secretion of IL-8, which is a strong chemoattractant for inflammatory cells at the site of infection (Fig. 16.2).

Arcobacter causes abortion and stillbirth in cows, sheep, and pigs. The organism has been isolated from the uterus, oviduct, and placental tissues. The organism is also isolated from the stomach of pigs showing gastric ulcer. In humans, especially in children, they cause gastroenteritis and has been routinely isolated from diarrheal patients. *Arcobacter* is also thought to cause chronic enteritis in adults. The symptoms include nausea, abdominal pain, vomiting, fever, chills, and diarrhea. Arcobacter-associated gastrointestinal illness is self-limiting; thus, antibiotic treatment may not be necessary.

Prevention, Control, and Treatment of *Campylobacter* and *Arcobacter*

Campylobacter spp. are considered normal inhabitant of livestock, poultry, and wild animals. Therefore, it is rather difficult to control the access of *C. jejuni* to raw foods, especially foods of animal origin. However, proper sanitation can be used to reduce its load in raw foods during production, processing, and future handling. Preventing consumption of raw foods of animal origin; heat treatment of a food, when possible; and preventing post-heat contamination are important to control *Campylobacter* in foods. Contamination of vegetables can be controlled by applying treated animal manures as fertilizer and washing produce in chlorinated or ozonated water. Good personal hygiene and sanitary practices must be maintained by food handlers to avoid campylobacter-related diarrhea. *Campylobacter* spp. are heat-sensitive with a decimal reduction time at 55 °C of 1 min.

Avoiding fecal contamination during slaughter can reduce the pathogen load in food. *Campylobacter* and *Arcobacter* are temperature-sensitive, and thus cold storage of meat at or near 4 °C can reduce bacterial counts. Storage in the presence of sodium lactate, sodium citrate, and sodium triphosphate can be effective in controlling *Arcobacter*. Heating of food to an internal temperature of 70 °C and irradiation with 0.27–0.3 kGy for 10 s can inactivate *Arcobacter*.

Experimental approach with fucosylated human milk oligosaccharides has demonstrated the inhibition of *C. jejuni* binding to the intestinal H-2 antigen. This and similar strategies could be used to control *Campylobacter* infection in humans.

Since the campylobacteriosis involves self-limiting diarrhea, antibiotic therapy is not required, but maintenance of hydration and electrolyte balance is advised. Antibiotic therapy is, however, needed for immunocompromised patients to control bacteremia and sepsis. Erythromycin and newer macrolides, azithromycin, and clarithromycin are effective against *C. jejuni* infection. Increased resistance of *Campylobacter* to fluoroquinolone discourages its therapeutic application.

Detection of *Campylobacter* and *Arcobacter*

Several selective isolation media have been formulated to isolate *Campylobacter* spp. from environmental, fecal, and food samples. Campylosel media used cefoperazone, vancomycin, and amphotericin B as selective agents. The CCDA (charcoal cefoperazone, deoxycholate agar) and CAT (cefoperazone, amphotericin B, teicoplanin) media have been used for isolation of *Campylobacter* at 37 °C under microaerophilic conditions, i.e., under oxygen concentrations of 5–10% and a CO_2 concentration of 1–15%. Sometimes a gas mixture of 15% carbon dioxide, 80% nitrogen, and 5% oxygen is used to create the microaerophilic environment.

PCR-based assays have been developed for detection of *Campylobacter* species, and the target gene included flagellin (*flaA*), 16S rRNA, and 16S/23S intergenic spacer region. *Campylobacter* species identification and typing have been done by using ribotyping, restriction fragment length polymorphism (RFLP), amplified fragment length polymorphism (AFLP), pulsed-field gel electrophoresis (PFGE), and randomly amplified polymorphic DNA (RAPD)-PCR methods. Whole genome sequencing is now used for identification and characterization of *Campylobacter* and *Arcobacter* species.

Arcobacter spp. have been isolated from food samples, poultry carcasses, drinking water, animals, humans, and aborted animal fetuses. An enrichment broth containing cefoperazone, bile salts, thioglycolate, and sodium pyruvate is used. Enrichment at 25 °C under aerobic environment is commonly practiced, which requires about 4–5 days. In addition, a commercial medium called modified charcoal cefoperazone deoxycholate agar (mCCDA) is used for isolation of *Arcobacter* species.

Identification of *Arcobacter* has been done by using various molecular tools that use 16S or 23S rRNA as probes including ribotyping, RFLP, AFLP, PFGE, and RAPD. Multiplex PCR method targeting the 16S and 23S rRNA genes has been developed for detection and identification of *Arcobacter* species.

Summary

Historically, *Campylobacter* and *Arcobacter* species are considered animal pathogens; however, in the last 40 years, both were implicated in outbreaks causing gastroenteritis in humans. These two pathogens are fastidious curved rods and have stringent growth requirements. *Campylobacter* is microaerophilic, and several of the species are thermophilic and are unable to grow below 30 °C. *Arcobacter* is aerotolerant and can grow below 30 °C. Both *Campylobacter* and *Arcobacter* are routinely isolated from livestock, poultry, and water. The outbreak of *Campylobacter* is associated with meat, poultry, and milk. Of 26 species of *Campylobacter*, *C. jejuni* is responsible for 95% of the outbreaks and is considered the most dominant pathogen. *Campylobacter* pathogenesis depends on the expression of several virulence factors that control their motility, chemotaxis, quorum sensing, bile resistance, adhesion, invasion, toxin production, growth inside the host cells, and iron acquisition. Bacteria possibly induce their own internalization through signaling events and rearrangement of the host cytoskeletal structure and survive inside the epithelial cells by expressing superoxide dismutase and catalase to deactivate host oxidative stress defense. Cytolethal distending toxin (CDT) arrests cell cycle division, disrupts the absorptive function of villous epithelial cells, and promotes diarrhea. The *Campylobacter*-induced diarrhea is mostly self-limiting; however, *Campylobacter* may cause fatal infection in immunocompromised patients. The patients suffering from *C. jejuni* infection may also develop Guillain–Barré syndrome characterized by generalized paralysis and muscle pain, and the reactive arthritis is characterized by arthritis in knee joints or lower back. The pathogenic mechanism of *Arcobacter* (*A. butzleri*) is not fully elucidated, but the mechanism is similar to *Campylobacter* infection as to the tissue tropism, adhesion, invasion, tissue damage, and inflammation. *Arcobacter* causes diarrhea in humans (in children) and abortion and stillbirth in cows, sheep, and pigs. Preventing consumption of raw foods of animal origin and

heat treatment of a food and preventing post-heat contamination are important to control *Campylobacter* in foods. In most cases, the campylobacteriosis is a self-limiting disease; thus, antibiotic therapy is not required; however, antibiotic is needed for immunocompromised patients to control bacteremia and sepsis.

Further Readings

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