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rates of primary antibiotic resistance in most H. pylori strains in a particular locale. For this reason, guidelines on optimal regimens for H. pylori eradication in individual countries are evolving, and physi cians should refer to the most up-to-date local guideline. The two most important factors in successful H. pylori treat ment are the patient’s close compliance with the regimen and the use of drugs to which the patient’s strain of H. pylori has not acquired resistance. Treatment failure following minor lapses in compliance is common and often leads to acquired resistance. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Increasing levels of primary H. pylori resistance to macrolides (azithromycin and clarithromycin are primarily used), levofloxacin, and—to a lesser extent—metronidazole are of grow ing concern. In most parts of the world (the main exception being northwestern Europe), the rate of primary macrolide resistance is sufficiently high that regimens containing clarithromycin plus one other antibiotic often fail; regimens with clarithromycin and two other antibiotics remain an option as the other two antibiotics are likely to eradicate H. pylori even if the strain is macrolide -resistant. When a patient is known to have been exposed—even remotely in time—to clarithromycin or a fluoroquinolone, these antibiotics usually should be avoided. Resistance to amoxicillin or tetracycline is unusual, even if these antibiotics have been given previously, and resistance to metronidazole is only partial; thus, there is no need to avoid using these antibiotics whether or not they have been previously prescribed. Whichever antibiotic regimen is used, meta-analyses show that using high rather than moderate doses of acid-suppressive PPIs with the antibiotics increases the effective ness of the regimen. Similarly, use of vonoprazan, a highly effective potassium-competitive acid blocker, originally licensed in Japan and now in several countries, including the United States, was asso ciated with higher eradication rates in conjunction with amoxicillin and clarithromycin, than when a PPI was used for acid suppression. Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain H. pylori for culture and because most microbiology laboratories are inexperienced in H. pylori culture. If initial H. pylori treatment fails, the usual approach is empirical re-treatment with another drug regimen (Table

168-2). The third-line approach ideally should be endoscopy, biopsy, and culture plus treatment based on documented antibiotic sensitivities. However, empirical third-line therapies are often used. Non-pylori gastric helicobacters are treated in the same way as H. pylori. However, in the absence of trials, it is unclear whether a positive outcome always represents successful treatment or whether it is sometimes due to natural clearance of the bacteria. ■ ■PREVENTION Carriage of H. pylori has considerable public health significance in economically richer countries, where it is associated with peptic ulcer disease and gastric adenocarcinoma, and in some, but not all, economi cally poorer countries, where gastric adenocarcinoma may be an even more common cause of cancer death late in life. If mass prevention were contemplated, vaccination would be the most obvious method: experi mental immunization of animals has given promising results, but vac cines in humans have thus far not been successful. However, given that H. pylori has co-evolved with its human host over millennia, preventing colonization on a population basis may have biological and clinical costs. For example, lifelong absence of H. pylori may be a risk factor for GERD complications, including esophageal adenocarcinoma. We have specu lated that the disappearance of H. pylori may also be associated with an increased risk of other emergent diseases reflecting aspects of the current Western lifestyle, such as childhood-onset asthma and allergy, as sup ported by both epidemiologic and animal model studies. Acknowledgment The authors wish to thank John C. Atherton, MD, FRCP, for his prior contributions to this chapter.

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Infections Due to

Campylobacter and Related Organisms ■ ■DEFINITION Bacteria of the genus Campylobacter and of the related genera Arcobacter and Helicobacter (Chap. 168) cause a variety of inflamma tory conditions. Although acute diarrheal illnesses are most common, these organisms may cause infections in virtually all parts of the body, especially in compromised hosts, and these infections may have late nonsuppurative sequelae. The designation Campylobacter comes from the Greek for “curved rod” and refers to the organism’s vibrio-like morphology.

■ ■ETIOLOGY Campylobacters are motile, non-spore-forming, curved, gram-negative rods. Originally known as Vibrio fetus, these bacilli were reclassified as a new genus in 1973 after their dissimilarity to other vibrios was recog nized. More than 20 species have since been identified. These species are currently divided into three genera: Campylobacter, Arcobacter, and Helicobacter. Not all of the species are pathogens of humans. The human pathogens fall into two major groups: those that primarily cause diarrheal disease and those that cause extraintestinal infection. The principal diarrheal pathogen is Campylobacter jejuni, which accounts for 80–90% of all cases of recognized illness due to campylo bacters and related genera. Other organisms that can cause diarrheal disease include Campylobacter coli, Campylobacter upsaliensis, Cam pylobacter lari, Campylobacter hyointestinalis, Campylobacter fetus, Arcobacter butzleri, Arcobacter cryaerophilus, Helicobacter cinaedi, and Helicobacter fennelliae. The two Helicobacter species causing diarrheal disease, H. cinaedi and H. fennelliae, are intestinal rather than gastric organisms; in terms of the clinical features of the illnesses they cause, these species most closely resemble Campylobacter rather than Helico bacter pylori (Chap. 168) and thus are considered in this chapter. The pathogenic roles of Campylobacter concisus (a member of the normal human oral microbiome), Campylobacter ureolyticus, and Campylo bacter troglodytis are uncertain. A new subspecies—C. fetus subspecies testudinum—has been described, chiefly in Asian patients; the very close resemblance of human isolates to strains isolated from reptiles suggests a food source.

The major species causing extraintestinal illnesses is C. fetus. However, any of the diarrheal agents listed above may cause systemic or localized infection as well, especially in compromised hosts. Nei ther aerobes nor strict anaerobes, these microaerophilic organisms are adapted for survival in the gastrointestinal mucous layer. This chapter focuses on C. jejuni and C. fetus as the major pathogens and prototypes for their groups. The key features of infection are listed by species (excluding C. jejuni, described in detail in the text below) in Table 169-1. PART 5 Infectious Diseases ■ ■EPIDEMIOLOGY Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and many household pets (including birds, dogs, and cats). These microorgan isms often do not cause illness in their animal hosts, but occasionally TABLE 169-1 Clinical Features Associated with Infection Due to “Atypical” Campylobacter and Related Species Implicated as Causes of Human Illness SPECIES COMMON CLINICAL FEATURES LESS COMMON CLINICAL FEATURES ADDITIONAL INFORMATION Campylobacter coli Fever, diarrhea, abdominal pain Bacteremiaa Clinically indistinguishable from C. jejuni Campylobacter fetus Bacteremiaa, sepsis, meningitis, vascular infections Diarrhea, relapsing fevers Not usually isolated from media containing cephalothin or incubated at 42°C Campylobacter

upsaliensis Watery diarrhea, low-grade fever, abdominal pain Bacteremiaa, abscesses Difficult to isolate because of cephalothin susceptibility Campylobacter lari Abdominal pain, diarrhea Colitis, appendicitis Seagulls frequently colonized; organism often transmitted to humans via contaminated water Campylobacter hyointestinalis Watery or bloody diarrhea, vomiting, abdominal pain Bacteremiaa Causes proliferative enteritis in swine Helicobacter fennelliae Chronic mild diarrhea, abdominal cramps, proctitis Bacteremiaa Best treated with fluoroquinolones Helicobacter cinaedi Chronic mild diarrhea, abdominal cramps, proctitis Bacteremiaa Best treated with fluoroquinolones; identified in healthy hamsters Campylobacter jejuni subspecies doylei Diarrhea Chronic gastritis, bacteremiab Uncertain role as human pathogen Arcobacter cryaerophilus Diarrhea Bacteremiaa Poultry, seafood sources. Cultured under aerobic conditions Arcobacter butzleri Fever, diarrhea, abdominal pain, nausea; or asymptomatic Bacteremiaa, appendicitis Cultured under aerobic conditions; enzootic in nonhuman primates Campylobacter sputorum Pulmonary, perianal, groin, and axillary abscesses; diarrhea Bacteremia Three clinically relevant biovars: sputorum, faecalis, and paraureolyticus aIn compromised hosts, especially including the elderly, and patients with immunodeficiencies, diabetes, and infection with HIV. bIn children. Source: Adapted from BM Allos, MJ Blaser: Clin Infect Dis 20:1092, 1995.

this can occur (especially in puppies); in such circumstances, puppy-tohuman transmission may be detected. In most cases, campylobacters are transmitted to humans in raw or undercooked food products or through direct contact with infected animals. In the United States and other developed countries, ingestion of contaminated poultry that has not been sufficiently cooked is the most common mode of acquisition (30–70% of cases). Other modes include ingestion of raw (unpasteur ized) milk or untreated water, contact with infected household pets, ingestion of contaminated seafood, travel to developing countries (campylobacters being a leading cause of traveler’s diarrhea; Chaps. 130 and 138), oral–anal sexual contact, cross-contamination from any of these sources, and (occasionally) contact with an index case who is incontinent of stool. Campylobacter infections are common. Active surveillance of food borne infections in the United States estimates the incidence of diarrheal disease due to campylobacters at ~20 cases per 100,000 persons—similar in incidence to Salmonella and more common than Shigella. Infections occur throughout the year, but the incidence peaks during summer and early autumn. Persons of all ages are affected; however, attack rates for C. jejuni are highest among young children and young adults, whereas those for C. fetus are highest at the extremes of age. Systemic infections due to C. fetus (and to other Campylobacter and related species) are most common among compromised hosts. Persons at increased risk include those with AIDS, immunoglobulin deficiencies, neoplasia, liver disease, diabetes mellitus, and generalized atherosclerosis as well as neonates and pregnant women; proton pump inhibitor use also increases risk. However, apparently healthy nonpreg nant persons occasionally develop transient Campylobacter bacteremia as part of a gastrointestinal illness (0.1–1% of cases). In contrast, in many developing countries where sanitation is poor, C. jejuni infections are hyperendemic, with the highest rates among children <2 years old. According to large prospective cohort studies in low- to middle-income countries, C. jejuni infections—even when asymptomatic—are associated with short stature (stunting) and with a particular microbiome signature. Rates of clinically apparent infec tion fall with age, as does the illness-to-infection ratio, consistent with progressive development of immunity. ■ ■PATHOLOGY AND PATHOGENESIS C. jejuni infections may be subclinical, especially in hosts in developing countries who have had multiple prior infections and may be partially

immune. Symptomatic infections mostly occur within 2–4 days (range, 1–7 days) of exposure to the organism. The sites of tissue injury include the jejunum, ileum, and colon. Biopsies show an acute nonspecific inflammatory reaction, with neutrophils, monocytes, and eosinophils in the lamina propria, as well as damage to the epithelium, including loss of mucus, glandular degeneration, and crypt abscesses. Biopsy findings may be consistent with Crohn's disease or ulcerative colitis, but these "idiopathic" chronic inflammatory diseases should not be diagnosed unless infectious colitis, specifically including that due to infection with Campylobacter species and related organisms, has been ruled out. The components of protective immunity to Campylobacter in humans are poorly understood. The high frequency of C. jejuni infections and their severity and recurrence among immunoglobulindeficient patients suggest that antibodies are important in protective immunity. Experience from field studies and human experimental infection models suggests that immune protection may be short-lived or incomplete in the absence of continuous exposure. Knowledge of the pathogenesis of infection is also incomplete. Both the motility of the strain and its capacity to adhere to host tissues appear to favor disease, but classic enterotoxins and cytotoxins (including cytolethal distending toxin) appear not to play substantial roles in tissue injury or disease production. The organisms have been visualized within the epithelium, albeit in low numbers. The documentation of a significant tissue response and occasionally of C. jejuni bacteremia further sug gests that tissue invasion is clinically significant, and in vitro studies are consistent with this pathogenic feature. The pathogenesis of C. fetus infections is better defined. Virtually all clinical isolates of C. fetus possess a proteinaceous capsule-like struc ture (an S-layer) that renders the organisms resistant to complementmediated killing and opsonization. As a result, C. fetus can cause bacteremia and can seed sites beyond the intestinal tract. The ability of the organism to switch the S-layer proteins expressed—a phenomenon that results in antigenic variability—may contribute to the chronicity and high rate of recurrence of C. fetus infections in compromised hosts.
■ ■CLINICAL MANIFESTATIONS The clinical features of infections due to Campylobacter and the related Arcobacter and intestinal Helicobacter species causing enteric disease appear to be highly similar. C. jejuni can be considered the prototype, in part because it is by far the most common enteric pathogen in the group. A prodrome of fever, headache, myalgia, and/or malaise often occurs 12–48 h before the onset of diarrheal symptoms. The most common signs and symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose watery stools to visibly bloody stools (~10% of cases in adults); most patients presenting for medical attention have ≥10 bowel move ments on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain is usually generalized but may become localized; C. jejuni infection may cause pseudoappendicitis. Fever may be the only initial manifestation of C. jejuni infection, a situation mimicking the early stages of typhoid fever. Febrile young children may develop convulsions, and both myocar ditis and pericarditis have been observed, especially in young men. Campylobacter enteritis is generally self-limited; however, symptoms persist for >1 week in 10–20% of patients seeking medical attention, and clinical relapses occur in 5–10% of untreated patients. Studies of common-source epidemics indicate that milder illnesses or asymptom atic infections may commonly occur. C. fetus may cause a diarrheal illness similar to that due to C. jejuni, especially in immunocompetent hosts. This organism also may cause either intermittent diarrhea or nonspecific abdominal pain without localizing signs. Sequelae are uncommon, and the outcome is benign. C. fetus may also cause a prolonged relapsing systemic illness (with fever, chills, and myalgias) with bacteremia that has no obvi ous primary source; this manifestation is especially common among compromised hosts. Secondary seeding of an organ (e.g., meninges, brain, bone, urinary tract, or soft tissue)

complicates the course, which may be fulminant. C. fetus infections have a tropism for vascular sites:

endocarditis, mycotic aneurysm, and septic thrombophlebitis may all occur. Infection during pregnancy often leads to fetal death. A variety of Campylobacter species and H. cinaedi can cause recurrent cellulitis with fever and bacteremia in immunocompromised hosts.

■ ■COMPLICATIONS About 90% of bacteremic infections are caused by C. jejuni and C. fetus, in roughly equal proportions, despite the manyfold greater incidence of C. jejuni infections. Overall, mortality has been reported at ~12%. Except in infection with C. fetus, bacteremia is uncommon, developing most often in compromised hosts—including those who are immuno compromised and diabetic—and at the extremes of age. Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host (bacteremia originating from enteritis, with patients responding well to antimicrobial therapy); and (3) sustained bacteremia or focal infec tion in a compromised host. Enteritis may not be clinically apparent. Immediate antimicrobial therapy, possibly prolonged, is necessary for suppression or cure of these infections. Campylobacter, Arcobacter, and intestinal Helicobacter infections in the elderly as well as in patients with AIDS or immunoglobulindeficient patients (most often common variable immunodeficiency) may be severe, persistent, and extraintestinal; relapse after cessation of therapy is common. Immunoglobulin-deficient patients also may develop osteomyelitis and an erysipelas-like rash or cellulitis. Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, and endovasculitis (leading to mycotic aortic aneurysm), osteoarticular infection, peritonitis, cellulitis, and septic abortion. All these complications are rare, except in immunocompromised or elderly hosts. Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection. The two most com mon postinfectious sequelae are reactive arthritis and Guillain-Barré syndrome. Reactive arthritis has been reported in up to 2.5% of cases, although nonspecific rheumatologic symptoms are more common (~10%). Reactive arthritis may develop several weeks after infection; population-based analysis shows that there is no association with the HLA-B27 phenotype. The knees are most frequently involved, but involvement of the ankles, wrists, and small joints of the hands is com mon, with an average of 3.2 joints affected. Guillain-Barré syndrome or its Miller Fisher (cranial polyneuropathy) variant follow either symp tomatic or asymptomatic Campylobacter infections uncommonly—i.e., in 1 of every 1000–2000 cases or, for certain C. jejuni serotypes (such as O19), in 1 of every 100–200 cases. Despite the low frequency of this complication, it is estimated that Campylobacter infections, because of their high incidence, may trigger 20–40% of all cases of Guillain-Barré syndrome. The presence of sialylated lipopolysaccharides on C. jejuni strains prompts a form of molecular mimicry that promotes autoim mune recognition of sialylated cell-surface molecules on axons. Immu noproliferative small-intestinal disease (alpha chain disease), a form of lymphoma that originates in small-intestinal mucosa-associated lymphoid tissue (MALToma), has been associated with C. jejuni; anti microbial therapy has led to marked clinical improvement. CHAPTER 169 Infections Due to Campylobacter and Related Organisms ■ ■DIAGNOSIS In patients with Campylobacter enteritis, peripheral leukocyte counts reflect the severity of the inflammatory process. In addition, stools from nearly all Campylobacter-infected patients presenting for medi cal attention in the United States contain leukocytes or erythrocytes. Gram- or Wright-stained fecal smears should be examined in all

suspected cases. When the diagnosis of Campylobacter enteritis is suspected on the basis of findings indicating inflammatory diarrhea (fever, fecal leukocytes), clinicians can ask the microbiology laboratory to attempt the visualization of organisms with characteristic vibrioid morphology by direct microscopic examination of stools with Gram's staining or to use phase-contrast or dark-field microscopy to identify the organisms' characteristic "darting" motility. Confirmation of the diagnosis of Campylobacter infection is based on identification of an

isolate from cultures of stool, blood, or another site; specific species can be identified by matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry. Campylobacter-specific media should be used to culture stools from all patients with inflam matory or bloody diarrhea. Because all Campylobacter species are fastidious, they will not be isolated unless selective media or other selective techniques are used. Failure to isolate campylobacters from stool by culture does not entirely rule out their presence. Although culture remains the diagnostic gold standard, species-specific real-time polymerase chain reaction (PCR) techniques appear more sensitive than culture. Although PCR and other culture-independent diagnostic test (CIDTs), including antigen detection tests, may detect nonviable bacteria and may be falsely positive, they are now used frequently to diagnose infection with Campylobacter and other enteric bacteria in clinical microbiology laboratories. The detection of the organisms in stool in the United States by culture almost always implies active or recent infection, but CIDT positivity is more questionable.

In any event, follow-up testing after the clinical resolution of an acute infection is rarely needed. Campylobacter sputorum, C. concisus, and related organisms ubiquitously found in the oral cavity are com mensals that only rarely have pathogenic significance. In patients with microscopic colitis, C. concisus can be more frequently detected than in controls, but whether detection of this common oral organism is a marker for colonic disease or is involved in pathogenesis is uncertain. Because of the low levels of metabolic activity of Campylobacter spe cies in standard blood culture media, Campylobacter bacteremia may be difficult to detect. ■ ■DIFFERENTIAL DIAGNOSIS The symptoms of Campylobacter enteritis are not sufficiently unusual to distinguish this illness from that due to Salmonella, Shigella, Yersinia, enterohemorrhagic Escherichia coli, and other pathogens. The com bination of fever and fecal leukocytes or erythrocytes is indicative of inflammatory diarrhea, and definitive diagnosis is based on culture, CIDTs, or demonstration of the characteristic organisms on stained fecal smears. Extraintestinal Campylobacter illness is diagnosed by culture. Infection due to Campylobacter should be suspected in the setting of septic abortion, and that due to C. fetus should be suspected specifically in the setting of septic thrombophlebitis. It is important to reiterate that (1) the presentation of Campylobacter enteritis may mimic that of ulcerative colitis or Crohn's disease, (2) Campylobacter enteritis is much more common than either of the latter (especially among young adults), and (3) biopsy may not distinguish among these entities. Thus, a diagnosis of inflammatory bowel disease should not be made until Campylobacter infection has been ruled out, especially in persons with a history of foreign travel, significant animal contact, immunodeficiency, or exposure incurring a high risk of transmission. PART 5 Infectious Diseases TREATMENT Campylobacter Infection Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses (Chap. 138). Even among patients presenting for medical attention with Campylobacter enteritis, not all clearly benefit from specific antimicrobial therapy. Indications for therapy include high fever, bloody diarrhea, severe diarrhea, persistence for

> 1 week, and worsening of symptoms. A 3-day course of azithromy cin (500 mg once daily) is the regimen of choice. A 1-day regimen of azithromycin (1000 mg given as two 500-mg tablets) can also be used. Alternative regimens for adults consist of fluoroquinolones— ciprofloxacin (500 mg by mouth twice daily for 3 days) or levofloxacin (750 mg daily for 3 days)—but resistance to this class of agents as well as to tetracyclines is substantial; ~27% of U.S. human isolates of Campylobacter in 2014 were resistant to ciprofloxacin, and rates are higher in many other countries; thus, travel-related Campylobacter infections should be considered a priori to be fluoroquinoloneresistant. Because macrolide resistance usually is much less com mon (<10%), these drugs are the empirical agents of choice. Patients infected with antibiotic-resistant strains are at increased risk of

adverse outcomes. Use of antimotility agents, which may prolong the duration of symptoms and have been associated with toxic megacolon and with death, is not recommended. Of note, C. jejuni and C. coli are resistant to trimethoprim and β-lactam antibiotics, including penicillin and most cephalosporins. For patients with immunocompromising conditions and uncom plicated enteritis caused by C. jejuni, therapy duration should be extended to 7–14 days. Bacteremic infections should always be treated with appropriate antibiotics to reduce the high rate of mor tality associated with these infections. For bacteremic or other sys temic infections, treatment with a carbapenem (imipenem, 500 mg IV every 6 h; or meropenem, 1–2 g IV every 8 h) should be started empirically, and susceptibility testing should always be performed. For life-threatening illness, gentamicin (1.0–1.7 mg/kg IV every 8 h after a loading dose of 1.5–2 mg/kg) can be added. In the absence of endovascular involvement, therapy for systemic infections should be administered for 7–14 days. For immunocompromised patients with systemic infections due to C. fetus and for patients with endovascular infections due to any species, prolonged therapy (up to 4 weeks) is usually necessary. For recurrent infections in immunocompromised hosts, lifelong therapy/prophylaxis is sometimes necessary. ■ ■PROGNOSIS Nearly all patients recover fully from Campylobacter enteritis, either spontaneously or after antimicrobial therapy. Volume depletion prob ably contributes to the few deaths that are reported. As stated above, occasional patients develop reactive arthritis or Guillain-Barré syn drome or its variants. Systemic infection with C. fetus is much more often fatal than that due to related species; this higher mortality rate reflects in part the population affected. Prognosis depends on the rapidity with which appropriate therapy is begun. Otherwise healthy hosts usually survive C. fetus infections without sequelae. Compro mised hosts often have recurrent and/or life-threatening infections due to a variety of Campylobacter species. ■ ■FURTHER READING Amour C et al: Epidemiology and impact of Campylobacter infection in children in 8 low-resource settings: Results from the MAL-ED Study. Clin Infect Dis 63:1171, 2016. Costa D, Iraola G: Pathogenomics of emerging Campylobacter Species. Clin Microbiol Rev 32:e00072, 2019. Dai L et al: New and alternative strategies for the prevention, control, and treatment of antibiotic-resistant Campylobacter. Transl Res 223:76, 2020. Man SM: The clinical importance of emerging Campylobacter species. Nat Rev Gastroenterol Hepatol 8:669, 2011. Marder EP et al: Incidence and trends of infections with pathogens transmitted commonly through food and the effect of increasing use of culture-independent diagnostic tests on surveillance—Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 2013–2016. Morb Mortal Wkly Rep 66:397, 2017. Nielsen HL: High risk of microscopic colitis after Campylobacter concisus infection: Population-based cohort study. Gut 69:1952, 2020. Riddle MS et al: ACG clinical

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