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Severe acute diarrhea

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Acute diarrhea causes considerable global morbidity and is a common presenting symptom in general practice in the United States [1]. Infection is the most common cause of acute diarrhea, and is related to environmental conditions including close living and working conditions, globalization of food production, contaminated food and water supplies, and inadequate sewage disposal [2].

Epidemiology

Diarrheal diseases are the second most common cause of death worldwide and the leading cause of childhood deaths [3,4]. In Great Britain, a prospective study followed 8000 adults over 4 months. Eight percent of adults reported one episode of diarrhea during the previous month, resulting in an estimate of one episode of acute diarrhea per person per year [5]. Mortality from diarrhea is usually related to dehydration and greatest in the elderly and children living in developing countries [6,7]. Severe acute diarrhea is more prevalent in vulnerable populations including travelers; the elderly; adults exposed to children; homosexual men; and individuals immunosuppressed by HIV infection, chronic steroids, or chemotherapy [8,9].

Definitions

The average stool output for men is 100 g of stool per day [10–12]. Objectively, diarrhea is defined as stool weight greater than 200 g in 24 hours [12]. Clinically, diarrhea is a change in stools, usually defined as

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passage of three or more loose or watery stools or one or more bloody stool in 24 hours [8]. Acute diarrhea lasts less than 14 days, whereas diarrhea lasting more than 14 days is termed “persistent diarrhea,” and longer than 1 month is termed “chronic” [12]. Severe acute diarrhea warrants immediate medical evaluation and hospitalization. The criteria for severe acute diarrhea include volume depletion, fever, six or more stools in 24 hours, an illness lasting longer than 48 hours, significant abdominal pain in individuals over 50 years, and immunocompromised patients [8,13].

History

Important clinical history includes the onset of illness, duration of symptoms, weight loss, presence of nocturnal diarrhea, and whether contacts are sick. It is also important to quantify and characterize the stools and the bloody stools.

Clues to the etiology of diarrhea can be obtained through a detailed history regarding travel to an endemic area; exposure to untreated water; medication use (particularly laxatives or antibiotics); and sexual preference. Additional helpful history includes occupational exposures, such as veterinarians, food handlers, and day care center workers [12–17].

Although dietary history is notoriously inaccurate, foods suspiciously linked to foodborne diarrheal illness are unpasteurized dairy products, undercooked meat, and fish. The timing of diarrheal symptoms with suspected recent food ingestion is also helpful [18].

Diarrhea may be associated with other gastrointestinal symptoms including nausea, vomiting, abdominal pain, fever, fecal urgency, and tenesmus. Volume status can be assessed from questions focusing on thirst, urination, dizziness, and syncope [8,9].

Physical examination

To assess the severity of acute diarrhea, physical examination should focus on signs of moderate or severe dehydration and signs of systemic toxicity. Extracellular volume can be assessed by vital sign abnormalities including fever, tachycardia, and postural hypotension [19]. Other physical examination findings of dehydration include assessment of jugular venous pressure, skin turgor, mucosal membranes, and capillary refill [20]. The presence of peritoneal signs on examination may suggest an infection with an invasive enteric pathogen, or an etiology requiring urgent surgical evaluation and management [9]. A rectal examination should be performed in all patients presenting with acute diarrhea, but especially in patients over the age of 50. The rectal examination helps the physician assess stool character, type of diarrhea, and presence of blood [21].

Laboratory evaluation

The frequency of isolating an organism from a stool culture in infectious diarrhea ranges from 2% to 40%, reflecting different populations undergoing testing, extent of testing performed by primary care providers, and the persistence of pathogens in stool [5,22–25]. The prevalence of identifiable infectious agents is underestimated because many patients do not seek medical attention for acute diarrhea and testing is not always performed. In one study, 22% of patients with gastroenteritis consulted a physician and only 5% submitted a stool sample [26]. Another study analyzed 1783 surveys from United States physicians assessing patients with acute diarrhea in the previous year to evaluate factors influencing their decision to obtain stool cultures. Stool cultures were requested from 79% of patients with a history of bloody stools, 40% of patients with nonbloody stools, and 53% of patients with diarrhea for longer than 3 days. Patients with AIDS, fever, or a history of recent travel were also more likely to have stool cultures performed [27].

Stool studies

Indications for stool studies in acute diarrhea are fever, bloody diarrhea, history of travel to an endemic area, an acute flare of inflammatory bowel disease, recent antibiotics, immunosuppression, employees involved in food handling, exposure to infants in day care centers, and history of anal intercourse [28]. One may need to notify the laboratory if special media, stains, or processing of the specimen is needed.

Fecal leukocyte, lactoferrin, and occult blood are often present in patients with diarrhea and diffuse colonic inflammation [29,30]. These tests are most helpful in febrile patients with moderate to severe acute infectious diarrhea because when positive, they lend support toward using empiric antimicrobial therapy, and when negative may eliminate the need for stool cultures [31].

Stool samples sent for culture should be fresh, within 2 hours after passage if possible, to allow best detection of organisms that decompose easily [32]. If stool samples are not available, a rectal swab can be placed in transport media and then cultured [8]. Stool studies are often inappropriately ordered [23]. Evaluation for ova and parasites is not cost effective in severe acute diarrhea [25].

Flexible sigmoidoscopy or colonoscopy

Flexible sigmoidoscopy and colonoscopy are indicated in some cases of severe diarrhea to evaluate colitis, distinguish between infection and inflammatory bowel disease, and look for pseudomembranes or signs of ischemia [33–35].

Differential diagnosis of severe acute diarrhea

Infections

Infections are the most common cause of acute diarrhea. Viruses account for 50% to 70% of acute infectious diarrhea, bacteria 15% to 20%, parasites 10% to 15%, and 5% to 10% of acute infectious diarrhea is of unknown etiology [8]. The following discussion focuses on common causes of severe acute diarrhea.

Vibrio cholerae and noncholera vibrios

Vibrio cholerae is a gram-negative curved rod that adheres to small bowel epithelial cells, releases an enterotoxin, and causes a small bowel diarrheal illness [36]. Between 1995 and 2000, 61 cases of *V cholerae* 01 were reported in the United States. Foreign travel and undercooked seafood harvested from the Gulf Coast account for most cases of cholera in the United States [37]. Noncholera vibrios, such as *V parahemolyticus*, also occur on coastal areas of the United States where contaminated shellfish may transmit disease and cause diarrhea. An outbreak of *V parahemolyticus* recently occurred in three states and was associated with shellfish harvested from the Long Island Sound [38].

Severe profuse watery diarrhea with prominent dehydration in an endemic area is usually caused by *V cholerae* serogroup 01. Other features are abrupt onset of illness and absence of blood or fecal leukocytes on stool examination [39]. Stools have a “rice water” appearance with little food residue. A history of gastric surgery and use of proton pump inhibitors or H₂ receptor blockers that decrease gastric acid increase susceptibility to cholera because more organisms survive transit [40]. Non-01 cholera vibrios produce several toxins and cause a wide range of illness, including watery diarrhea, dysentery, wound infections, and bacteremia [41]. *V vulnificus* can be fatal in patients with underlying liver disease [42].

In endemic areas during outbreaks or seasonal epidemics of cholera, watery diarrhea of all severity should be treated as cholera and stool culture done for confirmation. Darkfield microscopy can best identify organisms that classically are motile “shooting” bacteria [43]. Stool culture best detects the pathogen if performed on thiosulfate-citrate-bile-salts-sucrose agar [44]. Further identification of *Vibrio* species requires serotyping and serogrouping [41].

Treatment of *V cholerae* and noncholera vibrios rests on supportive measures including fluid and electrolyte replacement to decrease mortality [45]. Monitoring stool volume aids in the calculation of fluid deficits. In moderate to severe diarrhea, at least half of the calculated deficit should be replaced in the first 4 hours, and the remainder over the next 24 hours. Antibiotics decrease stool volume and shorten the clinical course of the diarrheal illness. When stool culture sensitivities are unknown, empiric treatment with tetracycline, doxycycline, or a fluoroquinolone can be administered [46].

Campylobacter jejuni

Approximately 2.4 million cases of *Campylobacter* occur in the United States, making it the most common cause of bacterial gastroenteritis [47]. It is acquired from ingestion of undercooked contaminated poultry and resembles *Salmonella* in that an animal (usually poultry) is the reservoir for human infection [48]. *Campylobacter* causes ileocolitis with either watery or hemorrhagic diarrhea. *Campylobacter* has also been causally linked to development of postinfectious reactive arthritis and Guillain-Barré syndrome [49–51].

Stool culture more accurately identifies *Campylobacter* if microaerophilic cultivation with inhibitory media is performed on the specimen [52]. Culture-proved severe *Campylobacter* can be treated with antibiotics, such as erythromycin or fluoroquinolones, to shorten the illness. Worldwide resistance is increasing and commonly occurs during therapy; it is important to confirm in vitro susceptibility [53–56].

Nontyphoidal Salmonella

Salmonellosis is one of the leading causes of foodborne disease in the United States. Nontyphoid salmonellosis occurs in approximately 1.4 million people in the United States each year, commonly during the summer and fall, and is associated with ingestion of contaminated poultry, eggs, and milk products [21,57]. Initially salmonellosis may present as a small bowel diarrhea, but often progresses to colitis [9].

Bacteremia occurs in 2% to 14%, especially in infants and the elderly [58–60]. Other risk factors for developing bacteremia from intestinal salmonellosis include immunosuppression, uremia, hemolytic anemia including sickle cell anemia, and malignancy [61–67].

Routine stool culture accurately identifies most salmonella. Treatment for nontyphoidal *Salmonella* is controversial because of increasing antibiotic resistance and because studies have not conclusively shown a difference in duration of illness or diarrhea in patients treated with antibiotics versus placebo [68]. In high-risk patients at risk for bacteremia, however, antimicrobial therapy is recommended with trimethoprim sulfasoxazole (TMP/SMX) or a fluoroquinolone [69].

Shigella

Shigella is another commonly documented foodborne disease, accounting for 10% to 20% of all cases of diarrhea in the United States [27]. As few as 200 organisms can initiate the disease [70]. Most transmission is through person-to-person contact, contributing to epidemics in day care centers and institutional settings. *Shigella* infection causes exudative colonic hemorrhagic diarrhea and may be complicated by the development of hemolytic uremic syndrome (HUS); thrombocytopenic purpura; and other extra-intestinal complications, such as arthritis [71–73].

Stool culture more accurately identifies *Shigella* if performed on xylose-lysine-desoxycholate or *Salmonella-Shigella* agar [74]. Antimicrobial therapy shortens the duration of illness [75,76]. If shigella is acquired in the United States, recommended treatment is TMP-SMX. If acquired abroad, a quinolone is generally recommended because TMP resistance is common [46].

Yersinia enterocolitica

Yersinia enterocolitica causes hemorrhagic diarrhea and severe abdominal pain that can mimic appendicitis [77]. Epidemics have been associated with contaminated milk. Transmission to humans from domestic and farm animals has also been described [78]. Stool culture more accurately identifies *Y enterocolitica* if it is sent for cold enrichment or *Yersinia*-selective agar [79]. For severe cases of yersiniosis, treat with a fluoroquinolone or ceftriaxone [80].

Clostridium difficile

Clostridium difficile should be suspected in patients with a history of antibiotics within 2 months of the onset of diarrhea, and in hospitalized patients developing diarrhea at least 72 hours after admission [81]. The overall incidence of *C difficile* in hospitalized patients is 28% and increases in the elderly [82–84].

Antibiotics change the normal intestinal flora, leading to increased proliferation of *C difficile* producing enterotoxin A and B, resulting in colitis and pseudomembranes [85]. Common antibiotics predisposing to *C difficile* infection are clindamycin, ampicillin, and cephalosporins [86]. Patients may develop fever, abdominal cramping, and leukocytosis. Typically, diarrhea is initially watery and voluminous with no gross blood or mucus, but in severe cases can progress to bloody diarrhea. Dehydration is mild except in very severe cases. Severe cases can have toxic megacolon or rarely perforation and death [85,87,88].

Stool examination reveals numerous red blood cells and fecal leukocytes. Stool culture for *C difficile* ideally needs anaerobic conditions. A positive stool culture does not distinguish disease from carriers. Diagnosis of disease rests on detection of toxin in the stool. Tissue culture is the gold standard but most laboratories use rapid enzyme immunoassay tests for toxin A or B or both, now giving way to ELISA tests [89,90]. Sigmoidoscopy or colonoscopy can be performed if immediate diagnosis of colitis is needed, and can show minimally erythematous colonic mucosa with edema, or granular, friable, or hemorrhagic mucosa with pseudomembranes [91].

Treatment for *C difficile* includes correction of dehydration, stopping antibiotics if possible, and metronidazole [92]. In severe cases, or in those who cannot take metronidazole, vancomycin is an alternative [93]. Relapse occurs in approximately 20% of treated patients [94–96].

Enterohemorrhagic Escherichia coli diarrhea

Enterohemorrhagic *Escherichia coli*, especially *E coli O157:H7*, can cause colitis [97]. Ingestion of undercooked ground beef has been most commonly implicated; however, many other food vehicles have been reported. Patients frequently have abdominal pain and hemorrhagic diarrhea. The most worrisome complications are HUS and thrombocytopenic purpura, which are more common in children [98–100].

Suspected enterohemorrhagic *E coli* should be cultured on sorbitol-MacConkey agar [101]. The Centers for Disease Control and Prevention recommends screening stool from all patients with a history of bloody diarrhea for *E coli O157:H7* or Shiga toxin by direct stool examination and confirmation by a reference laboratory if positive.

Antimicrobial therapy is controversial when *E coli O157:H7* and other Shiga toxin producing *E coli* are suspected [8]. Studies examining the administration of antibiotics during early infection concluded there might be increased toxin release from killed organisms leading to greater absorption and increased likelihood of developing HUS [102–104]. In a prospective study, however, treatment with TMP-SMX late in illness did not predispose to HUS [105]. Conflicting data have led to uncertainty regarding antibiotic treatment for this pathogen. Current recommendations suggest supportive treatment, monitoring for microangiopathic complications of HUS, and avoiding antibiotics especially in children with diarrhea.

Viruses

Viruses commonly cause diarrhea but it is rarely severe [106]. Norwalk virus, Rotavirus, Astrovirus, Calicivirus, Coronavirus, Enterovirus, and enteric adenovirus (type 40,41) are waterborne or foodborne illnesses with an incubation period of 1 to 3 days. Associated symptoms are abrupt onset of nausea and abdominal cramps followed by vomiting or diarrhea. Fevers occur in approximately 50% of affected individuals. Headache, myalgias, upper respiratory symptoms, and abdominal pain are common. Stool studies are negative for fecal leukocytes and blood. The illness is usually mild and lasts 1 or 2 days. Oral fluids are generally suggested; intravenous fluids are only needed in rare cases [107]. Bismuth subsalicylate can improve clinical symptoms of viral gastroenteritis [108].

Protozoa and parasites

Protozoa that may cause acute diarrhea include the colonic pathogen *Entamoeba histolytica*, and small intestine pathogens *Giardia lamblia*, *Isospora*, *Cyclospora*, *Microsporidium*, and *Cryptosporidium*. Infection may occur from travel to endemic areas and contact with contaminated food, water, or another infected individual. For example, a *Cyclospora cayotensis* outbreak occurred from ingestion of raspberries from Guatemala

[109]. Immunocompromised patients are most vulnerable to infection with these organisms. The laboratory should be advised of specific organisms that are being considered to improve the sensitivity of detection. Treatment is aimed at the specific organism.

Special cases

Immunocompromised individuals

Diarrhea has been reported in up to 60% of patients with AIDS in industrialized countries and in 95% of patients with AIDS in the developing world [110]. Organisms causing diarrhea in patients not on antiretroviral therapy are numerous and include *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora*, *Microsporidia*, *G lamblia*, *Strongyloides*, *E histolytica*, *Salmonella enteritidis*, *Campylobacter*, *Shigella*, *Mycobacterium avium*, cytomegalovirus, herpes simplex, Epstein-Barr virus, adenovirus, tuberculosis, and mycobacterium avium complex [111–113]. A full discussion of the pathogens commonly causing acute diarrhea in patients immunocompromised from AIDS, cancer chemotherapy, and bone marrow transplant is beyond the scope of this article. The treatment of diarrhea in immunocompromised patients is essentially the same as normal hosts, but may require prolonged courses of antimicrobial therapy. Patients with advanced immunocompromise (absolute CD4 count less than 200 cells/mm³) should have stool studies and start empiric treatment with a quinolone for bacterial sources of infection [113].

Noninfectious causes

There are important noninfectious causes of severe acute diarrhea. Inflammatory bowel disease can occasionally have an acute onset. This is more common with ulcerative colitis but can be seen with Crohn's disease. Symptoms include diarrhea with mucus, rectal bleeding, and abdominal pain. Young adults between the ages of 20 and 40 are typically affected but the elderly can also have inflammatory bowel disease. The diagnosis of ulcerative colitis relies on clinical history, stool studies to exclude infection, and either sigmoidoscopy or colonoscopy to document the extent of disease. Plain films can also provide information regarding the extent of disease and can diagnose the complication of toxic colon [114]. Medical management of ulcerative colitis includes glucocorticoids, aminosalicylates, and immunosuppressive agents including azathioprine and 6-mercaptopurine [115]. Colectomy is reserved for patients with severe attacks who fail to respond to medical treatment, complications of a severe attack, dysplasia, or carcinoma [116].

Medications may also cause acute diarrhea. The most common medications responsible for acute diarrhea are laxatives; antacids containing

calcium or magnesium; colchicine; antibiotics; sorbitol gums; and enteral tube feeds, especially if hypertonic. Diarrhea usually resolves after cessation of the medication [117].

Acute radiation enteritis may occur within hours to 3 weeks after treatment. The severity of the enteritis depends on the size of the radiation field, total dose of radiation received, and concurrent chemotherapy. Patients clinically have nausea, diarrhea, and abdominal cramps and nausea from increased intestinal motility, and decreased surface epithelium for absorption. The terminal ileum is frequently irradiated during treatment of pelvic malignancies; steatorrhea, decreased absorption of vitamin B₁₂, and bile acids may occur. Diarrhea generally resolves within 2 to 6 weeks after completion of radiation [118].

Intestinal ischemia should be considered in patients who have had an episode of hypotension or shock and subsequently develop bloody diarrhea from ischemic colitis, or profound diarrhea from small bowel ischemia. The elderly, patients with a history of hypercoagulable states, congestive heart failure, cardiac arrhythmias, recent myocardial infarction, unexplained abdominal distention, or gastrointestinal bleeding should also be evaluated for intestinal ischemia, and surgical consultation obtained for possible resection [34,119].

Management of severe acute diarrhea

Medical management of severe acute diarrhea includes fluid rehydration, electrolyte replacement, diet alteration, antimicrobial treatment, and symptomatic therapy (Fig. 1) [120].

Fluids

Fluids used for rehydration should contain sodium, potassium, and glucose [121–123]. Oral rehydration solutions were developed following the realization that in many small bowel diarrheal illnesses the intestine can still absorb water if glucose and salt are present to assist in the transport of water from the intestinal lumen. The oral rehydration solution recommended by the World Health Organization consists of 3.5 g sodium chloride, 2.5 g sodium bicarbonate, 1.5 g KCl, 20 g of the mixture in 1L of clean drinking water.

Intravenous fluid therapy is essential treatment in severely dehydrated patients who are hypovolemic, in shock, or who cannot tolerate oral rehydration therapy because of severe vomiting or altered mental status [9]. Ringer's lactate is recommended for adults. It is recommended that one calculate the total fluid deficit in severely dehydrated patients; give half within the first hour then the rest over next 3 hours [124]. The volume of fluid is based on rate of stool losses and degree of pre-existing dehydration. Oral potassium and oral fluids can also be administered with the

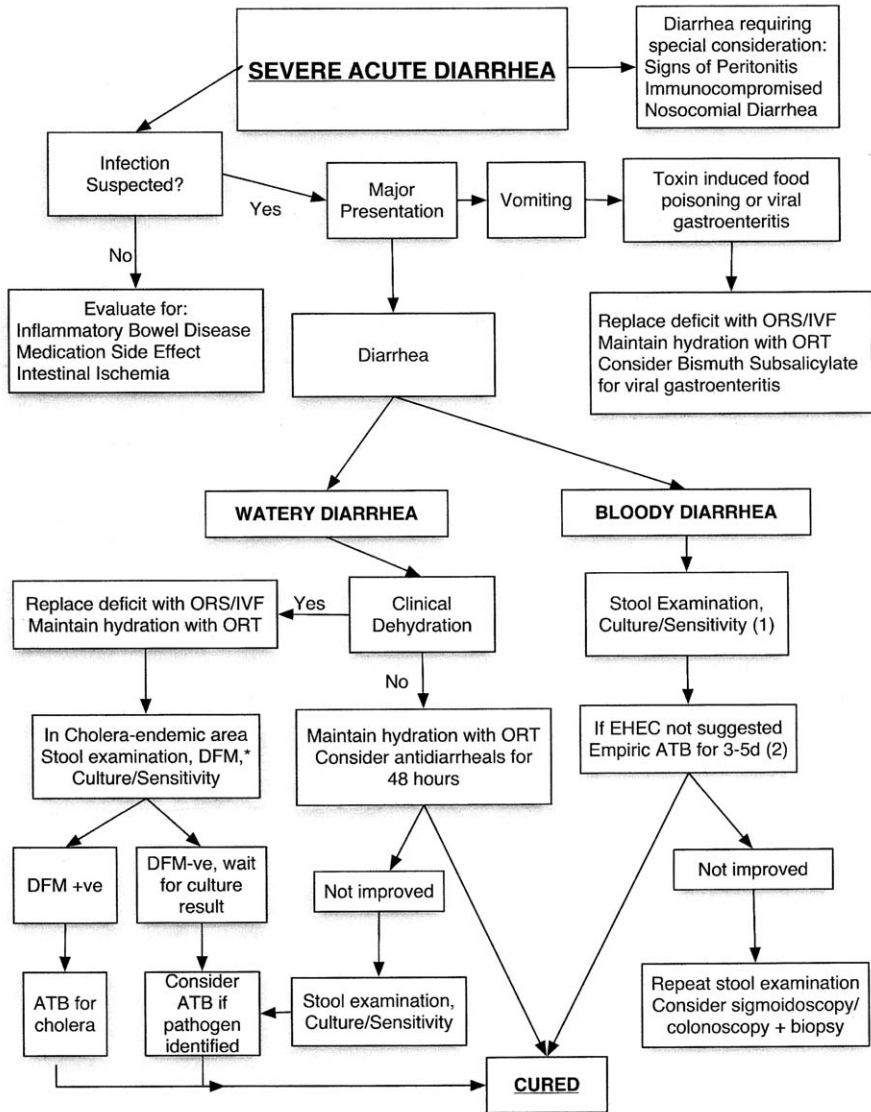


Fig. 1. Algorithm developed for the management of adult diarrhea. (1) Stool examination and culture methods depend on availability, affordability, and local practice of each community or country. (2) Strongly recommended for severely ill patients (select antibiotics according to sensitivity of local antibiogram). ATB, antibiotics; DFM, darkfield microscopy (if not available, look for “shooting bacteria” under light microscopy); EHEC, enterohemorrhagic *E coli*; IVF, intravenous fluid; ORT, oral rehydration therapy. (Adapted from Manatsathit S, Dupont HL, Farthing M, et al. Guideline for the management of acute diarrhea in adults. *J Gastroenterol Hepatol* 2002;17:S54–71; with permission.)

intravenous fluids if the patient is not vomiting and their mental status is intact. During fluid rehydration, urine output should be monitored and patients should be assessed periodically for signs of hyponatremia and hypernatremia [125].

Diet

The benefit of a specific dietary regimen other than oral hydration has not been well established. Adequate caloric intake during an episode of acute diarrhea facilitates enterocyte renewal [126]. Boiled starches and cereals consisting of rice, noodles, potatoes, wheat, and oat are generally tolerated in patients with watery diarrhea. Crackers, bananas, yogurt, soup, and boiled vegetables may also be consumed.

Antibiotics

Empiric antibiotics should be prescribed for patients with severe acute diarrhea manifested by symptoms of bacterial diarrhea. In this selected population of patients, antibiotics decrease length and severity of illness [127,128]. Additional criteria for empiric antibiotics are fever, occult blood, numerous fecal leukocytes in the stool, abdominal pain, more than six bowel movements in 24 hours, diarrhea lasting greater than 48 hours, and immunosuppression [129,130]. Travelers with severe acute diarrhea are usually infected with a bacterial pathogen and illness is shortened by antimicrobial therapy [131–133]. Before initiation of empiric antibiotics for severe acute diarrhea, all patients should be questioned carefully regarding their risk for *C difficile* and tested for the pathogen.

Commonly recommended empiric regimens include ciprofloxacin, TMP-SMX, or erythromycin until a specific pathogen with sensitivities is identified from stool examination and culture [8,9].

Symptomatic therapy

Antidiarrheal agents improve quality of life, can decrease stool frequency and stool volume, and shorten clinical illness [134,135]. In industrialized countries, antidiarrheal medications are cost effective and useful in returning people to work and school. There is controversy in their use when invasive pathogens are suspected. In patients with high fever, sepsis, bloody diarrhea, or immunocompromised patients, avoid antimotility medications because they can delay clearance of pathogens from the bowel, resulting in increased tissue invasion and prolonged disease [136,137].

In afebrile patients with nonbloody stools, antimotility agents, such as loperamide or diphenoxylate, may be used for the symptomatic treatment of patients with acute diarrhea. These agents work by slowing intraluminal flow of liquid, facilitating intestinal absorption [138]. Loperamide is the drug of choice because of its safety and efficacy. Diphenoxylate with

atropine is cheaper than loperamide but has central opiate effects and may have cholinergic side effects [139]. Both drugs may facilitate the development of HUS in patients infected with enterohemorrhagic *E coli* [140]. Patients should increase their fluid intake while taking antimotility agents because these agents may cause fluid pooling in the intestine, and mask fluid losses.

Bismuth subsalicylate is useful for prevention or treatment of travelers' diarrhea. It has antidiarrheal effects through an antisecretory salicylate moiety, and its antibacterial properties make it useful as prophylaxis in travelers' diarrhea [141–143]. Compared with placebo, bismuth subsalicylate reduces number of stools by approximately 50% [144].

Attapulgit is a clay-like substance that absorbs water, creating formed stools. It also adsorbs toxins made by bacteria and prevents toxin adherence to intestinal membranes [145,146]. Attapulgit is not effective in febrile bloody diarrhea and in general is less effective than loperamide, but is a safer medication because it is not absorbed [147].

Many drugs exert antisecretory effects through different mechanisms including inhibition of prostaglandins, cyclic AMP, inhibition of calmodulin, and enkephalinase inhibition of chloride channels. Oral enkephalinase inhibitor (Racecadotril) is currently in clinical trials. It is an antagonist of 5HT₃ receptors and prevents degradation of endogenous opioids (enkephalins), reducing hypersecretion of water and electrolytes into the intestinal lumen [148–150].

Summary

Acute diarrhea is commonly caused by an infection. Severe acute diarrhea warrants immediate medical evaluation and hospitalization. Indications for stool studies include fever; bloody diarrhea; recent travel to an endemic area; recent antibiotics; immunosuppression; and occupational risks, such as food handlers. Noninfectious causes include inflammatory bowel disease, radiation enteritis, and intestinal ischemia. Management of severe acute diarrhea includes intravenous fluid rehydration and empiric antibiotics. Use of antidiarrheal agents is controversial when invasive pathogens are suspected.

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