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Human *Campylobacter* Infections

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Campylobacter infection has long been associated with abortion or stillbirth. Subspecies *Campylobacter jejuni* and *Campylobacter coli* have been identified as the causative agents in many cases of inflammatory diarrhea. *Campylobacter pylori* infection has been associated with up to 80% of cases of type B gastritis and duodenal ulcer. Although diagnosis of *Campylobacter* enteritides has recently become more accurate, treatment modalities utilizing antibiotics remain controversial. Bismuth salts may be of adjunctive value with antibiotics in eradicating *C. pylori*.

Key words: *Campylobacter* • Gastritis • Ulcer, duodenal

Campylobacter (the name means curved rod) was initially recognized as a cause of abortion in sheep in the early 1900s. Then called *Vibrio fetus*, this organism was initially isolated from aborted sheep fetuses. A nonfermenting, motile (uniflagellate), nonspore-forming gram-negative bacillus, *Campylobacter* was first isolated from humans in 1947, when the organism was retrieved from blood cultures drawn from women in midpregnancy.

Often associated with abortion or stillbirth, this organism is now classified as *Campylobacter fetus*. Although a relatively infrequent isolate, it can be cultured from blood, cerebrospinal fluid, or abscess cavities. *Campylobacter* infection is often seen in debilitated or elderly patients.[1,2]

In 1957, King described "related vibrios" isolated from blood taken from infants who had bloody diarrhea.[3] Several years later, "related vibrios" were isolated from stool samples by using filtration and highly selective media. This was done first by Dekeyser and associates,[4] followed by Skirrow[5] and by Blaser and colleagues.[6] Over the last decade *Campylobacter* has been recognized as a major enteric pathogen.[7,8]

Campylobacter was originally classified with *Spirillum* in the family Spirillaceae on the basis of its spiral morphology and single unsheathed flagellum. In 1963, on the basis of its distinctive DNA content, Sebald and Veron[9] renamed *Campylobacter* as a separate genus distinct from *Vibrio*. The 2 major species infecting humans, initially called *C. fetus* subspecies *jejuni* and *C. fetus* subspecies *intestinalis*, have been renamed *C. jejuni* and *C. fetus* subspecies *fetus*.

As additional species and new disease associations are recognized, *Campylobacter* and its close relatives are associated with an increasing range of human disease.

Classification and Isolation

Distinguished from Enterobacteriaceae by its inability to ferment or oxidize carbohydrates, the genus

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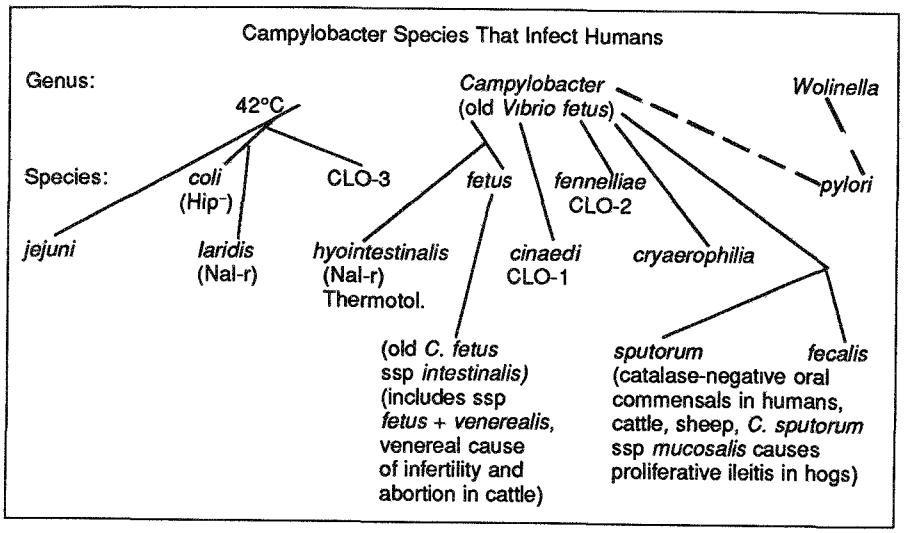

Figure 1. *Campylobacter species that infect humans. Hip⁻, hippurate⁻; Nal-r, nalidixic acid–resistant; Thermotol, thermotolerant (to 42° C).*

Campylobacter is a curved, motile, oxidase- and catalase-positive, microaerophilic gram-negative rod. It requires reduced oxygen and increased carbon dioxide for optimal growth.

C. jejuni and C. coli. The thermophilic species *C. jejuni* and *C. coli* are the most common agents causing inflammatory or invasive diarrhea in subjects living in temperate climates. This species grows best at elevated temperatures, around 42°C (107.6°F). This quality probably reflects an avian reservoir (Fig. 1).

C. jejuni/coli are usually resistant to cephalothin (*Seffin*) and sensitive to naladixic acid. They are separated biochemically by *C. jejuni*'s ability to hydrolyze hippurate. Isolation from fecal specimens requires either filtration through 0.65μm filters or the use of highly selective culture media. These media include Butzler's medium (cefazolin, colistin, bacitracin, novobiocin, and cyclohexamide in 15% sheep blood thioglycolate agar), Skirrow's medium (with polymyxin, vancomycin, and trimethoprim in Oxoid or Columbia agar with 7% lysed horse-blood), or Campy-BAP (with vancomycin, trimethoprim, polymyxin, cephalothin, and amphotericin in 10% sheep blood agar).

C. jejuni is further subdivided into more than 60 serotypes on the basis of heat-stable O antigens. *C. jejuni* may also be subdivided into more than 50 serotypes on the basis of heat-labile capsular or flagellar antigens.

Campylobacter laridis. C. laridis (meaning seagull) is a naladixic acid–resistant, thermophilic *Campylobacter* (NARTC). *C. laridis* commonly infects healthy seagulls. It has also been reported in children with mild recurrent diarrhea and in an elderly patient with terminal multiple myeloma and sepsis.[10]

C. pylori. C. pylori, referred to as "gastric CLO," is thermophlic and resistant to naladixic acid. However, Romaniuk and associates[11] have suggested a different classification based on 16s rRNA sequence homologies. *C. pylori* is more closely related to the anaerobic gram-negative human periodontal pathogen *Wolinella succinogenes*, or even to the sulfide-dependent marine bacterium *Thiovulum*, than to the *Campylobacter* genus (Fig. 1).

Cultivation of *C. pylori* requires reduced O_2 and increased CO_2 at 37°C over 3 to 6 days.

Other species. Initially called "*Campylobacter*-like organisms" (CLO), 3 additional species have been identified. *C. cinaedi* (Latin, "of a homosexual") and *C. fennelliae* (for Cynthia Fennell, who first isolated these organisms) are associated with proctocolitis in homosexual men.[12,13] The 3rd species, CLO-3, has not yet been named (Fig. 1).

These *Campylobacter* species (except CLO-3) do not grow at 42°C or with cephalothin and hence require special attention. They require several days to a week to culture *in vitro* and are often missed on stool culture.

Epidemiology

The number of cases of enteritis caused by *C. jejuni/coli* equal or exceed other causes of inflammatory enteritis.[2,8] Like nontyphoidal *Salmonella, C. jejuni/coli* appears to have a wide range of animal reservoirs. In addition to swine, cattle, sheep, horses, rodents, household pets, calves, and lambs, 30% to 100% of chickens, turkeys, and waterfowl are infected asymptomatically. Commercially prepared poultry is often culture positive. Although the organism is killed by pasteurization, chlorination, drying, or freezing, it may survive for days to weeks in salt or fresh water or in milk. Along with contaminated foods, these fluids serve as vehicles for the transmission of *C. jejuni/coli.*

Secondary transmission is relatively uncommon. Direct fecal–oral spread in day-care centers and among homosexual males seems less common than with *Shigella* or *Giardia.*

There appears to be considerable strain variation in the infectious dose of *C. jejuni.* Reported infectious doses for adults range from 500 to over a million organisms. The predominant season, as with other bacterial enteritides, is the warm or wet summer months. Males and females appear equally at

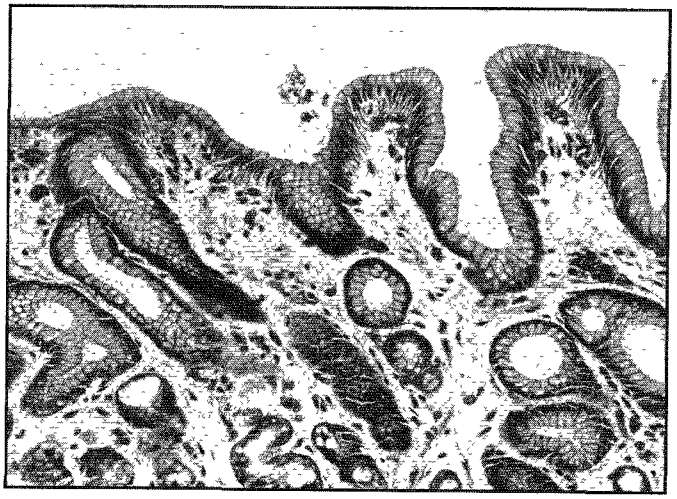

Figure 2A. *Antral mucosa, normal appearance (stained with hematoxylin and eosin, ×250).*

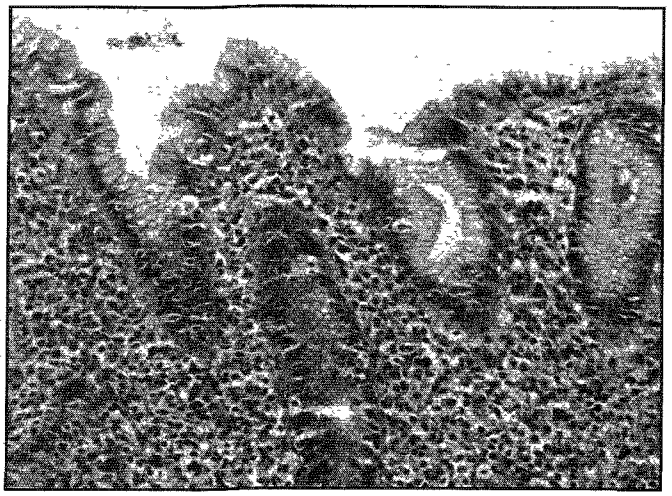

Figure 2B. *Antral mucosa infected with C. pylori. Mononuclear cells and polymorphonuclear leukocytes invade epithelium, and epithelial cells are irregular. This histological appearance is called active chronic gastritis (hematoxylin and eosin, ×250).*

risk. The highest attack rates are in young children.

To date, *C. laridis* appears to be predominantly carried by asymptomatic seagulls; infections in humans are rarely recognized.[10]

C. fetus probably has a domestic animal reservoir but remains a relatively rare cause of bacteremia in impaired hosts.

The 3 *Campylobacter*-like organisms include *C. cinaedi* (CLO-1), *C. fennelliae* (CLO-2), and CLO-3. These organisms are recognized predominantly among homosexual males who have inflammatory proctocolitis.

C. pylori has been isolated primarily from gastric mucosal biopsies of both dyspeptic and asymptomatic humans. *C. pylori* is characteristically associated with a type of chronic gastritis called type B gastritis or antral gastritis. This pathology can distinguish it from the rarer type A (autoimmune) gastritis of pernicious anemia.

Although *C. pylori* infection has only recently been described, the epidemiology of type B chronic gastritis is well known. Type B gastritis is present in about 10% of young adults and 50% of aged persons.[14] There is an increasing incidence with age. Forty percent to 50% of the population is infected by the age of 60.[15] The majority of persons (80%) who have type B gastritis have *C. pylori* infection. The majority of patients (90%) who have *C. pylori* infection have at least histological evidence of antral gastritis[16] (Fig. 2).

C. pylori–associated gastritis is often asymptomatic. However, *C. pylori* infection may predispose to dyspeptic symptoms even when an ulcer is not present. Persons who take antacids are more than twice as likely to have serological evidence of *C. pylori* infection than those who do not use antacids.[17]

Pathogenesis

C. jejuni. Several mechanisms seem to be important in the pathogenesis of *C. jejuni* enteritis. The organism is first attracted to mucus and fucose in bile. Flagellae enable its darting motility and may be involved in adherence of the organism to epithelial cells and mucus.

Both cell-damaging cytotoxins and choleralike enterotoxins have been identified in different strains of *C. jejuni.* These toxins may play a role in the development of the inflammatory or watery diarrhea that is seen in cases of *C. jejuni* infection contracted in tropical climates (Table I). The characteristic pathology of *C. jejuni* enteritis is inflammatory ileocolitis, including crypt abscesses that mimic inflammatory bowel disease. The heat-labile en-

Table I
Clinical Presentation of *C. jejuni* Infections*

	Industrialized Countries	Developing Countries
% of all diarrhea with *C. jejuni*	4.6–13 9	2–35
% of *C. jejuni* with		
fecal PMNs	73–93	22–46
blood in stool	60–65	5–17
Asymptomatic infection rates (%)	<1.3	0–39**

* Data from references 2, 15, 16, & 17; adapted from reference 18.
** Depending on age; 39% if younger than 2 years.

terotoxin, like cholera toxin, binds ganglioside Gm1 and is neutralized by anti-cholera toxin antibody. Studies done in Mexico revealed that the enterotoxin appears to elicit an antitoxic antibody response to *C. jejuni* infection.[18] However, the pathogenic role and significance of this enterotoxin in *C. jejuni* diarrhea remains unclear at present.

The characteristic pathology of *C. jejuni* enteritis is inflammatory ileocolitis including crypt abscesses that mimic inflammatory bowel disease.

In contrast to *C. fetus, C. jejuni* is sensitive to serum killing and is less likely to cause bacteremia.

Previous infection appears to confer homologous immunity to reinfection with the same strain. Immune milk appears to be protective in suckling animals, and there is a decrease in the illness-to-infection ratio with age among consumers of raw milk and among children in tropical, developing areas. This evidence suggests that some immunity to reinfection can develop.

C. pylori. As described, *C. pylori* specifically infects gastric mucus cells. It is almost invariably associated with polymorphonuclear and mononuclear cell infiltration of the mucosa and with the histological appearance of active chronic gastritis.[19] As a cause of gastritis, *C. pylori* has fulfilled Koch's postulates.

Ultrastructural examination of gastric mucosa colonized with *C. pylori* reveals distinct histological lesions called attachment pedestals. When *C. pylori* is found adjacent or attached to gastric mucosal cells, there is rounding of the luminal cell surface with loss of the short microvilli and disorganization of the cytoskeletal elements. A protein cytotoxin produced by the majority of *C. pylori* isolates has recently been described. This may account for the vacuolization in cultured intestinal mucosa cells.[20]

It is believed that *C. pylori* invasion of the mucus layer and the concomitant inflammatory response within the epithelium impair the ability of these sites to withstand acid and pepsin attack.

Clinical Manifestations

C. jejuni. The diarrheal illness caused by *C. jejuni/coli* is well known (Table I).[7,8,21-24] In industrialized countries *C. jejuni* infection is characterized by bloody diarrhea, fever, and abdominal pain. There are polymorphonuclear neutrophils on Gram's stain of fecal material.

Illness begins after a 1 to 7 day incubation period and is usually self-limited over 5 to 7 days. Five percent to 20% of cases may relapse. Untreated, the organism is shed for a median duration of 2 to 3 weeks. Asymptomatic chronic carriage beyond 2 to 3 months is rare.

As with many inflammatory enteritides, antimotility agents are contraindicated because they may contribute to toxic megacolon, reactive arthritis, polyneuritis, and even hemolytic uremic syndrome.

Infection with *C. jejuni* should be suspected when an inflammatory enteritis is diagnosed. This is especially true when the patient has a history of ingestion of unpasteurized milk or inadequately cooked poultry.

Gram's stain reveals sheets of fecal leukocytes or blood in the stool. On darkfield or phase-contrast microscopy *C. jejuni* may show characteristic darting motility. Carbol fuchsin Gram's stain may show characteristic "seagull" morphology.

Several series identify *C. jejuni* as the causative agent in 4% to 14% of all diarrheal cases occurring in temperate industrialized countries.[2,8] This range is much wider in developing countries, where *C. jejuni* is often associated with noninflammatory diarrhea or asymptomatically infects children younger than 2 years of age.

C. fetus. In contrast to *C. jejuni/coli*, the slow-growing *C. fetus* does not appear to be a major enteric pathogen. However, it is a relatively rare cause of intravascular or meningeal infections. It may occur in localized infections in elderly or debilitated hosts. Like *C. fetus* subspecies *venerealis* infection in animals, *C. fetus* subspecies *fetus* may cause septic abortions or stillbirths in humans.

C. pylori. Infection with *C. pylori* may be a causative factor in duodenal ulcer disease. At least 90% of patients with active duodenal ulcer craters have *C. pylori* infection documented in the antrum.[25,26] *C. pylori* often extends into the duodenal cap and colonizes islands of ectopic gastric mucosa on or near the duodenal ulcer border. Reports from Australia and Ireland indicate that duodenal ulcer patients who have been cleared of *C. pylori* infection have infrequent relapses. Consequently, maintenance therapy with H2 receptor antagonists is unnecessary.[27]

About 70% of patients with gastric ulcer have *C. pylori* infection.[24] When *C. pylori* infection is not present, chronic gastritis is usually absent.

C. pylori is also found in 50% to 60% of patients who are suspected of having a peptic ulcer on clinical grounds but do not have an ulcer crater at endoscopy. This population includes patients who have hiatus hernia, reflux esophagitis, duodenitis, irritable colon, and gallbladder disease. Also included are patients in whom no diagnosis can be made. Patients in this group are diagnosed as having nonulcer dyspepsia or "essential dyspepsia," a diagnosis of exclusion. Patients with

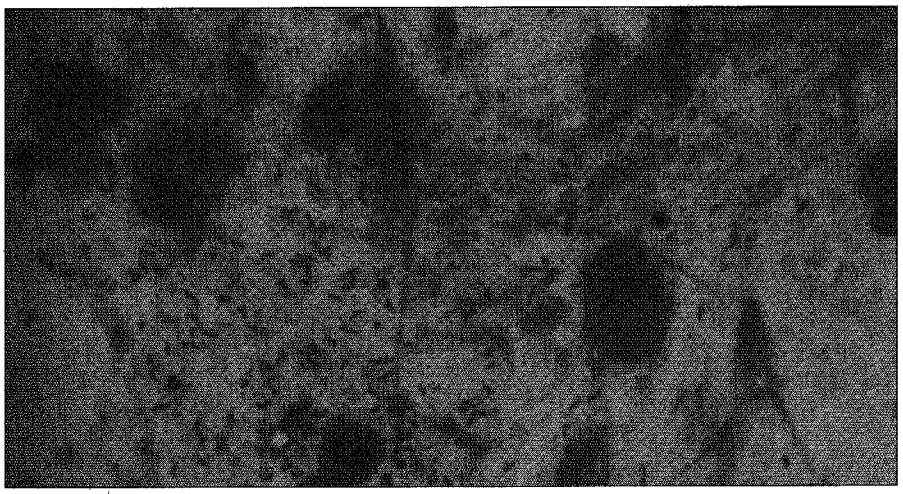

Figure 3. *Gram-stained smear of gastric biopsy from patient with gastritis; large numbers of curved C. pylori organisms are present (× 1000).*

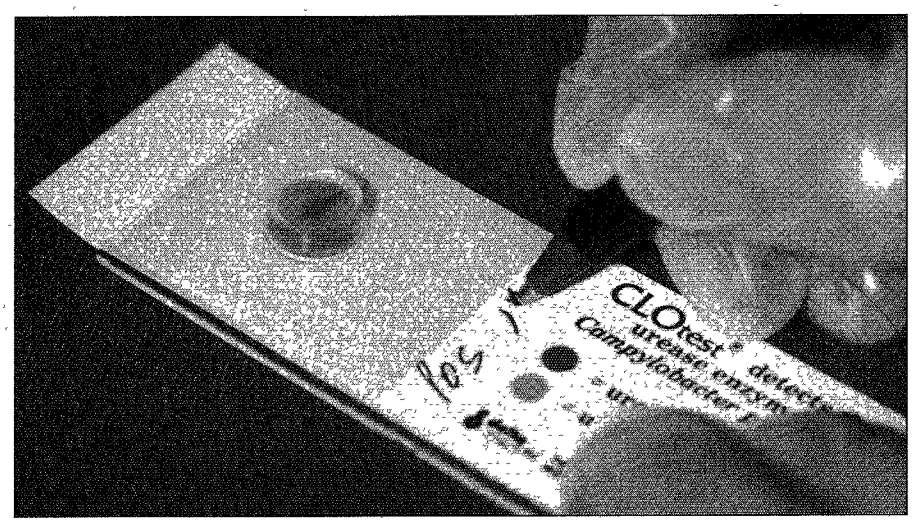

Figure 4. *CLOtest rapid urease test. By generating ammonia from urea present in gel, C. pylori organisms cause color change from yellow (acid) to alkaline (red). Duodenal ulcer sufferers often have very fast results; in this case the biopsy turned red in 1 minute.*

nonulcer dyspepsia often have vague symptoms such as burping, bloating, nausea, flatulence, and distention. Suspected causes are gastroduodenal motility disturbances, gastritis, and psychosomatic disorders. Bismuth salts have been used to treat dyspepsia for over a century. It is of interest that bismuth salts are bactericidal to *C. pylori in vivo*.[28]

The symptoms and signs of acute *C. pylori* infection can be derived from 2 reports of human volunteers who ingested the organism.[29,30] The subjects remained asymptomatic for 3 to 5 days until onset of colicky epigastric pain, bloating, nausea, vomiting, and halitosis. Acute neutrophil infiltration of the antral mucosa was present in the 1st week. Acid secretion was absent or greatly reduced after the 7th day and corresponded to the development of acute mucosal inflammation.

Outbreaks of epigastric discomfort and "epidemic hypochlorhydria" have been described following studies of gastric secretion in which the gastric contents were returned to the subjects' stomachs; these were probably related to a contaminated pH electrode. Seroconversion by those affected to *C. pylori* antibody positivity suggests that *C. pylori* may have been the causative agent.[31,32] As the organisms can be isolated from gastric juice aspirated from the stomach, it is possible that persons with gastroesophageal reflux might transmit *C. pylori* by kissing. However, data on transmission are lacking at present.

In the epidemic referred to above, 17 of 37 subjects undergoing acid secretion studies were affected. After these subjects experienced a mild upper gastrointestinal disturbance lasting a few days, pentagastrin-fast achlorhydria was noted. This was associated with acute inflammation of the acid-secreting mucosa and consequent progression to chronic inflammation. Three subjects still had achlorhydria after one year. Parietal cell failure was thought to be the cause because permeability of the mucosa was not greatly affected by the inflammation. In retrospect, ammonia generation by *C. pylori* bacteria may have neutralized the gastric acid. Also, acid secretion may have failed because of ammonia inhibiting the TCA cycle of the parietal cells.[33]

If infection with *C. pylori* is not eradicated, the infection enters a chronic phase that may persist indefinitely. When and if acid secretion returns to normal, the patient has a defective inflamed mucosa that has been rendered susceptible to acid and peptic digestion. The junctional areas where the antral epithelium (colonized by *C. pylori*) meets the parietal cell mucosa or the duodenal mucosa are most susceptible to ulceration.[34]

Most of the data available on the diagnosis of *C. pylori* infections are derived from endoscopic study of patients with gastric symptoms. Diagnosis is usually made by endoscopic biopsy of the gastric mucosa. *C. pylori* may be seen in Gram's

stains (Fig. 3) or phase-contrast microscopy of the fresh specimen. Culture requires 3 days and histology 2 days. Both methods are sensitive and specific means of diagnosis.

C. pylori produces so much urease that a biopsy urease test such as the CLOtest (Delta West ltd., Bentley, W. Australia) is a sensitive and specific indicator of infection.[35] The CLOtest usually gives a result before the patient leaves the endoscopy suite. In this test a mucosal biopsy is inserted into a buffered gel containing urea and a pH indicator. If urease is present, ammonia is generated. A pH change causes the color of the gel to change from yellow (acid) to red (alkaline) (Fig. 4).

Patients with *C. pylori* infection often have high antibody titers. ELISA tests specific for IgG antibody have a sensitivity and specificity of around 90%.[36] This provides a means of easily screening large numbers of persons for the infection. Serology cannot be used to confirm cure, however, because antibody titers remain high after successful treatment.

Recently, a noninvasive test has been developed based on the urease enzyme produced by *C. pylori*. Unlike serological tests, this test can be used to confirm eradication of the organism. Swallowed urea labeled with a carbon isotope forms ammonium and CO_2 if *C. pylori* is present in the gastric mucosa. The latter is expired in the breath and may be detected with a mass spectrometer or beta counter.[37]

Treatment

The major treatment of *Campylobacter* enteritis is supportive care.

In contrast to *Salmonella* infections, *C. jejuni* infections can be eradicated by antibiotics such as erythromycin.

In vitro, C. jejuni is usually resistant to penicillin, ampicillin, cephalosporins, and trimethoprim–sulfamethoxazole (*Bactrim, Septra*).

Treatment of *C. pylori* infection is difficult because *in vitro* sensitivities are not reliable predictors of the response to treatment. Phenoxymethyl penicillin, amoxicillin, erythromycin ethylsuccinate, doxycycline, tinidazole, metronidazole, ciprofloxacin (*Cipro*), and ofloxacin have been tried but have had less than a 30% success rate. For example, *C. pylori* typically becomes resistant during therapy with quinolones (ofloxacin) and nitroimidazoles (e.g., metronidazole).[38]

Bismuth salts such as colloidal bismuth subcitrate (CBS) are effective *in vitro* and suppress infection of the stomach. However, relapse occurs in 50% to 70% of patients within a month.[26] When CBS is combined with antibiotics, higher eradication rates are possible (50% to 75%). Notably, the organism does not develop antibiotic resistance to nitroimidazoles when CBS is added to the regimen.[39] At present these regimens are experimental. Bismuth may accumulate to potentially toxic levels in patients with renal impairment. □

Editorial Comment

This excellent update on disease due to the *Campylobacter* species reviews current knowledge of infections due to these organisms, which until 20 years ago were virtually unrecognized as human pathogens. Diarrhea has been regarded as the most common infection due to *Campylobacter*, but this report indicates that peptic disease and gastritis may be the most important human disease caused by this species.

C. jejuni, one of the most common causes of diarrhea in developed countries, is probably even more prevalent in developing countries, although accurate data from these areas are difficult to obtain. In adults, *Campylobacter* diarrhea is almost always self-limited, and the course of the disease seems to be little affected by antibiotic administration. Recently the cost-effectiveness of routine culture for *Campylobacter* has been raised. However, a positive culture may obviate the need for further investigation to determine the cause of bloody diarrhea. Erythromycin, currently the drug of choice for the treatment of *Campylobacter* diarrhea, is poorly tolerated in adults, so avoidance of antibiotics is an attractive option. In young children antibiotic therapy may interrupt fecal–oral transmission.

The authors emphasize the close association and probable causative role of *C. pylori* in patients with peptic ulcer disease. Antibiotic therapy has been disappointing in these patients; the combination of bismuth salts with antibiotics continues to be experimental at present.

The other clinical settings in which *Campylobacter* infections appear are proctocolitis in homosexual males and serious systemic infection (including meningitis) in any immunosuppressed patient.

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