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Review

Bacterial hemorrhagic enterocolitis

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Bacterial diarrhea can be classified into two clinical entities, noninflammatory diarrhea and inflammatory diarrhea syndromes. The latter type of diarrhea is characterized by bloody and puruloid mucus stool, and is often accompanied by fever, tenesmus, and severe abdominal pain. Pathogenic bacteria causing the inflammatory diarrhea syndrome include *Salmonella*, *Vibrio*, *Shigella*, enteroinvasive and enterohemorrhagic *Escherichia coli*, *Campylobacter*, *Yersinia*, *Chlamydia*, and *Clostridium difficile*. The pathologic changes in the inflammatory diarrhea syndrome range from a superficial exudative enterocolitis to a transmural enterocolitis with overt ulceration. This syndrome is also designated as bacterial hemorrhagic enterocolitis because of its usual manifestation by bloody diarrhea. The diagnostic approach needs information on the patient's age, travel history, epidemiological associations, sexual practice, and medical history, including usage of antibiotics. Bacterial information can be obtained by microscopic study, culture, and the identification of specific bacterial toxins. Flexible colonoscopy with biopsy is useful for the differentiation of bacterial hemorrhagic enterocolitis from idiopathic ulcerative colitis and ischemic colitis. Physicians should be familiar with the diagnostic modalities used to detect the specific pathogens causing hemorrhagic bacterial enterocolitis; namely, bacterial culture, serology, histology, and nucleic acid technologies.

Key words: bacterial hemorrhagic enterocolitis, *Shigella*, *Escherichia coli*, *Campylobacter*, *Clostridium*

Introduction

Bacterial diarrhea occurs mostly through the fecal-oral route by the ingestion of food contaminated with infectious agents. From a clinical standpoint, bacterial diarrhea can be classified into two clinical entities, noninflammatory diarrhea and inflammatory diarrhea syndromes.[1] Most patients with the former type of diarrhea show a self-limiting clinical course that does not require specific therapy. This type of diarrhea is caused by pathogenic bacteria, such as enterotoxigenic *Escherichia coli* and *Staphylococcus*. Infection with such microorganisms can alter the normal absorptive and secretory processes of the enterocytes, leading to afebrile watery diarrhea without the passage of blood or pus. In contrast, the latter type of diarrhea is characterized by bloody and puruloid mucus stool, and is often accompanied by fever, tenesmus, and severe abdominal pain. Pathogenic bacteria causing the inflammatory diarrhea syndrome include *Salmonella*, *Vibrio*, *Shigella*, enteroinvasive and enterohemorrhagic *Escherichia coli*, *Campylobacter*, *Yersinia*, *Chlamydia*, and *Clostridium difficile*. These organisms may produce exotoxins or cytotoxins following adherence to and invasion into the epithelium, or they may trigger the release of cytokines and chemical mediators involved in the attraction of inflammatory cells.[2] The pathologic changes in the inflammatory diarrhea syndrome range from a superficial exudative enterocolitis to a transmural enterocolitis with overt ulceration. This syndrome is also designated as bacterial hemorrhagic enterocolitis because of its usual manifestation by bloody diarrhea. In clinical practice, prolonged bacterial hemorrhagic enterocolitis mimics other inflammatory conditions, such

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as ulcerative colitis, Crohn's disease, radiation colitis, ischemic colitis, and diverticulitis.[3]

Salmonella species

Salmonella species, members of the Enterobacteriaceae family, are gram-negative, rod-shaped bacilli, and are close relatives of *Escherichia coli* species. This bacterium causes enteric fever and enterocolitis, as well as focal infections (meningitis, septic arthritis, osteomyelitis, cholangitis, and pneumonia).[4,5] Enteric fever (typhoid fever) is primarily caused by *Salmonella* Typhi and *S.* Paratyphi, while enterocolitis is associated with infections with over 2200 serotypes of *Salmonella*, including *S.* Enteritidis and *S.* Typhimurium species. Nontyphoidal salmonellosis appears to be sporadic, with a peak disease incidence during warm months. The incidence of this infection has been estimated as less than 20 cases per 100000 population in the United States. The annual reports of cases of nontyphoidal salmonellosis by Japanese public health centers have numbered between 4000 and 6000 (Salmonellosis in Japan, Infectious Agents Surveillance Report 2000, information obtained from the Internet). As shown in Fig. 1, the predominant serotype isolated in recent years has been *S.* Enteritidis, except in the year of 1999, when an outbreak of *S.* Oranienburg infection caused by the ingestion of contaminated cuttlefish chips was reported.[6] Almost 80% of infections are derived from pets (turtles and lizards), other animals, and the ingestion of animal products (poultry, eggs, and meats). Contaminated gastrointestinal endoscopes are also implicated as a source of infection. The incubation period is dependent on the condition of the bacteria and host, but is usually 6–72 h.

The clinical symptoms and signs of typhoid fever include sustained fever, abdominal pain, splenomegaly, bacteremia, and skin rashes. Erosive lesions in Peyer's patches sometimes result in the presentation of frank bloody stool, unless infected persons are receiving appropriate medical treatment. On the other hand, presenting symptoms in nontyphoidal *Salmonella* infection are nausea, vomiting, and abdominal pain, and bloody diarrhea can occur as well. Such symptoms begin 8 to 48 h after the ingestion of contaminated food, and usually last 3 to 5 days in patients with gastroenteritis and 2 to 3 weeks in those developing enterocolitis. Low gastric acidity, either due to age, resection of the stomach, or the usage of drugs such as H_2 receptor blockers, increases the susceptibility and severity of the infection because of inability to kill bacteria by gastric acid. Younger children, especially infants less than 1 year old, and persons aged over 60 are susceptible to nontyphoidal *Salmonella* infection, with a tendency to develop more severe diseases.

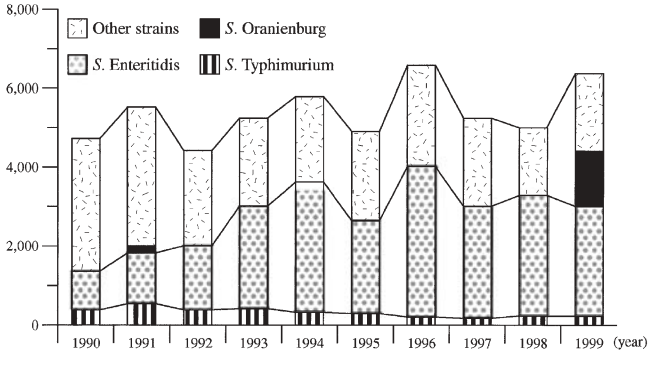

Fig. 1. The number of nontyphoidal *Salmonella* infections in Japan (Infectious Agents Surveillance Report 2000, information obtained from the Internet)

The laboratory diagnosis of *Salmonella* infection requires identification by bacterial cultures, using stool, rectal swab, or endoscopic biopsy specimens. Culturing stool specimens containing fecal leukocytes can increase the percentage of positive cultures. The ulcers found by colonoscopy in patients with typhoid fever have a characteristic oval contour with raised margins and a clear white base, and their distribution parallels the anatomical location of intestinal Peyer's patches (terminal ileum and right-sided colon) that undergo ulceration.[7,8] In contrast, the colonoscopic features in patients with nontyphoidal salmonellosis include hyperemia, friability of the mucosa, ulcerations, aphthous erosions, and deep fissures, with segmental involvement of the colon.[9,10]

Most cases of *Salmonella* infection in the gastrointestinal tract are self-limiting; therefore, supportive therapy with fluids, electrolytes, and anti-motility agents is chosen to improve the general condition of the patients. It is recommended that the patient avoid milk and dairy products, because this infection often yields transient lactose deficiency. Caffeine-containing products should be also avoided, considering their positive effects on levels of cyclic AMP in the enterocytes, which effects may worsen the diarrhea. Antibiotic therapy is not routinely recommended for the treatment of mild-to-moderate *Salmonella* gastroenteritis. However, antimicrobial therapy with fluoroquinolones, trimethoprim-sulfamethoxazole, ampicillin, or third-generation cephalosporins should be initiated for patients who are severely ill or those with risk factors for developing extraintestinal spread of infection.

Vibrio species

Members of *Vibrio* species, motile and gram-negative curved rods, cause a number of important infectious syndromes in the gastrointestinal tract. Epidemic cholera, which is caused by *Vibrio cholerae*, remains a

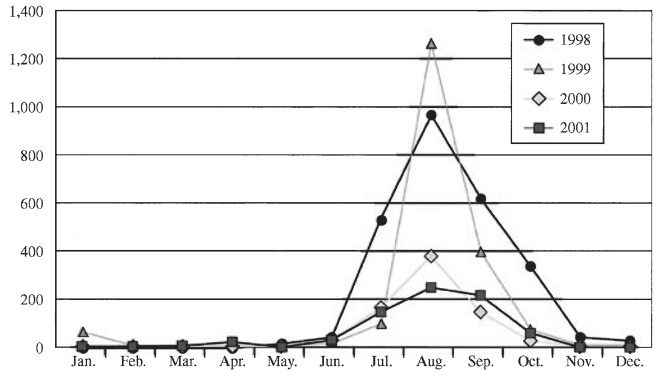

Fig. 2. The number of *Vibrio parahaemolyticus* infections in Japan (Infectious Agents Surveillance Report 2002, information obtained from the Internet)

worldwide public health concern.[11] Other vibrioses are also associated primarily with gastrointestinal illness. *V. parahaemolyticus* is the most common and best-characterized bacterium among the noncholera *Vibrio* species.[12] Food poisoning caused by this bacterium is the second most common cause of food poisoning after that caused by *Salmonella* infection. As shown in Fig. 2, monthly isolation during recent years shows a summer-prevalent pattern, with a peak in August (*V. parahaemolyticus* in Japan, Infectious Agents Surveillance Report 2002, information obtained from the Internet). Undercooked fish or shellfish, and especially raw seafood may be the source of oral transmission. The incubation period is generally 9 to 25 h.

Patients with *V. parahaemolyticus* infection complain of nausea, vomiting, and abdominal cramping, and may have watery or bloody diarrhea and fever. The bacteria cause diarrhea by producing several hemolysines after they invade the intestinal mucosa.[13,14] These toxins cause hemolysis in human red blood cells, and this ability is closely linked to the enteropathogenicity. The diagnosis is confirmed by culturing the bacteria from stool or rectal swab specimens, using selective media. Wagatsuma agar is used to detect hemolysin-positive blue-green colonies (Kanagawa phenomenon).[15]

The disease is usually self-limiting, and resolves within 3 to 4 days. Although it is not always necessary to achieve a cure in noncholera *Vibrio* infections, tetracycline or doxycycline can diminish the duration and severity of gastrointestinal symptoms. Other antibiotics, such as imipenem, may be also active, especially when the patient presents with a liver complication.

Shigella species

Shigella species are nonmotile, gram-negative bacilli, and are classified into four major subgroups, *Shigella dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*, on the basis of biochemical and antigenic characteristics. *S. dysenteriae* and *S. flexneri* are the predominant species causing endemics and pandemics in developing countries, while *S. sonnei* accounts for most of the reported cases of shigellosis in developed countries, including Japan, the United States, and Western Europe.[16] All *Shigella* species are capable of elaborating a potent toxin with enterotoxic, cytotoxic, and neurotoxic properties (Shiga toxin).[17] Severe bloody diarrhea occurs more frequently in persons infected with high toxin-producing strains than in those infected with low toxin-producing ones. The disease caused by these bacteria is highly contagious, and the ingestion of small numbers of organisms is sufficient to yield clinical symptoms in infected volunteers.[18] According to a surveillance report of infectious agents in Japan (Shigellosis in Japan, Infectious Agents Surveillance Report 2001, information obtained from the Internet), the number of notified patients with shigellosis has ranged from 202 to 616 per year during the 10 years 1990–2000, among whom cases associated with foreign travel accounted for 43% (Table 1). In the patients infected overseas, more than half were infected in Asian countries, including India, Indonesia, and Thailand. As for those with domestic infection, three outbreaks were reported, all of which were caused by *S. sonnei*. One outbreak was derived from the consumption of sushi prepared by a cook infected with the organism. A subsequent survey found infected persons in several prefectures. The isolates from people infected in these outbreaks were found to show almost identical DNA patterns by analysis with pulse-field gel electrophoresis. Most transmission of shigellosis occurs by way of the fecal-oral route through close personal contact or by way of infected food or water. In developed countries, the following two populations are at particular risk for *Shigella* infection; children in day-care centers or nursery schools and male homosexuals (gay bowel syndrome).[19,20] In the latter group, cases are almost always due to *S. flexneri* infection transmitted by anal-oral sexual practices. The isolated serotype is related to the age of patients; *S. sonnei* is more frequent before the age of 15 years, while *S. flexneri* is more common in patients older than 15 years. The incubation period ranges from 6 h to 9 days. In Japan, shigellosis used to be one of the legally defined infectious diseases whose reporting was controlled by the enforcement of a former prevention law. However, this infection has been classified as a category II communicable disease since April, 1999, when a new law concerning the prevention of infectious diseases, and their medical care was introduced. All physicians who have encountered confirmed or suspected cases of shigellosis and asymptomatic carriers are obliged to report promptly to the prefectural government through a nearby health center.

Table 1. The number of *Shigella* infections in Japan

Year	*Shigella dysenteriae*	*Shigella flexneri*	*Shigella boydii*	*Shigella sonnei*	*Shigella* unidentified	Total number of cases
1990	7 (7)	84 (55)	15 (13)	271 (147)	0	377 (222)
1991	2 (2)	74 (40)	8 (7)	485 (129)	0	569 (178)
1992	4 (3)	65 (44)	11 (10)	399 (157)	0	479 (214)
1993	8 (7)	70 (42)	10 (8)	478 (184)	0	566 (241)
1994	3 (3)	83 (55)	7 (6)	267 (137)	0	360 (201)
1995	8 (8)	56 (36)	17 (13)	295 (200)	0	376 (257)
1996	6 (4)	83 (47)	7 (5)	312 (146)	0	408 (202)
1997	12 (9)	63 (39)	12 (8)	234 (187)	5 (1)	326 (244)
1998	7 (5)	167 (27)	1 (0)	441 (83)	0	616 (115)
1999	2 (2)	108 (24)	8 (5)	262 (83)	0	380 (114)
2000	4 (4)	29 (15)	4 (4)	165 (63)	0	202 (86)

Numbers in parentheses indicate numbers of patients infected overseas
Information obtained from the Internet (Infectious Agents Surveillance Report 2001)

The clinical symptoms of shigellosis usually begin with fever, fatigue, anorexia, and malaise, and watery diarrhea that progresses to bloody diarrhea and dysentery. The dysentery is characterized by abdominal cramps and tenesmus, with the frequent passage (usually 10 to 30 times per day) of stools consisting of blood, mucus, and pus. The severity of the diarrhea is related to the extent of the inflammatory lesions in the colon. Progression to severe dysentery is most common in infections with *S. dysenteriae* and *S. flexneri*, and occurs less frequently in *S. sonnei* infection. Severe shigellosis can lead to the development of toxic colonic dilation (toxic megacolon) and perforation, which is more common in patients infected with *S. dysenteriae*.[21] The diagnosis of shigellosis needs bacterial cultures using stool, rectal swab, or endoscopic biopsy specimens. It should be noted that stool specimens with leukocytes or blood increase the yield of *Shigella*. Polymerase chain reaction may be used to reduce the time required for obtaining positive results.[22] The characteristic findings on colonoscopy include erythema, edema, loss of vascular pattern, punctate hemorrhagic spots, mucosal friability, aphthoid erosions, star-shaped ulcers, and the adherence of grayish-white mucopurulent materials.[23,24] The most common involvement site is the rectosigmoid colon, and the disease can extend continuously toward the proximal colon. The mucosal appearance may become patchy during the later recovery stage.[24]

The use of antibiotics in patients with bloody diarrhea or dysentery will help reduce the duration of illness and shorten the period of the carriage state. Many *Shigella* strains are resistant to ampicillin, sulfonamides, streptomycin, cloramphenicol, and tetracyclines; the drugs of choice for the treatment of shigellosis have been 4-fluoroquinolones (e.g., ciprofloxacin) and sulfamethoxazole trimethoprim. It should also be kept in mind that data from Japanese infectious disease centers and hospitals have shown that more than 69% of clinical isolates were resistant to sulfamethoxazole trimethoprim and tetracyclines during the period 1999–2000, although all these strains showed sensitivity to quinolones (Shigellosis in Japan, Infectious Agents Surveillance Report 2001, information obtained from the Internet). Patients with immunodeficiency may be subject to relapsing infection, with bacteremia, and this can be cured by prolonged treatment with quinolones.

Escherichia coli species

Escherichia coli, a commensal in the gastrointestinal tract, exhibits five main pathogenic varieties; namely, enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroadherent *E. coli* (EAEC), enteroinvasive *E coli* (EIEC), and enterohemorrhagic *E. coli* (EHEC).[25,26] The EPEC strains are associated with diarrhea in hospitalized infants and in nursery outbreaks. The ETEC strains are a major cause of bacterial gastroenteritis in persons traveling in tropical or subtropical areas, as well as being a major cause of infantile diarrhea. The EAEC strains may cause persistent diarrhea in children, although their bacterial and clinical significance is poorly understood. In these infections, patients mostly develop frequent bowel movements, within 1 to 2 days of exposure, that reflect the action of enterotoxins on the intestinal mucosa. The clinical manifestations are similar whether the enterotoxin is heat-stable or heat-labile.

In contrast to the above three pathogenic subtypes, the EIEC and EHEC strains yield hemorrhagic enterocolitis manifested by frequent bloody or mucoid diarrhea. The pathogenesis of enterocolitis induced by the EIEC strains is essentially identical to that caused by infections with *S. flexneri* and *S. sonnei*, except that the minimum infective doses required for the development of the disease are higher for the EIEC strains as com-

pared with the latter species. The EIEC strains invade the colonic epithelium and provoke a significant inflammatory response that causes a dysentery-like disease. The incubation period is usually 2 to 3 days after the ingestion of contaminated food. The EHEC strains are the most important subtype responsible for hemorrhagic colitis. The specific form of *E. coli* identified as O157:H7 was first recognized in 1983 in an outbreak of infection.[27] Since then, this unique serotype has been increasingly accepted as a cause of numerous outbreaks and sporadic cases of acute bloody and nonbloody diarrhea.[28] *E. coli* O157:H7 does not elaborate heat-stable or heat-labile toxins, nor does it invade the gut epithelium. The primary virulence factors are designated as verotoxins because of their cytotoxic effects on cultured Vero cells, or as Shiga-like toxins because of a striking structural and functional similarity to the Shiga toxins derived from *S. dysenteriae*.[29,30] The intestinal uptake of these cytotoxins may lead to systemic complications, such as hemolytic uremic syndrome and thrombocytopenia.[28,31] In Japan, infection with O157:H7 has been classified as a category III infectious disease under the new infectious disease control law enacted in April, 1999. All physicians are obliged to notify new cases to the public health centers. The number of reported cases of infection with O157:H7 was approximately 100 per year during 1991–1995. In 1996, the number of cases abruptly increased to 3022, and since then the number has remained at a similar level, of about 2000 per year (Enterohemorrhagic *Escherichia coli* in Japan, Infectious Agents Surveillance Report 2001, information obtained from the Internet). Almost two-thirds of strains were isolated from June through September, and this seasonal variation may reflect the fact that fecal shedding of O157:H7 increases during warm months. Cattle appear to be a reservoir of infection; most outbreaks could be traced to the consumption of inadequately cooked beef, raw milk, or other products contaminated by the intestinal contents of cattle, among which frozen beef has been recognized as an important source causing "diffuse outbreaks" of O157:H7 infection.[32] Outbreaks of bloody diarrhea secondary to O157:H7 infection have also been linked to fecal contamination of rural water systems. *E. coli* O157:H7 has been shown to survive for prolonged periods in water, and protecting water sources by adequate chlorination could prevent the transmission. The incubation period of O157:H7 ranges from 1 to 8 days, but is usually 3 to 4 days after the ingestion of the contaminated food or water.

In infection with the EIEC strains, patients complain of fever, malaise, lower abdominal pain, and watery diarrhea, with the passage of small amounts of blood or mucus. In contrast, a broad spectrum of clinical symptoms has been described in patients infected with the EHEC strains. At first, the infection causes abdominal cramps and watery diarrhea that is followed by bloody diarrhea by the second or third day of the illness. The passage of gross blood or clots may be experienced in severe cases. The illness may be confused with inflammatory bowel disease or ischemic colitis. High-grade fever is rare, and about half of the patients have nausea and vomiting. These symptoms usually subside in about 1 week. Hemolytic uremic syndrome and thrombocytopenia may occur 2 to 14 days after the onset of diarrhea in a small percentage of patients, especially in children under 5 years of age and in older adults. Diagnosis of infection with the EIEC strains depends on the isolation of the responsible organisms by microbiological methods, plus the serotyping of *E. coli* somatic (O) and flagellar (H) antigens. Examination of stools in persons infected with *E. coli* O157:H7 consistently reveals the presence of leukocytes and red blood cells. Culturing stool on MacConkey culture medium, where it yields sorbitol-negative colonies, makes the bacterial diagnosis of O157:H7.[33] Specific identification requires immunological tests using antisera against O157 and H7 antigens. It is noted that positive results are obtained more frequently in stool specimens tested within 6 days after the onset of diarrhea than in those tested thereafter. Colonosocpic findings observed in this infection include mucosal hyperemia, shallow ulcerations (Fig. 3), marked edema, ready hemorrhage, erosions, and longitudinal ulcer-like lesions throughout the colon.[34] Computed tomography (CT) scans show thickening of the colonic wall (target sign, Fig. 4) and inflammatory changes in the mesenteric fat, in which the most prominent changes are detected in the right colon.[35,36] Histopathological examination of biopsy specimens demonstrates histological changes due to

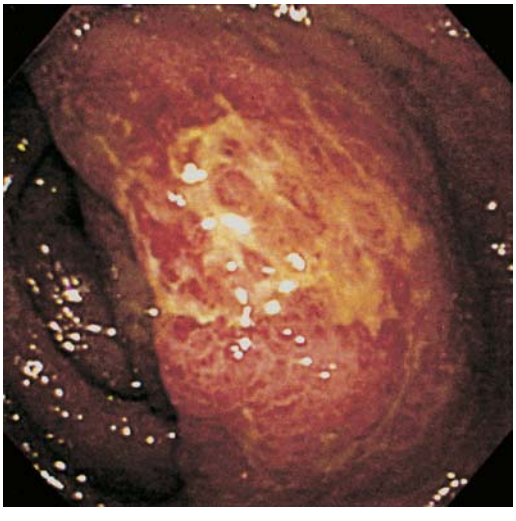

Fig. 3. Colonoscopic features of shallow ulcerations with surrounding hyperemic mucosa (sigmoid colon) in enterohemorrhagic *Escherichia coli* (EHEC) colitis

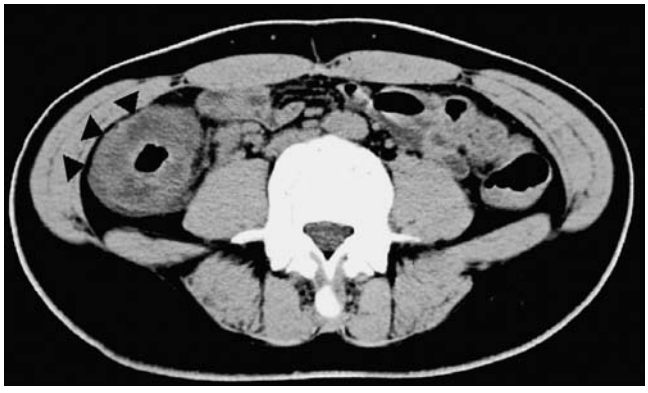

Fig. 4. Computed tomographic features (target sign, *triangles*) of colonic wall thickening (ascending colon) in enterohemorrhagic *Escherichia coli* (EHEC) colitis

ischemia and toxic injury, and edema, submucosal hemorrhage, and fibrin exudation are the most distinctive features.[36,37]

There are no specific recommendations for treatments to benefit patients with acute enterocolitis caused by the EIEC or EHEC strains. A reasonable approach for the treatment of patients infected with the EIEC strains is to begin treatment with ampicillin or ciprofloxacin. Similarly, the effectiveness of antibiotic therapy has not been documented in infections with *E. coli* O157:H7. Some strains of O157:H7 may increase the production of Shiga-like toxins when they are exposed to antibiotics to which they are sensitive, such as ampicillin, tetracycline, and norfloxacin. Nevertheless, a recent report from Japan suggests that antimicrobial therapy with fosfomycin, when administered within the first 2 days of the illness, may prevent the development of hemolytic uremic syndrome.[38]

Campylobacter species

Campylobacter species, motile, gram-negative rods or spirals, consist of many subtypes, among which *Campylobacter jejuni* accounts for the majority of cases of acute inflammatory diarrhea reported in industrialized nations.[39] The mechanisms by which *C. jejuni* causes enterocolitis are largely unknown, but invasiveness and toxin production may be involved in the pathogenesis. Enterocolitis caused by *C. jejuni* shows a peak in early summer, but sporadic cases are reported throughout the year. According to a report of infectious agents in Japan, the number of *Campylobacter* strains isolated numbered around 700 to 1300 per year during 1994–1998 (Campylobacteriosis in Japan, Infectious Agents Surveillance Report 1999, information obtained from the Internet). Although person-to-person spread by fecal-oral transmission is speculated to be important, this route may have only a limited role, because the infective doses of *Campylobacter* required to cause the disease are much higher than those of *Salmonella*.[40] The major source of human infection could be traced to the ingestion of contaminated milk or inadequately cooked poultry and eggs. Exposure to sick pets, especially puppies, has also been implicated in several outbreaks. The incubation period of *C. jejuni* is usually 1 to 6 days.

The clinical symptoms in *C. jejuni* infection range from asymptomatic carriage to life-threatening toxic megacolon. The common clinical symptoms are nausea, lower abdominal cramping, and diarrhea. Abdominal pain may be so localized as to mimic acute appendicitis. The diarrhea may be watery or bloody; however, massive intestinal hemorrhage is rare. These symptoms usually resolve within 1 week, but may persist for 1 to 3 weeks in severely ill patients. Some patients with *C. jejuni* infection have relapsing episodes of bloody diarrhea, which may be confused with ulcerative colitis. Recurrent and chronic infection is generally reported in immunocompromised hosts.[41] In the most severe form of enterocolitis, toxic megacolon and mesenteric adenitis may occur as intestinal complications. Extraintestinal manifestations resulting from bacteremia occur in certain patients infected with *C. jejuni*. Reiter syndrome, characterized as reactive arthritis, may follow *C. jejuni* enterocolitis, and this condition is observed more frequently in patients who carry the HLA-B27 phenotype.[42,43] Guillain-Barre syndrome, characterized by muscle weakness and sensory nerve abnormalities, is now regarded as a chronic sequel of enterocolitis induced by *C. jejuni*, especially by those organisms belonging to the serotype HS:19.[44] Cross-reacting antibodies recognizing both *C. jejuni* lipopolysaccharide (LPS) and antigenic determinants with nerve gangliosides are speculated to contribute to the development of the nerve damage following *C. jejuni* infection.[45]

Laboratory examinations show fecal leukocytes and erythrocytes in most patients with *C. jejuni* infection. *Campylobacter* can be identified by culturing stool or colonic tissue samples at 42°C under an atmosphere of 5% O_2 and 10% CO_2, using highly selective media (Skirow's media) after they have been placed in special transport media. The yield of *C. jejuni* may be higher from colonic tissue culture than from stool culture.[46,47] Colonoscopic findings show segmental edema, loss of normal vascular pattern with ulceration, and patchy involvement of mucosa.[48]

Most patients with mild or moderate *C. jejuni* enterocolitis show a self-limiting illness; therefore, the usage of antibiotics has been in question in these patients. Severely ill patients, especially debilitated or immunocompromised persons, appear to benefit from antibiotic therapy, and erythromycin or ciprofloxacin are the drugs of choice.

Yersinia species

Yersinia enterocolitica and *Y. pseudotuberculosis*, gram-negative aerobic bacilli, are the main subtypes of *Yersinia* species that are pathogenic for humans.[49] The virulence of *Yersinia* is associated with the direct injection of proteins, such as *Yersinia* protein kinase A (YpkA) and YopE, into eukaryotic cells.[50,51] Invasive *Yersinia* strains produce a suppurative infection of Peyer's patches and mesenteric lymph nodes, with the potential to cause systemic infection.

Y. enterocolitica and *Y. pseudotuberculosis* cause similar symptoms and signs; infection with the former bacterium is associated primarily with watery diarrhea and the latter with the swelling of mesenteric lymph nodes. Most patients with *Y. enterocolitica* show right abdominal pain and diarrhea lasting 1 to 2 weeks. Other symptoms include nausea, vomiting, and fever. About 40% of patients present with symptoms suggestive of appendicitis; however, laparotomy finds inflammation of the terminal ileum and enlarged mesenteric lymph nodes with normal appendix. *Yersinia* infection may cause migratory polyarthritis, Reiter's syndrome (common in HLA B27-positive subjects), and erythema nodosum.[42,52] The diagnosis of *Yersinia* infection depends on a special stool culture technique in which detection can be enhanced by cold incubation at 20°C to 25°C. Hemagglutination is a useful indirect test to detect *Yersinia* infection, and agglutinin titers in the range of 1:128 in previously healthy individuals are suggestive of infection. A barium enema study demonstrates thickening of mucosal folds; round filling defects in the mucosa, indicative of swelling of lymphoid tissue; and fine irregularities in the margin, without narrowing of the lumen, in the terminal ileum.[53] Colonoscopic examination consistently shows round or oval elevations with or without ulcers in the terminal ileum.[54] Some patients may have a regular array of light yellow oval aphthae from the rectum to the cecum that mimics Crohn's disease.[55]

The value of antimicrobial therapy is not clear, because most mild or moderate forms of *Yersinia* infection are self-limiting. However, patients with severe illness or systemic infection are usually treated with tetracycline, chloramphenicol, or ciprofloxacin.

Chlamydia species

Chlamydia species, which are obligate, intracellular organisms, consist of three major subgroups, *Chlamydia psittaci*, *C. trachomatis*, and *C. pneumoniae*. According to the serovar classification system, *C. trachomatis* can be further subdivided into lymphogranuloma venereum (LGV) and nonLGV strains.[56] Infection with *C. trachomatis* represents the most common sexually transmitted disease, with the incidence increasing. The main reservoir of infection is presumed to be asymptomatically infected persons; the incidence of cervical infection in women has ranged from 5% to 10% and that of urethral infection in men from 3% to 10% in industrialized countries. Infection with *C. trachomatis*, especially LGV strains L1, L2, and L3, accounts for approximately 20% of proctitis in gay men, in whom asymptomatic carriage occurs in 2% to 5%. Anorectal infection in homosexual men presumably results from direct inoculation during passive anal intercourse with infected persons.[57] This infection may also be seen in heterosexual women.

Patients with chlamydial proctitis present with bloody diarrhea and mucopurulent discharge, and, less commonly, with tenesmus and mild rectal pain. NonLGA strains or serovars can cause mild proctitis, whereas rectal inoculation with LGA strains may cause more severe forms of ulcerative proctocolitis.[58] This infection mimics Crohn's disease because of the occurrence of chronic diarrhea and perianal fistula formation. *C. trachomatis* infection is determined by culturing stool or rectal swabs plated onto McCoy cells. Usage of 0.2 M sucrose-phosphate for transport increases the positive results. Colonoscopy can yield normal findings or reveal mild inflammatory changes with mucosal friability, small erosions, and follicles in the lower 10–15 cm of the rectum.[58] Histopathological examination of rectal biopsy specimens shows distinctive features consisting of granulomatous inflammation, inflammatory cell infiltrates (neutrophils and eosinophils), and crypt abscesses.

In adults, treatment with tetracycline has been recommended for uncomplicated *C. trachomatis* infection, but longer usage is considered for proctitis and other forms of LGV infection. Two antimicrobial agents, floxacin and azithromycin, have been shown to be of value in selected patients.

Clostridium species

Clostridium species, gram-positive, spore-forming anaerobic rods, are now recognized as one of the most common causes of antibiotic-associated diarrhea.[59] Colonization by *C. difficile* follows alteration of the endogenous microflora by antibiotics (e.g., clindamycin, ampicillin, and cephalosporins), anti-neoplastic or immunosuppressive drugs (e.g., doxorubicin, 5-fluorouracil, and methotrexate), and infection by other intestinal pathogens. *C. difficile* produces two heat-labile exotoxins, toxin A (308 Kd) and toxin B (250 Kd), both of which are, possibly, responsible for disease manifestations.[60,61] The cDNA sequence shows

considerable homology between toxin A and toxin B; thereby, they could share a common intracellular mechanism of action. After binding to appropriate receptors on the brush border of intestinal epithelial cells, the toxins are internalized and act within the cells to modify proteins of the Rho subfamily, a group of guanosine triphosphate (GTP)-binding proteins. Modification of Rho proteins by the toxins results in the rounding up of cells and redistribution of the actin cytoskeleton.[62] The opening of tight junctions finally ends up with cell death. This cytotoxic effect provides the basis for the cytotoxic assay for the presence of toxigenic *C. difficile* in stool samples. These exotoxins, especially toxin A, also elicit a profound inflammatory response in the lamina propria, including the stimulation of leukocyte chemotaxis and the production of cytokines and inflammatory mediators. Most cases of *C. difficile* colitis occur as nosocomical infections in hospitals or longterm care facilities. Hospitalized patients are prone to develop colitis because of the frequent use of antibiotics in an environment where *C. difficile* is prevalent. The potential risk factors for symptomatic disease in patients who acquire *C. difficile* colonization include the severity of underlying illnesses, advanced age greater than 60 years, and reduced levels of serum IgG antibody to toxin A.[63] Colonization usually occurs by the fecal-oral route, and ingested spores of *C. difficile* can survive in conditions of physiologic gastric acidity and germinate in the colon. *C. difficile* infection shows a disease spectrum consisting of fulminant colitis, pseudomembranous colitis, antibiotic-associated colitis without pseudomembrane, antibiotic-associated diarrhea, and an asymptomatic carrier state.[59]

Patients with pseudomembranous colitis or colitis without pseudomembrane complain of diarrhea and crampy abdominal pain that typically begin during the first week of antibiotic therapy. Fever, chills, and dehydration may occur in those with severe colitis. Fulminant colitis can develop, with tachycardia, guarding, decreased bowel sounds, ascites, and toxemia. In contrast, diarrhea and crampy abdominal pain are less severe in patients with antibiotic-associated diarrhea. Stool cultures for *C. difficile* isolation (which used to be assumed to be difficult to carry out, because of its slow growth, requirement of anaerobic culture conditions, and tendency to die quickly during isolation procedures) provide physicians with reliable bacteriological information once the bacteria are isolated. The cytotoxins (both toxins A and B) can be detected by bioassays using human fibroblasts, or more conveniently, by commercially available enzyme immunoassays.[64] The latter tests have been adopted by most hospital laboratories as a standard test to detect *C. difficile* cytotoxins. In patients with pseudomembranous colitis, the diagnosis can be confirmed by colonoscopy, which reveals yellow-white, raised plaques, varying from 2 to 10 mm in size, over the mucosal surface, usually associated with patchy or diffuse colonic erythema.[65] The rectum and sigmoid colon are usually involved, but approximately 10% of cases involve only the proximal colon. Biopsy specimens from a pseudomembrane may show the characteristic "summit lesion", an eruption of debris, fibrin, mucus, and leukocyte infiltration overlying a microulceration of the surface epithelium.[66] In contrast, colonoscopic examination may reveal only a diffuse or patchy nonspecific colitis, without the formation of pseudomembranes, in patients presenting with mild diarrhea. Plain abdominal X-ray films may show acute dilation of the colon, which assists physicians in making a diagnosis of pseudomembranous colitis.[67] Computed tomographic scans are also useful, because patients with this condition often have findings of colonic wall thickening and nodularity, the accordion sign, pericolonic stranding, and ascites.[68]

The first step in the treatment of antibiotic-associated *C. difficile* colitis is discontinuation of the responsible antibiotic therapy. Further treatment with antimicrobial agents is needed to eradicate *C. difficile* infection in patients with moderate or severe colitis. Oral administration of vancomycin is usually effective in treating *C. difficile* colitis. The response to vancomycin is proved with the disappearance of *C. difficile* toxins within 2 to 3 days and the resolution of the colitis within 1 week. Metronidazole is also effective; however, it should be kept in mind that some *C. difficile* strains are resistant to this antimicrobial agent. Despite the high response rates to antimicrobial therapy with vancomycin or metronidazole, recurrence of symptoms occurs in 10% to 20% of patients, usually within the first 2 weeks after the cessation of therapy. Seriously ill patients could be treated with decompressive colonoscopy with intracolonic vancomycin administration.[69]

Summary

In daily practice, physicians often encounter bacterial infections of the lower gastrointestinal tract, with bloody diarrhea. *Shigella*, hemorrhagic and enteroinvasive *Escherichia coli*, *Campylobacter*, and *Clostridium* are the major bacterial pathogens that cause bacterial hemorrhagic enterocolitis. It is important to recognize that this condition produces a variety of clinical symptoms and signs, as well as acute bloody diarrhea, crampy abdominal pain, and fever. Also to be considered is that some bacterial infections may cause a severe form of colitis, such as toxic megacolon. The diagnostic approach needs information on the patient's age, travel history, epidemiological associations, sexual practice, and medical history, including the usage of

antibiotics. Bacterial infections can be diagnosed by microscopic study, culture, and the identification of specific bacterial toxins. Flexible colonoscopy with biopsy is useful for the differentiation of bacterial hemorrhagic enterocolitis from idiopathic ulcerative colitis and ischemic colitis. Physicians should be familiar with the diagnostic modalities used to detect the specific pathogens causing hemorrhagic bacterial enterocolitis; namely, bacterial culture, serology, histology, and nucleic acid technologies.

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