CLINICAL PRACTICE

Bacterial Diarrhea

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 47-year-old man reports a 1-week history of diarrhea, with grossly bloody stools for the past 5 days. He reports no history of travel, contacts with sick persons, or underlying gastrointestinal disease. How should he be evaluated and treated for an infectious cause of his illness?

THE CLINICAL PROBLEM

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Foodborne bacterial diarrhea is an emerging health threat that is attributable to the increased consumption of fresh vegetables and fruits, the challenges associated with producing large quantities of inexpensive foods, the increasing importation of foods from developing regions, and the growing pattern of consumption of foods in public restaurants.[1] Of the more than 5.2 million cases of bacterial diarrhea that occur each year in the United States, 80% are a result of foodborne transmission.[2] Person-to-person spread occurs if only a small amount of a pathogen is required for infection; these pathogens include shigella, Shiga toxin–producing *Escherichia coli*, and protozoal and viral agents.

Bacterial enteropathogens lead to an estimated 46,000 hospitalizations and 1500 deaths each year in the United States. The four most commonly reported bacterial enteropathogens in the United States — campylobacter, nontyphoid salmonella, Shiga toxin–producing *E. coli*, and shigella — are associated with an estimated cost of $7 billion annually.[3] The first three of these organisms are spread to humans from animal reservoirs and are currently threatening our food supply.[1] The highest incidence of campylobacter and salmonella infection occurs among infants, presumably because of cross-contamination in the household and the lower number of organisms required to cause clinical infection in infants than in older children and adults.

Table 1 lists the projected incidence of illness caused by bacterial enteropathogens in the United States and the typical clinical manifestations of these illnesses. In addition to these organisms, other bacterial enteropathogens cause variable numbers of cases of diarrhea. Aeromonas species occur worldwide but are particularly important in tropical regions; they cause acute or persistent diarrhea or dysenteric diarrhea (passage of grossly bloody stools). *Plesiomonas shigelloides* is a cause of acute diarrhea associated with seafood consumption and international travel. Enterotoxigenic *E. coli* is a growing cause of foodborne diarrhea, and enteroaggregative *E. coli* is an inadequately studied but potentially important cause of endemic diarrhea in children in the United States. Although bacterial enteropathogens are of the greatest importance for children living in the developing world, this article concentrates on bacterial diarrhea in the United States, which is similar to that in other industrialized regions. A previous review provides additional information about infectious diarrhea.[6]

STRATEGIES AND EVIDENCE

EVALUATION

The clinician should consider specific bacterial enteropathogens on the basis of the disease setting and clinical features of the illness. When bacterial enteropathogens are suspected, a stool culture or toxin assay will help to establish the diagnosis. Most laboratories are set up to routinely look for shigella, salmonella, and campylobacter when stools are cultured. In the evaluation of bloody diarrhea, the laboratory should further be instructed to look for Shiga toxin–producing *E. coli*. With seafood-associated diarrhea or dehydrating cholera-like diarrhea, the laboratory should be instructed to look for choleraic and noncholeraic vibrios. Indications for stool culture include the presence of severe diarrhea (passage of six or more unformed stools per day), diarrhea of any severity that persists for longer than a week, fever, dysentery, and multiple cases of illness that suggest an outbreak. Stool cultures are not routinely recommended in most cases of watery diarrhea or traveler's diarrhea because of the low yield of bacterial pathogens. In most cases of infectious diarrhea, a single stool sample efficiently collected and studied by a competent laboratory is satisfactory for the workup. When multiple stool samples are obtained from patients with diarrhea, the increased yield of bacterial pathogens is approximately 20% (one in five additional samples is positive).[7] Pathogens associated with specific clinical syndromes are described below.

CONDITIONS ASSOCIATED WITH BACTERIAL DIARRHEA

Acute Watery Diarrhea

Most bacterial and nonbacterial enteropathogens produce acute watery diarrhea, so this condition is clinically nonspecific. The rate of underreporting of cases of acute watery diarrhea that are caused by detectable enteric pathogens, including most cases of diarrhea caused by salmonella and campylobacter, is substantial[8]; it is estimated that the cause is identified in fewer than 3% of cases in the United States. Compounding the problem of low rates of identification, many of the potentially important agents that cause watery diarrhea are not detectable by means of routine diagnostic laboratory tests; these agents include enterotoxigenic *E. coli*, enteroaggregative *E. coli*, enteroinvasive *E. coli*, noncholeraic vibrios, and noroviruses.

The clinical manifestations of strains of diarrheogenic *E. coli* and diagnostic tests to detect them are summarized in Table 2. Specific strains of diarrheogenic *E. coli* are associated with characteristic clinical and epidemiologic features and distinct detection requirements. Thus, it is inappropriate to refer to *E. coli* diarrhea without considering the specific type. Molecular studies with the use of genome microarray analysis have helped to define the pangenes of *E. coli* and offer insights into phylogenetic relationships.[11]

Dysentery

Passage of bloody stools suggests possible bacterial colitis. The four major causes of bloody diarrhea in the United States, in descending order of frequency of occurrence, are shigella, campylobacter, nontyphoid salmonella, and Shiga toxin–producing *E. coli*.[12] Other organisms may also cause dysentery, including aeromonas species, noncholeraic vibrios, and *Yersinia enterocolitica*. It is estimated that only 5% of organisms that cause bloody diarrhea in the United States and that are detectable by laboratory tests are identified.[2]

Shiga toxin–producing *E. coli* strains cause watery diarrhea that becomes bloody in 1 to 5 days in 80% of patients; characteristic features of this condition include severe abdominal pain and cramps and passage of five or more unformed stools per 24 hours in the absence of fever.[13] Infection by Shiga toxin–producing *E. coli* is the main cause of renal failure in childhood. In the hemolytic–uremic syndrome, Shiga toxin released in the gut enters the bloodstream and reaches the renal endothelium. Two thirds of children with the hemolytic–uremic syndrome require dialysis; the associated mortality rate is 3 to 5%. Although Shiga toxin–producing *E. coli* strains characteristically cause hemorrhagic colitis, manifestations of ischemic colitis may also occur.[14]

Approximately 40% of Shiga toxin–producing *E. coli* infections in the United States are non-O157 strains. Non-O157 Shiga toxin–producing *E. coli* can cause the same spectrum of disease as O157 strains. Unlike most O157:H7 strains, the non-O157 strains are usually sorbitol-fermenting. Strains of Shiga toxin–producing *E. coli* can be examined for the presence of Shiga toxin–carrying bacteriophages in their genome; these influence the spread of Shiga toxin genes.[15] It appears that Shiga toxin 2 is more important in the pathogenesis of the hemolytic–uremic syndrome than

Table 1. Bacterial Enteropathogens That Cause Enteric Disease.*

Enteropathogen	Estimated No. of U.S. Cases/Yr	Clinical and Epidemiologic Features	Diagnostic Evaluation
Clostridium difficile	>250,000 occur in hospitals,[4] many more develop in outpatient settings	Diarrhea, often with fever or dysenteric characteristics, and leukocytosis after administration of antibacterial drugs in elderly patients with coexisting conditions; occurs more commonly in outpatient settings, in children, in patients receiving proton-pump inhibitors, and in patients with inflammatory bowel disease	Stool test for *C. difficile* toxin (enzyme immunoassay for toxins A and B, cytotoxicity tissue-culture assay for toxin B), microbiologic culture, or two-stage test (glutamate dehydrogenase test as a screen followed by enzyme immunoassay for toxins A and B)
Shigella	450,000[2]	Severe diarrhea, often with fever or dysenteric characteristics, with high risk of person-to-person spread due to low inoculum required for infection	Conventional stool culture
Nontyphoid salmonella	1.4 million[2]	Acute watery diarrhea, often with fever, occasionally with dysenteric characteristics; 95% of cases are a result of foodborne transmission (from poultry or hens' eggs); commonly seen in infants because of cross-contamination in household; recently identified vehicles of transmission are peanut butter and possibly pistachios	Conventional stool culture
Campylobacter jejuni	1.4 million–2.4 million[2,5]	Acute watery diarrhea, often with fever or dysenteric characteristics; foodborne transmission accounts for 80% of cases (often from poultry); many infections acquired during international travel	Conventional stool culture
Shiga toxin–producing *Escherichia coli*, including *E. coli* O157:H7 and non-O157 strains	100,000[2]	Watery diarrhea progressing to passage of bloody diarrhea; infection acquired from food (ground beef or contaminated produce) (in 52% of patients), person-to-person spread (in 14%), water and wading pools (in 9%), contact with animals (in 3%), laboratories (in <1%), and unknown sources (in 21%); important reservoir in cattle	Stool culture with the use of sorbitol–MacConkey agar for nonfermenting bacteria followed by serotyping for O157, then H7 with enzyme immunoassay of stool for Shiga toxins; send *E. coli* from positive stools to reference laboratory for serotyping
Vibrio cholerae 01 (choleraic)	50[2]	Acute dehydrating diarrhea in endemic regions; low-level endemicity in U.S. Gulf Coast states	Stool culture in special salt-containing media (TCBS) with study of isolates for O1 serotype
Noncholeraic vibrios	8000[2]	Watery diarrhea often with dysenteric characteristics; associated with shellfish and seafood	Stool culture in special salt-containing media (TCBS)
Enterotoxigenic *E. coli*	79,000[2]	Acute watery diarrhea; cause of nearly half of cases of traveler's diarrhea, important cause of diarrhea in children in developing regions; growing cause of foodborne disease in the United States	Stool culture for *E. coli*, followed by assay for heat-labile cholera-like enterotoxin and heat-stable enterotoxins by ELISA, DNA hybridization, or PCR methods
Typhoid and paratyphoid salmonella	800[2]	Systemic toxic effects and fever, abdominal symptoms (pain, ileus, diarrhea, constipation); most infections acquired during international travel; organism reservoir is infected humans	Blood and stool culture

Yersinia enterocolitica	96,000[2]	Acute watery diarrhea, may cause fever and dysentery and a pseudo-appendicitis condition; seen most commonly in northern countries (e.g., Scandinavia and Canada) but is seen worldwide as a cause of acute diarrhea, with animal reservoir including swine and cattle	Organism identified in selective gram-negative media such as MacConkey agar incubated at 25 to 28°C
Staphylococcus aureus	185,000[2]	Foodborne outbreak of vomiting lasting ≤12 hr, with an incubation period of 2–7 hr	Characteristic clinical manifestations; food may be cultured for staphylococcus or enzyme immunoassay may be performed for enterotoxin in food
C. perfringens	250,000[2]	Potentially very large foodborne outbreaks of watery diarrhea without fever or vomiting; incubation period of 8–14 hr	Confirmed in foodborne outbreaks by detecting ≥10^6 *C. perfringens* spores/g of feces in affected persons or ≥10^5 organisms/g in food
Bacillus cereus	27,000[2]	Foodborne outbreaks of gastroenteritis; two syndromes resembling *S. aureus* with vomiting after 2–7 hr or *C. perfringens* disease with watery diarrhea after 8–14 hr	Confirmed in foodborne outbreaks by detecting >10^5 organisms in food

* ELISA denotes enzyme-linked immunosorbent assay, PCR polymerase chain reaction, and TCBS thiosulfate citrate bile sucrose agar.

Shiga toxin 1.[16] Laboratory evaluation of bloody stools should include assays for sorbitol-negative *E. coli*, followed by serotyping for O157:H7 strains, as well as examination of the stools for Shiga toxins 1 and 2 by means of commercial enzyme immunoassay.[17] In cases in which fecal testing for Shiga toxin is positive but testing for sorbitol-fermenting *E. coli* O157 is negative, isolates can be examined in a reference laboratory for a non-O157 Shiga toxin–producing *E. coli* serotype.

Food Poisoning

Food poisoning is the term used when a preformed toxin in food is ingested, resulting in an intoxication rather than an enteric infection.[18] *Staphylococcus aureus* causes vomiting within 2 to 7 hours after the ingestion of improperly cooked or stored food containing a heat-stable preformed toxin. *Clostridium perfringens* causes watery diarrhea without vomiting within 8 to 14 hours after the ingestion of contaminated meat, vegetables, or poultry. Strains of *Bacillus cereus* from contaminated fried rice, vegetable sprouts, or other food items produce one of two toxins that may result in disease resembling that caused by *S. aureus* or *C. perfringens*, depending on the toxin produced. Most cases of food poisoning are of short duration, with recovery occurring in 1 to 2 days. Although it is possible to confirm the cause of food poisoning by microbiologic methods, these are rarely used, and the diagnosis is made in nearly all cases clinically without laboratory confirmation.

Traveler's Diarrhea

Traveler's diarrhea occurs when persons from industrialized regions venture into developing tropical and semitropical areas with reduced levels of personal and food hygiene. Bacterial enteropathogens cause up to 80% of cases.[19] The diarrhea-producing *E. coli* (enterotoxigenic *E. coli*, enteroaggregative *E. coli*, and possibly diffusely adherent *E. coli*) account for more than half of cases occurring in Latin America, Africa, and South Asia (the Indian subcontinent).[19] Shigella, salmonella, campylobacter, aeromonas species, noncholeraic vibrios, and plesiomonas also cause this condition. Although pathologic types of *E. coli* are important in South Asia and Southeast Asia, the invasive organisms (campylobacter, shigella, and salmonella) are relatively more important causes of traveler's diarrhea in Asia than in the other high-risk regions.

Table 2. Types of *Escherichia coli* That Cause Diarrhea.*

Type	Pathogenesis	Clinical and Epidemiologic Features	Diagnostic Evaluation
Enteropathogenic *E. coli*	Typically belong to one of 17 serotypes, show attaching-and-effacing histopathological features, and have aggregation of polarized actin with pedestal formation at the site of attachment; virulence factors include plasmid-mediated bundle-forming pili that lead to focal attachment and the chromosomal *eae* gene encoding intimin, responsible for tight epithelial attachment and loss of microvilli; typically produce both bundle-forming pili and *eae*; atypical types produce *eae* but not bundle-forming pili	Classic types cause hospital nursery outbreaks and pediatric diarrhea worldwide; atypical types may be more important causes of diarrhea in children and adults but remain largely unstudied in most populations	Virulence assays have largely replaced serotyping, including demonstration of focal attachment to HEp-2 cells, DNA probe for enteroadherence factor, or PCR to identify bundle-forming pili and intimin
Enterotoxigenic *E. coli*	Produce heat-labile cholera-like enterotoxin working through adenylate cyclase secretory pathways, a small-molecular-weight heat-stable enterotoxin working through guanylate cyclase secretory pathways, and colonization factor antigen gut-attachment fimbriae	Important cause of pediatric diarrhea in the developing world; most important cause of traveler's diarrhea; becoming important as a foodborne pathogen in the United States	Presence of a low-molecular-weight heat-stable enterotoxin, heat-labile cholera-like enterotoxin, or both by ELISA, DNA hybridization, traditional PCR, or real-time PCR
Enteroinvasive *E. coli*	Presence of shigella-like invasion plasmid	Common cause of acute shigella-like pediatric diarrhea in Brazil and eastern Europe; an occasional cause of sometimes large foodborne outbreaks in industrialized areas	Presence of invasion plasmid of shigella by DNA probe or PCR; classically these strains have been identified by development of conjunctivitis when instilled into the eye of a guinea pig (Sereny test)
Shiga toxin–producing *E. coli*	Release Shiga toxin 1 and Shiga toxin 2, harbor locus of enterocyte effacement and type III secretion system inducing the attaching-and-effacing lesions characterized by accumulation of actin pedestals (as in enteropathogenic *E. coli*); absorbed Shiga toxins lead to development of the hemolytic–uremic syndrome, with rate increased by Shiga toxin–producing *E. coli* inoculum size, serotype of Shiga toxin–producing *E. coli* (O157 to non-O157 strains), organism virulence and Shiga toxin type (Shiga toxin 2 more than Shiga toxin 1), host age (increased rate among children and the elderly), immune status and immune response (activation of complement), and use of drugs (e.g., antibiotics, proton-pump inhibitors, and antimotility drugs)	Important cause of watery diarrhea, progressing to bloody diarrhea (hemorrhagic colitis) in 1–5 days affecting all age groups in industrialized regions; the hemolytic–uremic syndrome follows colitis in children (in 10% of cases) and the elderly (in <10%) with 3–5% mortality; causes "ischemic colitis," especially in the elderly	Culture of a fecal sample on sorbitol–MacConkey media followed by testing sorbitol–nonfermenting *E. coli* for O157 and H7 lipopolysaccharides; in addition, the stool sample should be tested directly for Shiga toxin 1 and Shiga toxin 2 by enzyme immunoassay to improve the identification of O157 strains and to determine presence of non-O157 *E. coli*
Enteroaggregative *E. coli*	Strains harbor *aggR* regulon, encoding aggregative adherence fimbriae; strains heterogeneous and often possess other virulence factors (e.g., dispersin gene, Pic protease, pilin gene *aafA*, biofilm, cytotoxin proteins [Pet, EspP], and enterotoxins)	Important cause of diarrhea in children throughout the world, including the United States; organism associated with persistent pediatric diarrhea in developing regions; second most important cause of traveler's diarrhea; cause of AIDS-associated diarrhea	Detected by characteristic attachment pattern to HEp-2 cells or by PCR based on detection of *aggR* regulatory gene or other defined virulence property
Diffusely adherent *E. coli*	Show diffuse adherence to epithelial cells	Cause of diarrhea in children older than 1 yr in developing countries[9] and traveler's diarrhea[10]	Detected by characteristic attachment pattern in HEp-2 cells or by DNA probe or PCR for *Afa* and *Dr* genes

* AIDS denotes acquired immunodeficiency syndrome, ELISA enzyme-linked immunosorbent assay, and PCR polymerase chain reaction.

Patients with traveler's diarrhea should be treated empirically with antibiotics without stool examination[20] (Table 3). Antibiotics are also effective in prevention of the disease.[23] When chemoprophylaxis is used, most authorities recommend rifaximin at a dose of 200 mg once or twice a day (with major meals) while the person is in an area of risk[23]; an alternative regimen is two tablets (each tablet containing 262.5 mg) of bismuth subsalicylate with each meal and at bedtime (a total of eight tablets, or 2.1 g). In placebo-controlled trials involving U.S. students traveling in Mexico, the risk reduction in the development of traveler's diarrhea with the use of prophylactic rifaximin treatment was approximately 70%, and with bismuth subsalicylate, the risk reduction was 65%.[24] Indications for the use of chemoprophylaxis include an important trip (the purpose of which might be ruined by a short-term illness), underlying illness that might be worsened by diarrhea (e.g., congestive heart failure) or might make persons more susceptible to diarrhea (e.g., use of daily proton-pump inhibitor therapy), or cases in which previous bouts of traveler's diarrhea suggest increased susceptibility to illness.[25]

Nosocomial Diarrhea

Diarrhea commonly occurs in the hospital, where patients (often with coexisting conditions) are receiving drugs and feedings and there is exposure to *C. difficile* spores. Although *C. difficile* accounts for a minority of antibiotic-associated and hospital-associated diarrhea, it should be considered in patients with clinically significant diarrhea (passage of three or more unformed stools per day), toxic dilatation of the colon or otherwise unexplained leukocytosis, or both. Patients with this infection often pass watery diarrheal stools but may also pass grossly bloody stools. *C. difficile* diarrhea is increasing in frequency[26] and is associated with an increasing mortality rate.[27] Although *C. difficile* diarrhea has been viewed as a nosocomial condition, it is increasingly being seen in the outpatient setting. Risk factors for *C. difficile* diarrhea in the inpatient or outpatient setting include advanced age and coexisting conditions, alteration of intestinal flora by antimicrobial agents, and probably host genetics. The indigenous human intestinal microbiota is important to colonization resistance and recovery from antibiotic-associated and *C. difficile* diarrhea.[28] *C. difficile* diarrhea was recently reviewed in the *Journal*.[29]

TREATMENT

For all cases of diarrhea, attention to fluid and electrolyte replacement is fundamental. A diet of easily digestible food (such as tomato soup, chicken noodle soup, crackers, mashed potatoes, and boiled or baked vegetables and meats) or a "BRAT" (bananas, rice, applesauce, and toast) diet is often recommended for people with acute bacterial diarrhea, although randomized trials showing that these diets expedite recovery are lacking. Available data in children with acute diarrhea do support the continuation of oral feeding during the illness.[30] Drugs to improve symptoms, particularly antimotility drugs such as loperamide and diphenoxylate hydrochloride, can reduce the number of stools passed and may be useful in controlling the stool rate with watery diarrhea. They should not be used without concomitant antibacterial therapy in patients with fever or dysentery in whom the drug may lead to increased contact time of the enteropathogen with the gut mucosa; as long as appropriate antimicrobial therapy is given, there is no good evidence that antimotility drugs are harmful in bacterial diarrhea.

Therapy with antimicrobial agents is important in most cases of diarrhea caused by invasive or inflammatory bacterial pathogens and is useful in other noninvasive forms of bacterial diarrhea. Table 3 provides recommendations for antibiotic therapy in each form of bacterial diarrhea.

Two bacterial organisms require special consideration with regard to recommended therapy. The first is acute diarrheal disease caused by nontyphoid salmonellosis. Bacteremia complicates the infection in approximately 8% of normal healthy persons. Patients with bacteremia often present with high fever and systemic toxic effects. Risk factors in the host that are associated with a higher than 8% risk of systemic salmonella infection during bouts of gastroenteritis include extremes of age (younger than 3 months and 65 years or older), corticosteroid use, inflammatory bowel disease, immunosuppression, hemoglobinopathy including most cases of sickle cell disease, and hemodialysis. People with one of these risk factors and nontyphoid salmonellosis should be treated with antibacterial drugs. Antibiotics should also be given to patients with intestinal salmonellosis and a known abdominal aneurysm or prosthetic heart valve to prevent establishment of a focal salmonella infection.

Table 3. Antimicrobial Therapy in Bacterial Diarrhea.*

Diarrheal Disease	Treatment in Children	Treatment in Adults
Clostridium difficile diarrhea or colitis	Metronidazole, 7.5 mg/kg of body weight (maximum, 500 mg) thrice daily; or vancomycin, 10 mg/kg (maximum, 125 mg) four times a day for 10–14 days	Metronidazole, 500 mg thrice daily for milder cases; vancomycin, 125 mg four times a day (for more severe illness)[21]; or rifaximin, 400 mg four times a day for 10–14 days (monitoring for in vitro susceptibility is recommended, since the related drug, rifampin, may induce resistance)[22]
Shigellosis	Azithromycin, 10 mg/kg/day in once-daily dose for 3 days; or ceftriaxone, 50 mg/kg/day given once a day for 3 days	Ciprofloxacin, 750 mg once a day for 3 days; or azithromycin, 500 mg once a day for 3 days
Nontyphoid salmonellosis	None or ceftriaxone, 100 mg/kg/day in two equally divided daily doses for 7–10 days; or azithromycin, 20 mg/kg/day once a day for 7 days	None or levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7–10 days; or azithromycin, 500 mg once a day for 7 days; levofloxacin or azithromycin should be given to immunocompromised patients for 14 days
Enteric, fever including typhoid fever	Ceftriaxone, 100 mg/kg/day in two equally divided daily doses; or azithromycin, 20 mg/kg/day once a day for 7 days	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7 days; or azithromycin, 500 mg once a day for 7 days
Campylobacter jejuni diarrhea	Azithromycin, 10 mg/kg/day in a once-daily dose for 3–5 days; or erythromycin, 30 mg/kg/day in 2–4 divided doses for 3–5 days	Azithromycin, 500 mg once a day for 3 days; or erythromycin, 500 mg four times a day for 3 days
Aeromonas species diarrhea	Treat as shigellosis	Treat as shigellosis
Plesiomonas shigelloides diarrhea	Treat as shigellosis	Treat as shigellosis
Cholera (due to *Vibrio cholerae* 01)	Erythromycin, 30 mg/kg/day given thrice daily for 3 days; or azithromycin, 10 mg/kg/day in a once-daily dose for 3 days	Doxycycline, 300 mg in a single dose; or tetracycline, 500 mg four times a day for 3 days; or macrolide (erythromycin, 250 mg thrice daily; or azithromycin, 500 mg once a day) for 3 days
Diarrhea due to noncholeraic vibrios	None or treat as shigellosis	None or treat as shigellosis
Enterotoxigenic *E. coli* diarrhea, enteroaggregative *E. coli* diarrhea, or traveler's diarrhea	Azithromycin, 10 mg/kg/day in once-daily dose for 3 days; or ceftriaxone, 50 mg/kg/day given once a day for 3 days	One of the following: ciprofloxacin, 750 mg once a day for 1–3 days; azithromycin, 1000 mg in a single dose; or rifaximin, 200 mg thrice daily for 3 days
Shiga toxin–producing *E. coli* infection, including *E. coli* O157:H7 infection	None	None
Enteroinvasive *E. coli* infection	Treat as shigellosis	Treat as shigellosis

* Multiple drugs are listed as alternatives for patients who may have an allergy to the primary drug. The doses given are derived from clinical trials, and they may not reflect doses for currently approved indications. Other drugs (not listed) may be appropriate for these conditions. Ceftriaxone is administered intravenously; the other listed drugs are given orally.

The second organism requiring special consideration is Shiga toxin–producing *E. coli*. Some antibacterial drugs, including fluoroquinolones and trimethoprim–sulfamethoxazole, may increase the induction of phage-mediated production of Shiga toxin and theoretically could increase the risk of development of the hemolytic–uremic syndrome. However, an association between the use of these antibiotics and an increased risk of this syndrome has not been established, and other

Table 4. Selected Complications of Bacterial Enteric Infection.

Complication	Important Bacterial Agents	Clinical Considerations
Dehydration	*Vibrio cholerae*, any bacterial enteropathogen	Most important complication of all forms of acute watery diarrhea; should prompt aggressive fluid and electrolyte replacement, usually in hospital
Bacteremia	Salmonella, *Campylobacter fetus*	Organisms that deeply penetrate the intestinal mucosa are prone to cause bacteremia; certain high-risk conditions predispose to systemic salmonella infection
Hemolytic–uremic syndrome	Shiga toxin–producing *Escherichia coli*	Shiga toxin is absorbed, causing injury to endothelial cells of the glomerular capillaries with intravascular coagulation
Guillain–Barré syndrome	*Campylobacter jejuni*	Most cases occur as a result of molecular mimicry, with antibodies directed to campylobacter lipooligosaccharides and peripheral-nerve gangliosides; probability of development of Guillain–Barré syndrome within 2 mo after campylobacter infection estimated at <2/10,000 cases[40]
Reactive arthritis and iritis	Campylobacter, salmonella, *Shigella flexneri*, yersinia	Occurs in 2.1/100,000 cases of campylobacter infection and 1.4/100,000 cases of salmonella infection; affected persons may be HLA-B27–positive or HLA-B27–negative[41]
Postinfectious irritable bowel syndrome	Inflammatory bacterial pathogens (e.g., campylobacter) are most important, but most bacterial pathogens can produce the syndrome	Enteric bacterial infection with intestinal inflammation in a susceptible host leads to altered intestinal findings and postinfectious irritable bowel syndrome[42-44]; duration is ≥5 yr[45-47]

drugs, including fosfomycin, azithromycin, and rifaximin, do not appear to increase production of Shiga toxin.[31,32] In a mouse model, azithromycin inhibited a Shiga toxin–induced inflammatory response and prevented death.[33] Studies are needed to determine the effects of azithromycin and rifaximin on reducing diarrhea and decreasing the risk of the hemolytic–uremic syndrome among patients with Shiga toxin–producing *E. coli* dysentery. Pending such data, most authorities recommend supportive treatment only in patients with Shiga toxin–producing *E. coli* infection.

AREAS OF UNCERTAINTY

Foodborne bacterial diarrhea continues to occur at a high rate in the United States and other industrialized areas.[34] A newly established U.S. Food Safety Working Group has proposed increasing the number of food inspectors, modernizing federal laboratories, and updating regulatory laws controlling the food industry. In selected higher-risk foods (e.g., poultry), there may be a role for widespread food irradiation to reduce the risk of infection. Since most outbreaks (and many individual cases) are unrecognized, research is needed to identify improved methods of diagnosis and pathogen-reporting in patients with diarrheal disease.

Improved understanding is needed of factors that may influence susceptibility to bacterial diarrhea, including host genetics and the indigenous intestinal microbiota and associated colonization resistance. My colleagues and I have shown that genes encoding for inflammatory products are associated with susceptibility to a variety of types of bacterial diarrhea, including interleukin-8 and susceptibility to diarrhea due to enteroaggregative *E. coli*[35] or *C. difficile*[36]; lactoferrin[37] and osteoprotegerin (a cytokine belonging to a tumor necrosis factor receptor superfamily)[38] and susceptibility to traveler's diarrhea; and host interleukin-10 and susceptibility to enterotoxigenic *E. coli* diarrhea.[39]

Factors influencing the risks of medium-term and long-term complications of bacterial diarrhea

are uncertain. Table 4 reviews some potential complications, including the development of the Guillain–Barré syndrome (which has been recognized after campylobacter infection) and postinfectious irritable bowel syndrome (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

GUIDELINES

The American College of Gastroenterology[48] and the Infectious Diseases Society of America[49] have provided recommendations regarding therapy for bacterial diarrhea. The current recommendations differ from the guidelines for bacterial enteric infection for which antimicrobial resistance has become widespread (e.g., trimethoprim–sulfamethoxazole has been replaced by one of the fluoroquinolones for many forms of bacterial diarrhea in adults).

CONCLUSIONS AND RECOMMENDATIONS

The differential diagnosis and evaluation for suspected bacterial diarrhea depend on the setting in which illness occurs and associated clinical features. A stool culture should be obtained from all patients with severe diarrhea when diarrhea is prolonged, when fever or dysentery complicate the illness, or when an outbreak has occurred. A single examination of a diarrhea stool in a qualified laboratory is sufficient for the diagnosis of most cases of bacterial diarrhea. In patients with bloody diarrhea, such as the patient described in the vignette, fecal toxin assay by means of a commercial enzyme immunoassay is warranted in addition to stool culture. If testing for Shiga toxin is positive, the patient should receive supportive treatment but not antibiotic therapy, given the potential for some antibiotics to increase toxin production and the risk of the hemolytic–uremic syndrome. Antibiotic therapy is indicated for febrile dysentery that is not due to Shiga toxin–producing *E. coli*, moderate-to-severe cases of traveler's diarrhea, and in patients with culture-proven bacterial diarrhea.

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