

Case 3

Campylobacter jejuni

A 35-year-old man had been feeling unwell for a few days with nonspecific aches and pains in his joints and a slight headache. He put this down to a barbecue he had attended a few days previously, where he had also drunk a considerable amount of alcohol.

The following day he felt considerably worse with severe colicky abdominal pain and he developed bloody diarrhea, going to the lavatory 10 times during the day. This persisted overnight and he attended his local hospital's Emergency Department.

On examination he was noted to be dehydrated and rather pale. He was admitted to hospital for intravenous

rehydration and blood and feces samples were sent for culture. He was started on antibiotics and over the subsequent few days he improved with lessening of the symptoms and was discharged home.

Some weeks later he began to develop weakness in his feet, which gradually affected his legs. He contacted his primary care physician who admitted him to hospital once again. Over the subsequent few days the paralysis affected his upper leg muscles, and gradually over the ensuing weeks slowly resolved with treatment.

1. What is the causative agent, how does it enter the body and how does it spread a) within the body and b) from person to person?

Causative agent

Campylobacter jejuni is a slender, motile nonspore-forming curved gram-negative bacterium (Figure 1) measuring 0.2–0.5 μm wide by 0.5–5.0 μm long, with a single unsheathed polar flagellum. Its genome has been sequenced. Several species of *Campylobacter* exist, two of which cause the majority of human disease: *C. jejuni* and *C. coli* (Table 1). Recent taxonomic studies on the genus have reassigned some campylobacters to two new genera: *Arcobacter* and *Helicobacter*.

C. jejuni has a typical gram-negative cell wall structure with a hydrophobic outer membrane consisting of **lipopolysaccharide (LPS)**. The major fatty acids are tetradecanoic, hexadecanoic, hexadecenoic, octadecanoic, and 19 cyclopropane. *C. jejuni* is subdivided into Penner serogroups based on the **antigenic variation** of the LPS and further subdivided by **phage types**. Although serogrouping is not used routinely in epidemiological studies it is important as certain Penner groups can cause immune-mediated diseases (see below). *Campylobacter* can be typed by molecular methods such as **restriction fragment length polymorphism (RFLP)** and **multi-locus enzyme electrophoresis (MLEE)**.

The organism is microaerophilic, requiring an atmosphere of 5–10% oxygen and 10% CO_2 .

The two main human pathogens are thermotolerant and can grow at 42°C, which is used as a selective condition for clinical isolates.



Figure 1. *Campylobacter jejuni*: a silver stain showing the 'seagull' morphology of *Campylobacter* sp.

Table 1. The different species of *Campylobacter* and the three genera in the Campylobacteraceae

<i>Campylobacter</i>	<i>C. fetus</i>
	<i>C. coli</i>
	<i>C. concisus</i>
	<i>C. curvus</i>
	<i>C. fetus</i> subsp. <i>fetus</i>
	<i>C. fetus</i> subsp. <i>veneralis</i>
	<i>C. gracilis</i>
	<i>C. helveticus</i>
	<i>C. hominis</i>
	<i>C. hyoilei</i>
	<i>C. hyointestinalis</i> subsp. <i>hyointestinalis</i>
	<i>C. hyointestinalis</i> subsp. <i>lawsonii</i>
	<i>C. insulaenigrae</i>
	<i>C. jejuni</i> subsp. <i>doylei</i>
	<i>C. jejuni</i> subsp. <i>jejuni</i>
	<i>C. lanienae</i>
	<i>C. lari</i>
	<i>C. mucosalis</i>
	<i>C. rectus</i>
	<i>C. showae</i>
<i>C. sputorum</i> subsp. <i>bubulus</i>	
<i>C. sputorum</i> subsp. <i>mucosalis</i>	
<i>C. sputorum</i> subsp. <i>sputorum</i>	
<i>C. upsaliensis</i>	
<i>Arcobacter</i>	<i>A. butzleri</i>
	<i>A. cryaerophilus</i>
	<i>A. nitrofigilis</i>
<i>Helicobacter</i>	See case study 12

C. jejuni is found widely in the animal kingdom and is part of the normal flora of many food-source animals, for example poultry, lamb, pig. The commonest meat source is poultry. Campylobacteriosis is thus a **zoonosis**, with infection being acquired principally from contact with animals or eating poorly cooked meats, for example barbeques, or from sandwiches containing contaminated meat. Infection can also be acquired from raw milk contaminated at source, contaminated water sources, or less frequently from birds breaking the top of milk bottles on the doorstep and thereby contaminating the milk. Infection can also be acquired from close contact with animals such as in children's zoos or with infected dogs.

Entry into the body

Entry of the organism is via the mucosal surfaces of the intestine where it mostly remains. Most cases are caused by **serovar O19**, although other serovars have also been implicated, for example O1 and O5. The infectious dose is about 500–1000 organisms and colonization affects the small and large intestine, with the terminal ileum and colon affected most often. Mesenteric **adenitis** regularly occurs. The shape and motility of the organisms enables them to penetrate the mucus layer where they adhere to the enterocytes and are internalized utilizing microfilament/microtubule-dependent mechanisms. Important in the internalization are the

Campylobacter invasion antigens (Cia), which are secreted by a flagellar secretion apparatus (the evolutionary forerunner of the **type III secretion apparatus**).

Spread within the body

C. jejuni rarely causes a **bacteremia**, and remains in the gastrointestinal tract, causing a **terminal ileitis** and **colitis**. Systemic infections are more commonly associated with *Campylobacter fetus* subsp. *fetus*, which principally causes diseases of the reproductive system in sheep or cattle and infections in immunocompromised humans. *C. fetus* subsp. *fetus* possesses an S-layer (protein microcapsule), which is antiphagocytic and may explain its tendency to cause **septicemia**.

Person to person spread

Direct person to person spread is uncommon.

Epidemiology

It is difficult to give figures on a worldwide basis of the incidence of disease due to the differences in reporting such cases. However, in general, the incidence of disease is about 78 per 100 000 population, with a peak at 0–4 years of age and a second peak at 15–24 years, although all ages are susceptible. In the UK the number of reported cases has increased from 24 809 in 1986 to 46 236 in 2006. There is a seasonality to infection, with most cases in different countries occurring in the spring–summer and declining in the winter months. In the UK the highest rate of laboratory-confirmed cases occurs in June. In the UK it is the principal cause of gastroenteritis and in the USA it is second to *Salmonella* infection. Confirmed disease is notifiable in Austria, Denmark, Finland, Germany, Italy, Sweden, and Norway. In the UK, a case of *C. jejuni* infection would be notifiable as a ‘food poisoning’ case without giving the identity of the organism.

2. What is the host response to the infection and what is the disease pathogenesis?

Innate immunity

Following invasion of the enterocytes, an acute inflammatory reaction occurs with infiltration of the **lamina propria** by granulocytes.

Adaptive immunity

Soon after infection the host mounts an antibody response, which peaks at about 2 weeks and declines over the following weeks. The main antigens are flagella, outer membrane proteins (OMPs), and LPS. Since antibodies to OMP and LPS cross-react with myelin components this can lead to the development of **Guillain-Barre** or the **Miller Fisher syndromes** (see below).

Little is known about the role of the cell-mediated response. However, CD4+ T-helper cells are involved in the production of **IgG** and **IgA** antibodies to the bacterial antigens.

Pathogenesis

Ulceration of the epithelium with crypt **abscesses** occurs following infection.

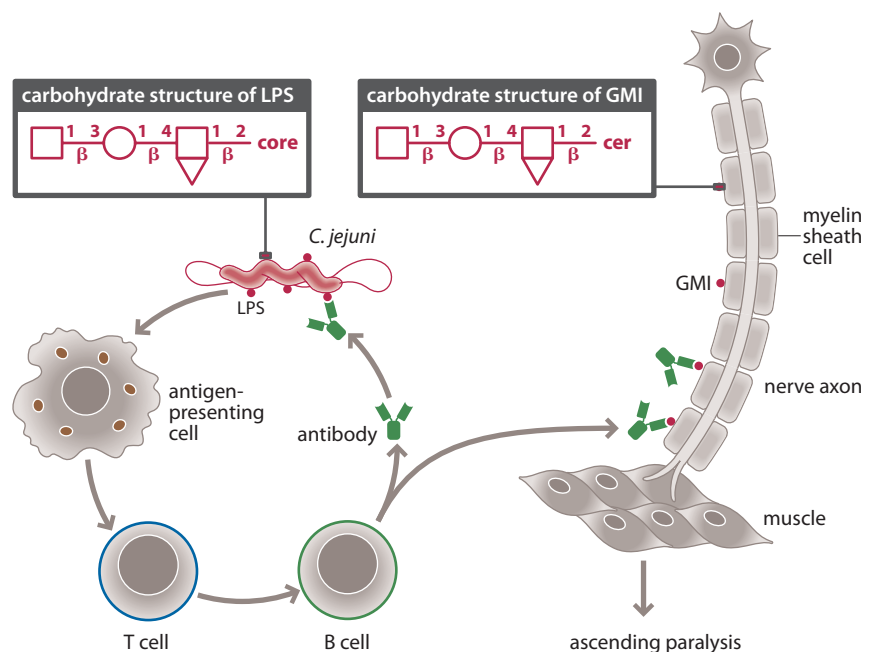
Cytotoxins have been identified from some strains and apparently non-toxicogenic strains can still cause disease. **Cytolethal distending toxin** is present in most strains of *C. jejuni* and induces cell cycle arrest leading to **apoptosis**. It is coded for by three genes – *cdtA*, *cdtB*, and *cdtC* – and is internalized by **endocytosis**. The toxin prevents dephosphorylation (and therefore activation) of CDC2, the catalytic subunit of the cyclin-dependent kinase, which is necessary for cell cycle events and thus causes G₂ arrest. One of the genes (*cdtB*) codes for a deoxyribonuclease and it may be related to the induction of cell cycle arrest. However, its precise role in disease is unclear. Neurological complications (e.g. Guillain-Barre syndrome) can occur, caused by antibodies cross-reacting with gangliosides of the myelin sheath (Figure 2).

3. What is the typical clinical presentation and what complications can occur?

The incubation period is commonly 1–3 days but can be as long as 8 days. Infection may be symptomless in a proportion of individuals. A typical clinical presentation is one of generalized systemic upset with fever and **myalgia** accompanied by abdominal pain and diarrhea. Diarrhea may range from a few loose motions to profuse and watery or grossly bloody. The symptoms may last from a day or two to over a week in about 20% of patients and are generally self-limiting, although relapses may occur in about 10% of patients.

In severe cases of **enterocolitis**, **toxic megacolon** may occur and rare cases of **cholecystitis** or **pancreatitis** have been reported. Three major extraintestinal complications are recognized. The commonest complication is reactive **arthritis**, which occurs in about 1% of cases and occurs several weeks after the initial infection.. It is more common in subjects who are HLA B27. The **hemolytic uremic syndrome** may also follow

Figure 2. Putative mechanism for development of Guillain-Barre syndrome. Antibodies raised against the lipopolysaccharide (LPS) component of the cell wall of some *Campylobacter* strains cross-react with GM1 gangliosides in the myelin sheath of the nerve, due to a structural similarity, leading to damage, loss of nerve conduction, and paralysis.



infection and usually comes on within a few days. Infection may be followed by the Guillain-Barre or the Miller Fisher syndrome variant. Although a rare complication, because campylobacteriosis is so common, an infection with *C. jejuni* is the cause of these immune pathologies in about 50% of cases. Other extraintestinal complications that have occasionally been reported are **IgA nephropathy** and **interstitial nephritis**.

4. How is this disease diagnosed and what is the differential diagnosis?

Campylobacter enteritis is confirmed by the isolation of the organism from the feces using a charcoal-based selective medium and culturing under microaerobic conditions at 42°C. In resource-limited countries a rapid means of provisional diagnosis is to look at a wet preparation of feces under the microscope, where the rapid motion of the *Campylobacter* can be seen – in contrast to *Shigella* dysentery where there is no obvious microbial movement as *Shigella* are nonmotile. **Pus** cells are also prominent. *C. jejuni* may also be detected using the **polymerase chain reaction (PCR)**.

Differential diagnosis

It is not possible to make a microbiological diagnosis from the clinical presentation, so all the other causes of gastroenteritis are in the differential diagnosis such as *Shigella*, *Salmonella*, *Escherichia coli*, and so forth. Additionally, as the presentation may be severe with bloody diarrhea, **inflammatory bowel disease** may also be confused with campylobacteriosis.

5. How is the disease managed and prevented?

Management

The disease is self-limiting and in most cases no therapy is required. In severe cases, particularly if it lasts for several days, the patient may have to be admitted to hospital for rehydration. Also antibiotics should be given in severe cases. Erythromycin or ciprofloxacin are the two most frequently used, although for both agents, antibiotic-resistant isolates are increasing in prevalence due to overuse of antibiotics in both human and veterinary practice. In the presence of macrolide- or quinolone-resistant isolates, alternative agents such as tetracycline (except in children) or clindamycin may be used. *Campylobacter* is not susceptible to β -lactams, with the exception of co-amoxiclav. If systemic spread occurs gentamicin can be used but is not useful for the enteric infection.

Prevention

Preventive measures rely mainly on adequate food hygiene and establishing disease-free animal stocks.

A vaccine does not yet exist but is being actively developed.

SUMMARY

1. What is the causative agent, how does it enter the body and how does it spread a) within the body and b) from person to person?

- *Campylobacter* is microaerophilic.
- The cell wall has a typical gram-negative structure.
- The antigenic variation of the LPS is the basis for the Penner groups.
- It is one of the commonest causes of gastroenteritis globally.
- Infection occurs at any age, with peaks in children and young adults.
- Infection is a zoonosis.
- The commonest food source is poultry.
- The organism is located in the small and large intestine.

2. What is the host response to the infection and what is the disease pathogenesis?

- Motility and the organism's spiral shape are important in colonization.
- The infectious dose is about 500–1000 organisms.
- Cell invasion involves *Campylobacter* invasion antigens.
- Invasion involves the microtubules.
- *Campylobacter* produces a cytolethal distending toxin, which causes cell cycle arrest and apoptosis.
- Histologically there is epithelial ulceration and infiltration by granulocytes.
- Antibodies produced in response to the organism can cross-react with myelin.

3. What is the typical clinical presentation and what complications can occur?

- The incubation period is 1–8 days, usually 1–3 days.
- Presents with constitutional symptoms.
- Gastrointestinal symptoms are colicky abdominal pain and diarrhea, which may contain blood.
- Complications include megacolon, reactive arthritis, hemolytic uremic syndrome, and Guillain-Barre syndrome.

4. How is this disease diagnosed, and what is the differential diagnosis?

- Diagnosis is by culture on selective medium incubated microaerobically.
- Differential diagnosis is other bacterial causes of diarrhea and dysentery including *Shigella*, *Salmonella*, *E. coli*, and inflammatory bowel disease.

5. How is the disease managed and prevented?

- Most infections require no treatment.
- In severe cases rehydration and antibiotics may be required.
- Prevention is largely by adequate food processing and hygiene.

FURTHER READING

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MULTIPLE CHOICE QUESTIONS

The questions should be answered either by selecting True (T) or False (F) for each answer statement, or by selecting the answer statements which best answer the question. Answers can be found in the back of the book.

1. **How can *C. jejuni* be typed?**
 - A. Based on the lipopolysaccharide.
 - B. By the Widal reaction.
 - C. By phage typing.
 - D. By the isoprenoid content.
 - E. By MLEE.
2. **Which of the following are true of *C. jejuni*?**
 - A. The organism grows in 48 hours on agar.
 - B. It is a strict anaerobe.
 - C. It is acquired by the oral route.
 - D. Infection occurs in childhood.
 - E. It is a rare infection.
3. **Which of the following are correct statements concerning the host response to *C. jejuni*?**
 - A. Few granulocytes are recruited to the area.
 - B. There is a strong IgA response.
 - C. *C. jejuni* is resistant to complement.
 - D. Epithelial ulceration occurs.
 - E. Crypt abscesses occur.
4. **Which of the following are virulence factors of *C. jejuni* involved in pathogenesis of disease?**
 - A. Type IV secretion apparatus.
 - B. Cytotoxic distending toxin.
 - C. Arabinogalactan.
 - D. Lipopolysaccharide.
 - E. VacA.
5. **Which of the following may be due to infection with *C. jejuni*?**
 - A. Megacolon.
 - B. Miller Fisher syndrome.
 - C. Enterocolitis.
 - D. Keratitis.
 - E. Septicemia.
6. **Which of the following are typical signs and symptoms of *C. jejuni* infection?**
 - A. Colicky lower abdominal pain.
 - B. Fever.
 - C. Bloody diarrhea.
 - D. Skin rash.
 - E. Splenomegaly.
7. **Which of the following are important in the routine diagnosis of *C. jejuni* infection?**
 - A. Culture.
 - B. Urea breath test.
 - C. Serology.
 - D. PCR.
 - E. String test.
8. **Which of the following antibiotics are used to treat gastroenteritis caused by *C. jejuni*?**
 - A. Erythromycin.
 - B. Metronidazole.
 - C. Spiromycin.
 - D. Gentamicin.
 - E. Ciprofloxacin.
9. **Which one of the following complications of infection affects the nervous system?**
 - A. Guillain-Barré syndrome.
 - B. Hemolytic uremic syndrome.
 - C. Reiter syndrome.
 - D. Miller Fisher syndrome.
 - E. Anti-Tourette syndrome.