

## CLINICAL PRACTICE

## Acute Infectious 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 authors' clinical recommendations.

**An otherwise healthy 23-year-old man presents after the acute onset of watery diarrhea that has persisted for two days. He reports associated nausea and cramping but no emesis and is febrile, with a temperature of 38.7°C (101.7°F). How should he be evaluated and treated?**

## THE CLINICAL PROBLEM

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Despite reductions in mortality worldwide, diarrhea still accounts for more than 2 million deaths annually<sup>1</sup> and is associated with impaired physical and cognitive development in resource-limited countries.<sup>2</sup> In the United States, an estimated 211 million to 375 million episodes of acute diarrhea occur each year (1.4 episodes per person per year); such episodes are responsible for more than 900,000 hospitalizations and 6000 deaths annually.<sup>3,4</sup>

Acute diarrhea, defined as an increased frequency of defecation (three or more times per day or at least 200 g of stool per day) lasting less than 14 days, may be accompanied by nausea, vomiting, abdominal cramping, clinically significant systemic symptoms, or malnutrition. We focus here on acute infectious diarrhea in immunocompetent adults in industrialized countries.

## STRATEGIES AND EVIDENCE

## MICROBIOLOGY

The Foodborne Diseases Active Surveillance Network (FoodNet) of the Centers for Disease Control and Prevention (CDC) collects data on the incidence of diarrhea attributable to nine enteropathogens in 13 percent of the U.S. population (37.4 million people) living in nine states. Of these, the pathogens responsible for the most cases of diarrhea in 2002 were salmonella (16.1 cases per 100,000 population), campylobacter (13.4 cases per 100,000 population), shigella (10.3 cases per 100,000 population), *Escherichia coli* O157:H7 (1.7 cases per 100,000 population), and cryptosporidium (1.4 cases per 100,000 population); vibrio, yersinia, listeria, and cyclospora were reported in fewer than 1 person per 100,000.<sup>5</sup> Other enteropathogens for which diagnostic testing is readily available include *Clostridium difficile*, giardia, rotavirus, and *Entamoeba histolytica*. Additional agents of infectious diarrhea for which clinical diagnostic testing is not routinely available include enterotoxigenic, enteropathogenic, enteroaggregative, and enteroinvasive strains of *E. coli*, toxin-producing *Clostridium perfringens*, *Staphylococcus aureus*, *Bacillus cereus*, and noroviruses.

## EVALUATION

Thorough clinical evaluation of a patient who presents with acute diarrhea is essential in order to guide a cost-effective, evidence-based approach to initial diagnostic test-

ing and therapy. In six studies conducted between 1980 and 1997, the diagnostic yield of stool cultures ranged from 1.5 to 5.6 percent.<sup>6</sup> The estimated cost of \$952 to \$1,200 per positive culture can be reduced through improved selection and testing of the specimens submitted. As is indicated in Figure 1, the initial clinical evaluation of the patient with acute diarrhea should focus on the assessment of the severity of the illness, the need for rehydration, and the identification of likely causes on the basis of the history and clinical findings.

Because most diarrheal illnesses are self-limited or viral, and nearly half last less than one day,<sup>3</sup> microbiologic investigation is usually unnecessary for patients who present within 24 hours after the onset of diarrhea, unless such patients are dehydrated or febrile or have blood or pus in their stool. The characteristics of the illness, the epidemiologic setting, and the public health implications help to determine whether and what types of fecal testing are appropriate. The major epidemiologic and clinical features associated with common enteropathogens are listed in Table 1.

In the United States, most diarrheal illnesses occur during the winter months; these illnesses are commonly associated with noroviruses (in families and in outbreaks, including those in nursing homes)<sup>7</sup> or rotaviruses (in young children). Since these illnesses are typically short-lived (lasting one to three days) and self-limited, supportive fluid therapy is usually sufficient. Systemic illness, fever, or bloody stools should prompt routine stool testing for salmonella, shigella, campylobacter, and (especially if there are bloody stools) Shiga toxin-producing *E. coli*. When diarrhea is persistent or recurring, or if the history (for instance, of fever or tenesmus) is equivocal, fecal testing by means of microscopy for polymorphonuclear leukocytes or by means of immunoassay for the neutrophil marker lactoferrin can quickly provide additional laboratory evidence to support a presumptive diagnosis of inflammatory diarrhea.

In equivocal cases, the negative predictive value of fecal lactoferrin testing may help to determine the need for routine bacteriologic culture for campylobacter, salmonella, and shigella.<sup>8</sup> In developed countries, the sensitivity and specificity of fecal leukocytes for inflammatory diarrhea are 0.73 and 0.84, respectively, and the sensitivity and specificity of lactoferrin for inflammatory diarrhea are 0.92 and 0.79, respectively; in resource-poor countries, the ranges are broader.<sup>9</sup>

Other testing is necessary in special circumstanc-

es (Fig. 1). In patients who present with an acute onset of bloody diarrhea (especially without fever) or the hemolytic-uremic syndrome, fecal testing for Shiga toxin should be performed, along with cultures for *E. coli* O157:H7. Bloody diarrhea in recent immigrants or travelers returning from regions where *E. histolytica* is endemic (such as tropical Africa, Asia, or Latin America) should also prompt fecal testing for that pathogen.<sup>10</sup> A report by a patient of recent ingestion of shellfish should prompt special cultures for vibrio species. Persistent abdominal pain, fever, mesenteric adenitis, erythema nodosum, or other immunologic manifestations may suggest *Yersinia enterocolitica* or *Y. pseudotuberculosis*, culture for which is enhanced by cold enrichment.

The microbiologic evaluation of hospitalized patients or those with recent exposure to antibiotics in whom diarrhea develops should focus on the diagnosis of toxigenic *C. difficile*,<sup>11</sup> the most common recognized cause of nosocomial diarrhea. Testing for other pathogens in patients who have been hospitalized for more than 72 hours is discouraged, except in an outbreak or in patients 65 years of age or older with preexisting medical conditions, patients with human immunodeficiency virus (HIV) infection, patients with neutropenia, and patients with suspected systemic spread of enteric infection.<sup>12</sup>

Exposure of a traveler or hiker to untreated water and illnesses that persist for more than seven days should prompt evaluations for protozoal pathogens, especially giardia and cryptosporidium. The testing of one or two specimens by means of enzyme immunoassay has a sensitivity of more than 95 percent and is considerably better than older methods based on microscopical examinations. Less common but readily treatable protozoal causes of persistent diarrhea in normal or immunocompromised persons include *Cyclospora cayatanensis* and *Isoospora belli* (which can be identified by means of acid-fast staining of stool specimens). In patients with advanced HIV disease, especially those who have fewer than 50 CD4+ lymphocytes per cubic millimeter, stool studies for cryptosporidium, microsporidia, cyclospora, and isospora and blood cultures or biopsies for *Mycobacterium avium* complex and cytomegalovirus should be considered.<sup>13</sup> Fecal evidence of inflammation in persistent diarrhea should arouse concern about inflammatory bowel disease,<sup>14</sup> particularly if the presence of a treatable inflammatory pathogen such as shigella, salmonella, campylobacter, *C. difficile*, or *E. histolytica* has been ruled out.

**APPROACHES TO THERAPY***Rehydration and Nutrition*

Regardless of the causative agent, initial therapy should include rehydration. Unless the patient is comatose or severely dehydrated, oral rehydration with a glucose-based electrolyte solution is preferred. The standard formulation recommended by the World Health Organization (WHO) or a newer reduced-osmolarity formula for children can be life-saving in resource-poor regions and is valuable in the industrialized world for infants, the elderly, immunocompromised patients, and anyone with profuse watery diarrhea (information is available on the Web at [http://www.who.int/child-adolescent-health/New\\_Publications/CHILD\\_HEALTH/WHO\\_FCH\\_CAH\\_01.22.htm](http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO_FCH_CAH_01.22.htm)). Most adults in developed countries who have acute diarrhea, including travelers, should be encouraged to drink fluids and take in salt in soups and salted crackers. Nutritional support with continued feeding improves outcomes in children. The use of a "BRAT" diet (bananas, rice, applesauce, and toast) with avoidance of milk products (since a transient lactase deficiency may occur) is commonly recommended, although supporting data are limited.<sup>15</sup>

*Nonspecific Symptomatic Therapy*

Nearly 400 over-the-counter products are promoted in the United States for their antidiarrheal properties, but few have been demonstrated to be effective in randomized, controlled trials. Only in the cases of loperamide, bismuth subsalicylate, and kaolin has sufficient evidence of efficacy and safety been collected to permit labeling as an antidiarrheal agent.<sup>16</sup>

Loperamide, the antimotility agent of choice for adults, inhibits intestinal peristalsis and has antisecretory properties, but unlike other opiates (such as codeine, diphenoxylate, and paregoric), it does not penetrate the nervous system and has no substantial potential for addiction.<sup>17</sup> When it is used with antibiotics for traveler's diarrhea<sup>18</sup> or bacillary dysentery,<sup>19</sup> it may reduce the duration of diarrhea by as much as one day. Because antimotility agents have been implicated in prolonged fever in human volunteers with shigellosis,<sup>20</sup> toxic megacolon in patients with *C. difficile* infection, and the hemolytic-uremic syndrome in children infected with Shiga toxin-producing *E. coli*,<sup>21</sup> these agents should be avoided in patients with bloody diarrhea or suspected inflammatory diarrhea.

Although it has not been as effective as lopera-

mid in direct comparisons,<sup>22</sup> bismuth subsalicylate can alleviate stool output in children<sup>23</sup> or the symptoms of diarrhea, nausea, and abdominal pain in patients with traveler's diarrhea.<sup>24</sup> Bismuth subsalicylate significantly decreased the median duration of experimental norovirus illness from 27 hours to 20 hours.<sup>25</sup> There are insufficient data from clinical trials to support the use of adsorbents such as kaolin-pectin, activated charcoal, and at-pulgite. Given the limited scientific evidence, limited clinical benefit, and concern about the toxicity of antidiarrheal agents, pediatric guidelines discourage their use in children.<sup>26,27</sup>

*Antimicrobial Therapy*

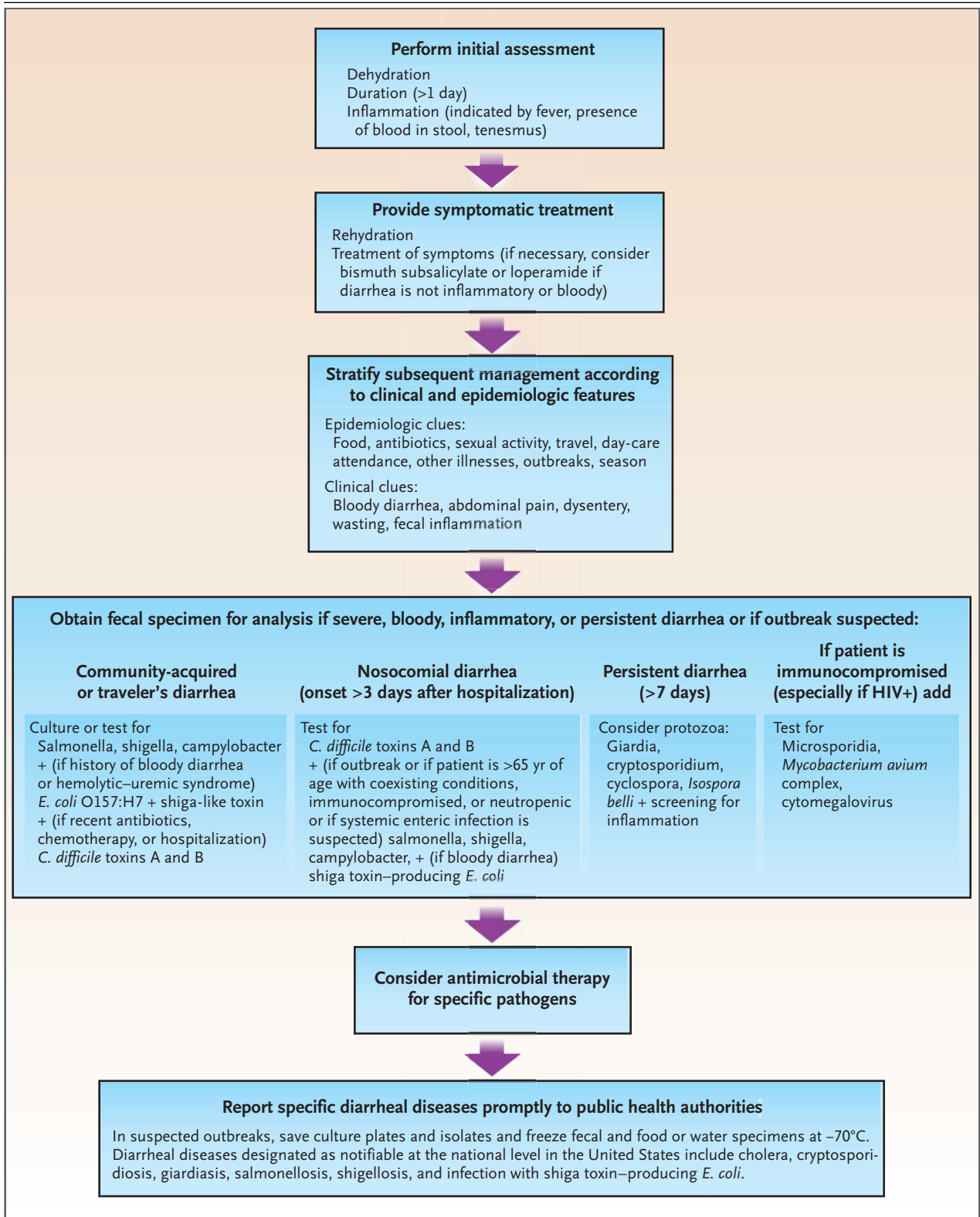
Whereas appropriate antibiotics are effective in the treatment of shigellosis, traveler's diarrhea, *C. difficile*-associated diarrhea, and, if given early, campylobacteriosis, antibiotics may prolong the duration of shedding of salmonella<sup>28</sup> or *C. difficile*<sup>29</sup> and may increase the risk of life-threatening complications of Shiga toxin-producing *E. coli* infection.<sup>30</sup> The clinical benefit should be weighed against the cost, the risk of adverse reactions, and the risk of harmful eradication of normal flora or the induction of Shiga-toxin production.<sup>31</sup> Antibiotic therapies for specific pathogens are listed in Table 2.

**COMMUNITY-ACQUIRED PATHOGENS**

Randomized, controlled trials in patients with shigellosis have demonstrated that appropriate an-

**Figure 1 (facing page). Approach to the Evaluation and Management of Infectious Diarrhea.**

To assess dehydration, note the general appearance and alertness of the patient, the pulse, the blood pressure, the presence or absence of postural hypotension, the mucous membranes and tears, sunken eyes, skin turgor, capillary refill, and jugular venous pressure. Rehydration is usually possible with oral rehydration solution: 3.5 g of sodium chloride, 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride, and 20 g of glucose or glucose polymer (such as sucrose) in 1 liter of water provides a solution with 90 mM sodium, 20mM potassium, 80 mM chloride, 30 mM bicarbonate, and 111 mM glucose. Alternatively, one level teaspoon of table salt and eight level teaspoons of sugar per liter of water provide 86 mM sodium to which one cup of orange juice or two bananas can be added for potassium. Details on the clinical and epidemiologic features of diarrhea caused by common enteropathogens are provided in Table 1. Reporting requirements are available from the CDC (<http://www.cdc.gov/epo/dphsi/phs/infdis.htm>).



**Table 1. Epidemiologic Settings and Clinical Features of Infection with Selected Diarrheal Pathogens.**

Pathogen	Common Epidemiologic Settings or Modes of Transmission*	Clinical Features						
		Fever	Abdominal Pain	Bloody Stool	Vomiting, Nausea, or Both	Fecal Evidence of Inflammation	Heme-Positive Stool	
Salmonella	Outbreaks due to foodborne transmission, community-acquired	Common	Common	Occurs	Occurs	Common	Variable	
Campylobacter	Community-acquired, consumption of undercooked poultry	Common	Common	Occurs	Occurs	Common	Variable	
Shigella	Community-acquired, person-to-person	Common	Common	Occurs	Common	Common	Variable	
Shiga toxin-producing <i>E. coli</i> (including O157:H7)†	Outbreaks due to foodborne transmission, especially through ingestion of undercooked hamburger or raw seed sprouts	Atypical	Common	Common	Occurs	Often not found	Common	
<i>C. difficile</i> ‡	Nosocomial spread, antibiotic use	Occurs	Occurs	Occurs	NC	Common	Occurs	
Vibrio	Ingestion of seafood	Variable	Variable	Variable	Variable	Variable	Variable	
Yersinia	Community-acquired, foodborne transmission	Common	Common	Occurs	Occurs	Occurs	Occurs	
<i>E. histolytica</i> §	Travel to tropical regions, recent emigration from such regions	Occurs	Occurs	Variable	Variable	Variable	Common	
Cryptosporidium¶	Outbreaks due to waterborne transmission, travel, immunocompromised hosts	Variable	Variable	NC	Occurs	None to mild	NC	
Cyclospora	Outbreaks due to foodborne transmission, travel	Variable	Variable	NC	Occurs	NC	NC	
Giardia	Day care, outbreaks due to waterborne transmission, IgA deficiency	NC	Common	NC	Occurs	NC	NC	
Norovirus**	Winter outbreaks of vomiting or diarrhea in families, nursing homes, schools, or on cruise ships, or after ingestion of undercooked shellfish	Variable	Common	NC	Common	NC	NC	

\* If the illness can be linked to the ingestion of a particular food or meal, as in an outbreak, the incubation period can be deduced and the differential diagnosis narrowed accordingly. If the incubation period is less than 6 hours, *S. aureus* and *B. cereus* are likely causes; if the incubation period is 6 to 24 hours, *C. perfringens* and *B. cereus* are likely causes; and if the incubation period is 16 to 72 hours, possible causes include noroviruses, enterotoxigenic *E. coli*, vibrio, salmonella, shigella, campylobacter, yersinia, Shiga toxin-producing *E. coli*, giardia, cyclospora, and cryptosporidium. NC denotes not characteristic.

† Bloody diarrhea in an afebrile patient is suggestive of Shiga toxin-producing *E. coli* infection, although this is not always the cause.

‡ Leukocytosis is found in approximately 50 percent of patients.

§ Classically, patients with intestinal amebiasis present with heme-positive or bloody stools.

¶ Although cryptosporidiosis is typically considered to be noninflammatory in the United States, fecal evidence of inflammation is common in children with cryptosporidiosis in developing countries.

|| Fatigue, which may be profound, is reported in more than 90 percent of patients with cyclosporiasis.

\*\*Vomiting occurs more frequently than diarrhea in children; diarrhea occurs more frequently in adults.

timicrobial therapy shortens the average duration of diarrhea by 2.4 days or more, decreases the duration of fever and tenesmus, and reduces the excretion of infectious organisms.<sup>32,33</sup> Antimicrobial therapy is of greatest benefit when it is started early, and it probably reduces person-to-person spread. Increased resistance now limits the effectiveness of trimethoprim-sulfamethoxazole, ampicillin, and nalidixic acid, which were once considered optimal therapies for shigellosis. Clinical trials have established the efficacy of newer fluoroquino-

lones for adults with shigellosis,<sup>33,34</sup> and accumulating data suggest that ciprofloxacin is also safe and effective in children with shigellosis.<sup>35</sup>

In immunocompetent patients with campylobacteriosis, erythromycin reduces carriage of the organism but reduces diarrhea only when it is given within four days after the onset of symptoms.<sup>36,37</sup> Immunocompromised patients (particularly those who have the acquired immunodeficiency syndrome [AIDS] and those who are pregnant, who have an increased risk of complications of campylobacter

**Table 2. Antimicrobial Recommendations for Infections with Specific Pathogens.\***

Organism	Recommendations for Adults
Shigella	Fluoroquinolones (e.g., treatment for 1–3 days with ciprofloxacin, 500 mg orally twice daily; norfloxacin, 400 mg orally twice daily; or levofloxacin, 500 mg orally once daily); if susceptible, trimethoprim–sulfamethoxazole, 160 mg and 800 mg, respectively, twice a day for 3 days may be used.
Nontyphi species of salmonella	Not recommended in healthy host with mild or moderate symptoms, but if illness is severe or patient <12 mo of age or >50 yr of age or with prostheses, valvular heart disease, severe atherosclerosis, cancer, or uremia, treatment with trimethoprim–sulfamethoxazole (if susceptible) or fluoroquinolone, as above, for 5–7 days, or ceftriaxone, 100 mg/kg of body weight/day in 1 or 2 divided doses.
<i>E. coli</i> (enterotoxigenic, enteropathogenic, or enteroinvasive)	Fluoroquinolones (e.g., treatment for 1–3 days with ciprofloxacin, 500 mg orally twice daily; norfloxacin, 400 mg orally twice daily; or levofloxacin, 500 mg orally once daily); if susceptible, treatment for 1–3 days with trimethoprim–sulfamethoxazole, 160 mg and 800 mg, respectively, twice daily may be used.
<i>E. coli</i> Shiga toxin–producing (O157:H7)	Antimotility agents and antibiotics should be avoided, particularly trimethoprim–sulfamethoxazole and fluoroquinolones.
Yersinia	Antibiotics not usually required; for severe infections, doxycycline and aminoglycoside (in combination), trimethoprim–sulfamethoxazole, or fluoroquinolone therapy.
<i>Vibrio cholerae</i> O1 or O139	Treatment with a single dose of doxycycline, 300 mg; treatment for 3 days with tetracycline, 500 mg 4 times daily; or single-dose treatment with fluoroquinolone.†
Toxigenic <i>C. difficile</i>	Treatment with any offending antimicrobial agents should be discontinued, if possible; treatment for 10 days with metronidazole, 250 mg 4 times daily to 500 mg 3 times daily.
Giardia	Treatment for 7–10 days with metronidazole, 250 to 750 mg 3 times daily.
Cryptosporidium	If illness is severe or patient is immunocompromised, either paromomycin plus azithromycin or nitazoxanide should be considered; in patients with AIDS, highly active antiretroviral therapy sufficient to achieve immunologic reconstitution is most effective; in immunocompetent children with cryptosporidiosis, nitazoxanide should be considered.
Isospora	Treatment for 7–10 days with trimethoprim–sulfamethoxazole, 160 mg and 800 mg, respectively, twice daily.
Cyclospora	Treatment for 7–10 days with trimethoprim–sulfamethoxazole, 160 mg and 800 mg, respectively, twice daily.
Microsporidia	Treatment for 3 wk with albendazole, 400 mg twice daily; highly active antiretroviral therapy sufficient to achieve immunologic reconstitution is effective in patients with AIDS.
<i>E. histolytica</i>	Treatment for 5–10 days with metronidazole, 750 mg 3 times daily, plus either treatment for 20 days with iodoquinol, 650 mg 3 times daily, or treatment for 7 days with paromomycin, 500 mg 3 times daily.

\* There is a growing body of evidence suggesting that the use of fluoroquinolones is safe in children, but they should be used with caution in children, given reports of damage to articular cartilage of young beagles in preclinical testing.

† Doxycycline and tetracycline may cause permanent discoloration of teeth during tooth development and are not recommended for use in children younger than 8 years of age.

infection) and patients with severe, prolonged, or relapsing illness may benefit from antimicrobial therapy. Dramatic increases in the rate of fluoroquinolone resistance (contemporaneous with the widespread use of fluoroquinolones in poultry feeds) now limit the usefulness of these agents in campylobacter infections.<sup>38</sup>

In uncomplicated salmonella gastroenteritis, antibiotics are not recommended, since they typically do not alleviate the diarrhea<sup>39</sup> and have been associated with prolonged carriage<sup>28</sup> and even relapse.<sup>40</sup> However, because bacteremia occurs in 2 to 4 percent of patients, persons who are at increased risk for dissemination or metastatic seed-

ing should receive antibiotics. These patients include those 12 months of age or younger and those older than 50 years; those with lymphoproliferative disorders, cancer, hemoglobinopathies, or AIDS; transplant recipients; patients with vascular grafts, artificial joints, degenerative joint diseases, or valvular heart disease; and patients who are taking corticosteroids.

Clues to the diagnosis of Shiga toxin–producing *E. coli* infection include bloody diarrhea (especially if the patient is afebrile) and a history of eating rare hamburger meat or seed sprouts. Given the concern that antimicrobial agents such as trimethoprim–sulfamethoxazole and quinolones induce

Shiga-toxin production<sup>31</sup> and may increase the risk of the hemolytic–uremic syndrome,<sup>30</sup> patients with suspected or documented infection with Shiga toxin–producing *E. coli* should receive supportive care. Risk factors for the development of the hemolytic–uremic syndrome with this infection remain controversial and are incompletely understood.<sup>41</sup>

**EMPIRICAL ANTIBIOTIC TREATMENT FOR COMMUNITY-ACQUIRED ILLNESS**

Empirical antibiotic treatment in adults who present with severe, community-acquired diarrhea (Table 3) reduces the average duration of illness by one to two days.<sup>28,42,43</sup> However, as noted above, the potential benefits must be weighed against the potential harm, such as prolonged fecal shedding of certain pathogens, the increased risk of relapse, and the increased risk of complications. In patients who have evidence of inflammatory diarrhea (fever, tenesmus, dysentery, or fecal leukocytes or lactoferrin) and in whom diarrhea is not thought to be attributable to Shiga toxin–producing *E. coli* or fluoroquinolone-resistant campylobacter, empirical treatment with an agent such as a fluoroquinolone antibiotic (or for children, trimethoprim–sulfamethoxazole), pending fecal testing, is reasonable.<sup>6,44</sup> Given the increasing incidence of fluoroquino-

lone-resistant campylobacter,<sup>38,45</sup> empirical therapy in immunocompromised or severely ill patients or travelers with inflammatory diarrhea (especially those who have traveled to southern Asia, where the rate of quinolone resistance exceeds 80 percent) might include erythromycin or azithromycin.

**TRAVELER’S DIARRHEA**

Although most cases of traveler’s diarrhea are self-limited, several clinical trials have demonstrated that fluoroquinolones or other agents — many of which are no longer used because of increased resistance — reduce the duration of diarrhea from three or four days to one or two days with as little as a single dose.<sup>46</sup> Although such data support a recommendation that travelers carry appropriate antibiotics for the self-treatment of diarrhea, most experts do not recommend antimicrobial prophylaxis for travelers (even those who are immunocompromised, whose highest risk may be for infection with pathogens that are not covered by the standard antimicrobial agents used). Use of bismuth subsalicylate (one to two 262-mg tablets taken four times daily) decreases the incidence of traveler’s diarrhea by 35 to 65 percent and appears to be safe when used for up to three weeks but may result in the blackening of the tongue and the stools.<sup>47,48</sup>

**Table 3. Considerations for Empirical Antimicrobial Therapy for Infectious Diarrhea.\***

Type of Illness	Recommendations for Adults	Comments and Alternatives
Moderate-to-severe traveler’s diarrhea	Treatment for 1–5 days with ciprofloxacin, 500 mg orally twice daily; norfloxacin, 400 mg orally twice daily; or levofloxacin, 500 mg orally once daily	Early treatment with a fluoroquinolone can reduce the duration of symptoms from 3–4 days to <1–2 days; in children, trimethoprim–sulfamethoxazole or a short course (1–3 days) of a fluoroquinolone should be considered.
Febrile, community-acquired diarrhea, especially if invasive disease is suspected	Treatment for 1–5 days with ciprofloxacin, 500 mg orally twice daily; norfloxacin, 400 mg orally twice daily; or levofloxacin, 500 mg orally once daily	In children, trimethoprim–sulfamethoxazole or a fluoroquinolone should be considered; in immunocompromised patients, the addition of erythromycin or azithromycin should be considered for fluoroquinolone-resistant campylobacter infection; antimotility agents, quinolones, and trimethoprim–sulfamethoxazole should be avoided if infection with Shiga toxin–producing <i>E. coli</i> is suspected (e.g., if there is bloody diarrhea in an afebrile patient).
Severe nosocomial diarrhea, pending results of assay for <i>C. difficile</i> toxin	Treatment with any offending antibiotics should be discontinued if possible; treatment with metronidazole, 250 mg 4 times daily to 500 mg 3 times daily (continued for 10 days if assay for <i>C. difficile</i> toxin is positive)	Metronidazole therapy should be discontinued if assay for <i>C. difficile</i> toxin is negative.
Persistent diarrhea with suspected giardia infection	Treatment for 7–10 days with metronidazole, 250 to 750 mg 3 times daily	

\* There is a growing body of evidence suggesting that the use of fluoroquinolones is safe in children, but they should be used with caution in children, given reports of damage to articular cartilage of young beagles in preclinical testing.

**NOSOCOMIAL DIARRHEA**

The treatment of *C. difficile*-associated diarrhea has been discussed in detail previously.<sup>11</sup> Many patients have improvement if therapy with broad-spectrum antibiotics can be discontinued. Oral metronidazole (which is less expensive) and oral vancomycin are effective in the treatment of *C. difficile*-associated diarrhea, with response rates of more than 90 percent and a mean time to improvement of three days, but relapses are common.<sup>11</sup>

**PERSISTENT DIARRHEA**

The protozoal pathogens that are most frequently associated with diarrhea that persists for more than 7 to 10 days, both in the United States and worldwide, are giardia and cryptosporidium. Giardia infections typically respond to metronidazole (the use of larger doses, if they are tolerated, may result in fewer treatment failures) or tinidazole. Cryptosporidium infection, in contrast, is notoriously difficult to treat, particularly in patients with AIDS and low CD4+ lymphocyte counts, in whom the most effective strategy is to facilitate immunologic reconstitution with optimal antiretroviral therapy.<sup>49</sup> Nitazoxanide, which was recently approved by the Food and Drug Administration (FDA) for use in children, may reduce oocyst shedding and diminish diarrhea.<sup>50</sup> Since these hardy oocysts are difficult to filter or to kill with chlorine, infections caused by them are best prevented by heating water or food to near-boiling temperatures. Finally, cyclospora infection, which can be detected by means of acid-fast staining of fecal specimens, is readily treated with trimethoprim-sulfamethoxazole.<sup>51,52</sup>

**AREAS OF UNCERTAINTY**

The inability to determine the specific causative agent when a patient is first seen greatly complicates management. Technology that will permit rapid, pathogen-specific diagnostic testing could mitigate the inappropriate use of antibiotics, help to track sources and outbreaks, and identify resistant pathogens or fecal contamination of food or water. Whether certain antibiotics increase risk whereas others prevent the hemolytic-uremic syndrome in patients with Shiga toxin-producing *E. coli* infections remains controversial.<sup>30,41</sup>

Drugs such as calmodulin inhibitors, chloride-channel blockers, enkephalinase inhibitors, and agents that block prostaglandin-mediated pathways are under study as antisecretory agents; at

present, their role remains uncertain. A poorly absorbed antibiotic, rifaximin, is effective in the treatment of traveler's diarrhea<sup>53</sup> and may prove useful for other bacterial diarrheal illnesses but has not been approved by the FDA. Improved therapy must also address the repair of damaged or inflamed mucosa, since the associated reduction in absorptive function and resulting malnutrition may impair child development and potentially reduce the efficacy of therapies for associated diseases.

**GUIDELINES**

Several groups have published guidelines for the management of acute diarrhea in adults.<sup>6,44,54</sup> The guidelines that the Infectious Diseases Society of America published in 2001, with which we still concur (available at <http://www.idsociety.org>), detail diagnostic strategies, treatment recommendations, and public health implications for adults, listing the quality and strength of evidence supporting each recommendation.<sup>6</sup> Several pediatric guidelines emphasize fluid management and the fact that antidiarrheal compounds are not useful.<sup>26,27,55</sup>

**CONCLUSIONS  
AND RECOMMENDATIONS**

In healthy patients with an acute onset of diarrhea, such as the patient described in the vignette, epidemiologic and clinical evaluation should be used to guide laboratory evaluation and management. For example, a recent history of eating raw oysters should prompt consideration and special culture for vibrio, and a recent history of antibiotic use should prompt testing for *C. difficile* toxin. Bloody diarrhea or a history of blood in the stool or of the ingestion of undercooked beef should prompt testing for Shiga toxin-producing *E. coli*; the presence of bloody diarrhea would also warrant testing for shigella, salmonella, and campylobacter. A history of immunocompromise, sickle cell disease, severe atherosclerosis, or intravascular prosthetic material should prompt the testing of blood and stool cultures for salmonella. Recent travel to a developing country would suggest infection with pathogens that typically cause traveler's diarrhea and would warrant empirical therapy with a single dose of a quinolone antibiotic (unless the travel was to southern Asia, which should arouse concern about infection with quinolone-resistant campylobacter). One might also consider empirical treatment for inflam-



matory diarrhea whose cause was suspected, on the basis of the exposure history, to be shigella or campylobacter infection (Tables 2 and 3).

If none of the above pathogens were present, but symptoms worsened or persisted for more than five days (especially if there was fever), we would order a fecal examination for inflammation to direct further testing for invasive pathogens (including salmonella, shigella, campylobacter, *C. difficile*, or *E. histolytica*); if the examinations were negative for these pathogens, we would evaluate the patient for inflammatory bowel disease. Patients with illness lasting

more than seven days should be tested for parasites (including giardia, cryptosporidium, cyclospora, and isospora). Finally, patients with recurrent or refractory giardiasis should be tested for possible immune compromise, such as immunoglobulin A deficiency, and patients with refractory cryptosporidiosis, cyclosporiasis, or isosporiasis should be tested for HIV infection.

Drs. Thielman and Guerrant are named as coinventors on a patent held by the University of Virginia for the use of glutamine derivatives in oral rehydration therapy. Dr. Guerrant is named as a coinventor on a patent held by the University of Virginia for a fecal lactoferrin assay. Neither coinventor receives any patent royalties.

## REFERENCES

- Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003;81:197-204.
- Guerrant RL, Kosek M, Lima AA, Lornitz B, Guyatt HL. Updating the DALYs for diarrhoeal disease. *Trends Parasitol* 2002;18:191-3. [Erratum, *Trends Parasitol* 2002;18:281.]
- Herikstad H, Yang S, Van Gilder TJ, et al. A population-based estimate of the burden of diarrhoeal illness in the United States: FoodNet, 1996-7. *Epidemiol Infect* 2002;129:9-17.
- Mead PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. *Emerg Infect Dis* 1999;5:607-25.
- Preliminary FoodNet data on the incidence of foodborne illnesses — selected sites, United States, 2002. *MMWR Morb Mortal Wkly Rep* 2003;52:340-3.
- Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001;32:331-51.
- Norovirus activity — United States, 2002. *MMWR Morb Mortal Wkly Rep* 2003;52:41-5. [Erratum, *MMWR Morb Mortal Wkly Rep* 2003;52:113.]
- Choi SW, Park CH, Silva TM, Zaenker EI, Guerrant RL. To culture or not to culture: fecal lactoferrin screening for inflammatory bacterial diarrhea. *J Clin Microbiol* 1996;34:928-32.
- Gill CJ, Lau J, Gorbach SL, Hamer DH. Diagnostic accuracy of stool assays for inflammatory bacterial gastroenteritis in developed and resource-poor countries. *Clin Infect Dis* 2003;37:365-75.
- Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr. Amebiasis. *N Engl J Med* 2003;348:1565-73.
- Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med* 2002;346:334-9.
- Bauer TM, Lalvani A, Fehrenbach J, et al. Derivation and validation of guidelines for stool cultures for enteropathogenic bacteria other than *Clostridium difficile* in hospitalized adults. *JAMA* 2001;285:313-9.
- Thielman NM, Guerrant RL. An algorithmic approach to the workup and management of HIV-related diarrhea. *J Clin Outcomes Management* 1997;4:36-47.
- Fine KD, Ogunji F, George J, Niehaus MD, Guerrant RL. Utility of a rapid fecal latex agglutination test detecting the neutrophil protein, lactoferrin, for diagnosing inflammatory causes of chronic diarrhea. *Am J Gastroenterol* 1998;93:1300-5.
- King CK, Glass R, Bresee JS, Duggan C. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003;52(RR-16):1-16.
- Food and Drug Administration. Antidiarrheal drug products for over-the-counter human use: final monograph: final rule. *Fed Regist* 2003;68(74):18869-82.
- DuPont HL, Flores Sanchez J, Ericsson CD, et al. Comparative efficacy of loperamide hydrochloride and bismuth subsalicylate in the management of acute diarrhea. *Am J Med* 1990;88:15S-19S.
- Petrucelli BP, Murphy GS, Sanchez JL, et al. Treatment of traveler's diarrhea with ciprofloxacin and loperamide. *J Infect Dis* 1992;165:557-60.
- Murphy GS, Bodhidatta L, Echeverria P, et al. Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Ann Intern Med* 1993;118:582-6.
- DuPont HL, Hornick RB. Adverse effect of lomotil therapy in shigellosis. *JAMA* 1973;226:1525-8.
- Cimolai N, Basalyga S, Mah DG, Morrison BJ, Carter JE. A continuing assessment of risk factors for the development of *Escherichia coli* O157:H7-associated hemolytic uremic syndrome. *Clin Nephrol* 1994;42:85-9.
- Johnson PC, Ericsson CD, DuPont HL, Morgan DR, Bitsura JA, Wood LV. Comparison of loperamide with bismuth subsalicylate for the treatment of acute travelers' diarrhea. *JAMA* 1986;255:757-60.
- Figueroa-Quintanilla D, Salazar-Lindo E, Sack RB, et al. A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. *N Engl J Med* 1993;328:1653-8.
- DuPont HL, Sullivan P, Pickering LK, Haynes G, Ackerman PB. Symptomatic treatment of diarrhea with bismuth subsalicylate among students attending a Mexican university. *Gastroenterology* 1977;73:715-8.
- Steinhoff MC, Douglas RG Jr, Greenberg HB, Callahan DR. Bismuth subsalicylate therapy of viral gastroenteritis. *Gastroenterology* 1980;78:1495-9.
- Armon K, Stephenson T, MacFarl R, Eccleston P, Werneke U. An evidence and consensus based guideline for acute diarrhoea management. *Arch Dis Child* 2001;85:132-42.
- Murphy MS. Guidelines for managing acute gastroenteritis based on a systematic review of published research. *Arch Dis Child* 1998;79:279-84.
- Wistrom J, Jertborn M, Ekwall E, et al. Empiric treatment of acute diarrheal disease with norfloxacin: a randomized, placebo-controlled study. *Ann Intern Med* 1992;117:202-8.
- Johnson S, Homann SR, Bettin KM, et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or metronidazole: a randomized, placebo-controlled trial. *Ann Intern Med* 1992;117:297-302.
- Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med* 2000;342:1930-6.
- Zhang X, McDaniel AD, Wolf LE, Keusch GT, Waldor MK, Acheson DW. Quinolone antibiotics induce Shiga toxin-encoding bacteriophages, toxin production, and death in mice. *J Infect Dis* 2000;181:664-70.
- Tong MJ, Martin DG, Cunningham JJ, Gunning JJ. Clinical and bacteriological evaluation of antibiotic treatment in shigellosis. *JAMA* 1970;214:1841-4.

33. Bennish ML, Salam MA, Haider R, Barza M. Therapy for shigellosis. II. Randomized, double-blind comparison of ciprofloxacin and ampicillin. *J Infect Dis* 1990;162:711-6.
34. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis. V. Comparison of azithromycin and ciprofloxacin: a double-blind, randomized, controlled trial. *Ann Intern Med* 1997;126:697-703.
35. Zimbabwe, Bangladesh, South Africa (Zimbasa) Dysentery Study Group. Multi-center, randomized, double blind clinical trial of short course versus standard course oral ciprofloxacin for *Shigella dysenteriae* type 1 dysentery in children. *Pediatr Infect Dis J* 2002;21:1136-41.
36. Salazar-Lindo E, Sack RB, Chea-Woo E, et al. Early treatment with erythromycin of *Campylobacter jejuni*-associated dysentery in children. *J Pediatr* 1986;109:355-60.
37. Anders BJ, Lauer BA, Paisley JW, Reller LB. Double-blind placebo controlled trial of erythromycin for treatment of *Campylobacter enteritis*. *Lancet* 1982;1:131-2.
38. Smith KE, Besser JM, Hedberg CW, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. *N Engl J Med* 1999;340:1525-32.
39. Sanchez C, Garcia-Restoy E, Garau J, et al. Ciprofloxacin and trimethoprim-sulfamethoxazole versus placebo in acute uncomplicated *Salmonella enteritis*: a double-blind trial. *J Infect Dis* 1993;168:1304-7.
40. Neill MA, Opal SM, Heelan J, et al. Failure of ciprofloxacin to eradicate convalescent fecal excretion after acute salmonellosis: experience during an outbreak in health care workers. *Ann Intern Med* 1991;114:195-9.
41. Safdar N, Said A, Gangnon RE, Maki DG. Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis: a meta-analysis. *JAMA* 2002;288:996-1001.
42. Dryden MS, Gabb RJ, Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. *Clin Infect Dis* 1996;22:1019-25.
43. Goodman LJ, Trenholme GM, Kaplan RL, et al. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. *Arch Intern Med* 1990;150:541-6.
44. DuPont HL. Guidelines on acute infectious diarrhea in adults. *Am J Gastroenterol* 1997;92:1962-75.
45. Nachamkin I, Ung H, Li M. Increasing fluoroquinolone resistance in *Campylobacter jejuni*, Pennsylvania, USA, 1982-2001. *Emerg Infect Dis* 2002;8:1501-3.
46. Cheng AC, Thielman NM. Update on traveler's diarrhea. *Curr Infect Dis Rep* 2002;4:70-7.
47. DuPont HL, Ericsson CD, Johnson PC, Bitsura JA, DuPont WW, de la Cabada FJ. Prevention of travelers' diarrhea by the tablet formulation of bismuth subsalicylate. *JAMA* 1987;257:1347-50.
48. Steffen R, DuPont HL, Heusser R, et al. Prevention of traveler's diarrhea by the tablet form of bismuth subsalicylate. *Antimicrob Agents Chemother* 1986;29:625-7.
49. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998;351:256-61.
50. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of nitazoxanide. *J Infect Dis* 2001;184:103-6.
51. Pape JW, Verdier RI, Boney M, Boney J, Johnson WD Jr. *Cyclospora* infection in adults infected with HIV: clinical manifestations, treatment, and prophylaxis. *Ann Intern Med* 1994;121:654-7.
52. Verdier RI, Fitzgerald DW, Johnson WD Jr, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000;132:885-8.
53. Steffen R, Sack DA, Riopel L, et al. Therapy of travelers' diarrhea with rifaximin on various continents. *Am J Gastroenterol* 2003;98:1073-8.
54. Manatsathit S, Dupont HL, Farthing M, et al. Guideline for the management of acute diarrhea in adults. *J Gastroenterol Hepatol* 2002;17:Suppl:S54-S71.
55. Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. The management of acute gastroenteritis in young children. *Pediatrics* 1996;97:424-35.

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