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# **Disease a Month<sup>®</sup>**

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## **Infectious Diarrhea**



### **Larry Goodman, MD**

Professor of Internal Medicine and Infectious Disease  
Rush Medical College  
Senior Vice President  
Rush-Presbyterian-St. Luke's Medical Center  
Chicago, Illinois

### **John Segreti, MD**

Associate Professor of Internal Medicine and Infectious Disease  
Rush Medical College  
Chicago, Illinois

# Disease-a-Month<sup>®</sup>

## Infectious Diarrhea

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## Infectious Diarrhea

**Abstract.**—Infectious diarrhea is an extremely common illness that affects millions of Americans annually. For most patients, the illness is a self-limited one. Its major risk is dehydration. However, for some patients, diarrhea can lead to severe dehydration or be associated with bacteremia and metastatic infection. Patients with these conditions require prompt treatment.

A large number of organisms have been associated with diarrhea in humans, and most laboratories routinely screen for *Salmonella*, *Shigella*, and *Campylobacter*. Other bacteria, parasites, and viruses account for a significant percentage of diarrhea cases and frequently go undetected. This article summarizes many of these pathogens and describes the settings in which they can be acquired.

Food distribution networks have made the delivery of previously rare foods to remote areas a commonplace occurrence; this has also led to new challenges in the diagnosis and prevention of food-borne illnesses. Outbreaks of diarrhea now frequently extend across many states. The identification of a rare strain of a bacterial pathogen or changes in the isolation rate of common pathogens may be early clues to the cause of such an ongoing outbreak.

Most enteric pathogens cause disease by either stimulating the secretion of fluids at the level of the small bowel or by irritating and invading the colon. Organisms that cause disease by the latter mechanism have the potential to invade the blood stream and spread to other parts of the body, including the bones and the central nervous system. Several organisms have been associated with specific postinfectious syndromes that are responsible for additional morbidity and mortality.

The antibiotic resistance of bacterial pathogens has been increasing, and this has a limiting effect on the empiric treatment choices available for suspected bacterial diarrhea. Careful attention to local sensitivity patterns and appropriate testing of the patient's isolate are among the important factors that lead to successful treatment decisions.

## In Brief

It is estimated that there are approximately 1.5 episodes of diarrhea per person per year in the United States. In developing nations, the incidence of diarrhea is much higher, and in many countries, diarrhea is the leading cause of potential years of life lost. Worldwide, children are the most affected by this condition, which causes more than 5 million child deaths annually. However, in the United States, more than half of the deaths attributed to diarrhea occur in the elderly population.

Diarrhea is acquired by ingesting a causal pathogen or toxin, and several foods are particularly common vehicles for the ones that cause diarrhea. Water is a common source of *Giardia lamblia*, *Cryptosporidium*, *Cyanobacterium*, and Norwalk virus. Milk is a common vehicle for *Salmonella*, *Campylobacter*, and *Yersinia*. Outbreaks of *Salmonella* and *Campylobacter* have been traced to contaminated chicken, and eggs have been the source of several large outbreaks of *Salmonella*. Fish have been the source of infections caused by *Vibrio*, Norwalk virus, and several toxins.

There are several key host defenses that decrease a person's chances of developing diarrhea after ingestion of a pathogen. The main ones are gastric acidity, small bowel motility, local antibody formation, and the colonic microflora. Of these, gastric acidity is the most important. A fasting pH of less than 4 eradicates most pathogens that are ingested, but this barrier is overcome if either a very large inoculum is ingested or if other foods are ingested first, which can buffer gastric acidity. Organisms cause diarrhea by the production of a toxin (enterotoxin, neurotoxin, or cytotoxin), by adherence to the mucosa, or by invasion of the tissue and blood stream. Many of these pathogenic properties can be transmitted to other organisms.

Fever, incubation period, and the presence of white blood cells in the stool are all useful clues when categorizing a diarrheal illness. Incubation periods shorter than 12 hours suggest an enterotoxin-producing organism; fever and white blood cells in the stool are generally associated with an invasive pathogen. The microbiology laboratory provides the definitive tests for diagnosis. Cultures and toxin assays are the gold standard diagnostic tests. When specific pathogens (such as *Vibrio*) are suspected, the laboratory must be informed so that appropriate testing can be performed.

More than half of the patients who develop bacterial gastroenteritis improve within 2 days. Although antibiotic therapy may further reduce this period, the real benefits of therapy are to treat patients who are particularly ill and possibly experiencing bacteremia and to eradicate the

organism from the stool, thereby decreasing secondary transmission. Enteric pathogens have become increasingly resistant to many common antibiotics, making treatment decisions more complex. The widespread use of antibiotics in animal feed and the overuse of antibiotics in humans have contributed to this serious problem.



Larry Goodman, MD, received his undergraduate and medical degrees from the University of Michigan. He completed his residency in internal medicine at Rush–Presbyterian–St. Luke’s Medical Center in 1979 and served as Chief Resident in Internal Medicine the following year. He completed his fellowship training in infectious disease at that institution in 1981 and then joined the Section of Infectious Disease. In addition to his clinical responsibilities, Dr Goodman has served as Assistant Dean of Clinical Curriculum for Rush Medical College, Associate Dean of Medical Student Programs, and Director of Inter-Institutional Affairs for Medical Affairs. In 1996, Dr Goodman was named Medical Director of Cook County Hospital. He has recently returned to Rush–Presbyterian–St. Luke’s Medical Center as the Senior Vice President of Medical Affairs and as a professor in the department of internal medicine.



John Segreti, MD, graduated summa cum laude from Loyola University of Chicago before receiving his medical degree from Rush Medical College. He completed his residency in internal medicine at Rush–Presbyterian–St. Luke’s Medical Center in 1983. While he was a third year resident, Dr Segreti was awarded the Department of Medicine Award for the Outstanding Medical Resident. Doctor Segreti completed a 3-year fellowship in infectious disease at Rush–Presbyterian–St. Luke’s Medical Center in 1986. He is currently an associate professor in the Department of Internal Medicine, Section of Infectious Disease, at that institution, and he serves as the hospital’s epidemiologist and the chair of its Infectious Control Committee.

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# Infectious Diarrhea

Diarrheal diseases are among the most common illnesses of the patients that come to a general practitioner. Diarrhea is also a common problem for travelers, and it is often seen in hospitalized patients. In each of these settings, there are key differences among the initial work-ups and treatments of the patients. An understanding of the basic pathophysiology of diarrhea and its common infectious and noninfectious causes greatly limits the differential diagnosis and, therefore, the cost of the work-up.

Estimates of the number of cases of diarrhea in the United States have ranged from 70 million annually to 1.5 episodes per person per year.<sup>1</sup> Although usually a self-limited condition, the impact of diarrhea, as measured by lost days of work, physician or hospital visits, or lost vacation days, is significant. Diarrhea has among the broadest differential of infectious causes of any common syndrome; bacteria, toxins, viruses, and parasites are all common causes, and sometimes fungi and mycobacteria may be the cause. Routine laboratory tests do not distinguish all of these agents, and toxins and viruses in particular frequently are not detected.

Today, with modern food processing, refrigeration, and distribution systems, food-borne outbreaks frequently encompass wide geographic areas. The association of diarrheal infections with subsequent syndromes that are not gastrointestinal (eg, *Escherichia coli* 01:57H7 with hemolytic uremic syndrome) demonstrates the impact that epidemiologic studies have had on our understanding of these infections and their sequelae.

Finally, although this review will mainly cover the infectious causes of diarrhea, there are numerous noninfectious causes of diarrhea that also must be considered for the differential diagnosis. Frequently a patient's history will be helpful in determining these other causes. Noninfectious causes should particularly be considered when dealing with a patient with persistent or recurrent diarrhea.

## Epidemiology

On a global scale, diarrhea accounts for approximately 5,000,000 child deaths annually, making it the leading cause of potential years of life lost in many parts of the world.<sup>2</sup> In many developing nations, diarrhea can occur at the rate of 15 to 20 episodes per person per year. Children are at a particular risk of developing diarrhea just after they are weaned from breast-feeding. In developed nations with adequate sewage and refriger-



ation systems, a frequency of 1 to 3 episodes of diarrhea per person per year is more typical.

Debilitated patients and patients at the extremes of age have a higher risk of dying from severe diarrhea, usually because of dehydration or the effects of the malabsorption of necessary medications. In the United States, a recent increase in mortality caused by diarrhea has been seen in the elderly. A review of all deaths associated with diarrhea from 1979 to 1987 found just over 28,500 cases in which diarrhea was listed as the primary cause of death. Of these deaths, 51% were of patients in the hospital who were more than 74 years old.<sup>3</sup> The age-specific annual mortality was higher for the elderly than for children 1 to 11 months old (14.8 deaths per 100,000 person years vs 7.8 deaths per 100,000 person years). A more recently published study in Cuba disclosed similar findings.<sup>4</sup> Between 1987 and 1993, 2394 Cubans died from diarrhea. Sixty-two percent of the patients that died were retired people, and mortality was highest in males more than 65 years old.

The most common health problem facing the more than 300 million people that travel internationally each year is travelers' diarrhea. The risk to the traveler varies and depends on the destination and the eating habits of the traveler. Relatively low-risk destinations include Canada, Australia, and Northern Europe. Southern Europe and several of the Caribbean Islands have a higher risk, and the areas with the highest risk for travelers are Latin America, Africa, parts of Asia, and the Middle East. Studies of people who have traveled to these highest-risk destinations have demonstrated an incidence of diarrhea of up to 50% to 60%.<sup>5,6</sup> Although most cases of travelers' diarrhea are self-limited, the loss of business or vacation days is significant and prompts many travelers to ask their physicians questions about prevention and treatment.

Diarrhea is a common condition of patients in the hospital. Although many of these cases have noninfectious causes, *Clostridium difficile* is recognized as the most common infectious cause; in several studies it accounted for about 25% of all cases.<sup>7,8</sup> The incidence of diarrhea among some hospitalized patient populations may rival the incidence seen in travelers. This makes clear the need for special prevention and treatment strategies. Also, unlike cases of diarrhea seen in other settings, the fact that a single pathogen accounts for such a high percentage of all nosocomial cases changes the diagnostic and therapeutic approach.

Several underlying illnesses greatly increase a patient's risk of infectious diarrhea. For example, hemolytic diseases such as sickle cell anemia are associated with a higher incidence of *Salmonella*, and children with common variable immune deficiency and X-linked agammaglobulinemia

are more susceptible to *Giardia*. Of all underlying illnesses, patients with acquired immunodeficiency syndrome (AIDS) have the highest incidence of diarrhea. Gastrointestinal symptoms are reported in 30% to 50% of patients with AIDS in developed countries and in nearly 90% of patients with AIDS who are in developing nations.<sup>9,10</sup>

Diarrhea is one of the most common infectious syndromes in the world. Appropriate management requires knowledge of the setting in which the patient became ill, the underlying disease state, and the physical findings and laboratory results at the time the patient presented with the condition. Diarrhea is a common final expression of infection with a myriad of pathogens. Optimal evaluation and treatment of each of these infections (as well as of cases caused by noninfectious organisms) can limit the duration of illness, the morbidity rate, the cost of work-up, and the spread of secondary infection.

## Acquisition of the Organism

Nearly all cases of infectious diarrhea are acquired from the ingestion of contaminated foods or beverages. Respiratory droplet (sneezing, coughing) and penetrating injury—common routes for other infections—are not modes of the spread of gastrointestinal pathogens. Infection caused by person-to-person contact does occur and, similarly, inanimate objects may also play a role in the spread of disease. In each of these scenarios, the contact facilitates fecal-oral spread. Also, when dealing with patients for whom *C difficile* is the cause, alteration of the bacterial flora of the gut with antibiotics or other medications appears to be critical.

Meticulous attention to the food and beverage one consumes can decrease the risk of infectious diarrhea, but only somewhat. Contaminated food often smells and tastes normal. Practical steps one can take include drinking only chemically treated or filtered water and avoiding milk products that are not pasteurized. When consuming food that is served warm, eating it at piping hot (steaming) temperatures is an added precaution.

Certain foods and beverages have been particularly associated with specific organisms. Table 1 summarizes this information. Water has been the documented vehicle for outbreaks of *Giardia*, *Campylobacter*, *Cryptosporidium*, *Cyanobacterium*, and Norwalk virus. In the United States, *Giardia* is the pathogen most commonly associated with waterborne outbreaks.<sup>11</sup> The surface water of lakes and streams frequently becomes contaminated with *Giardia* cysts from either human or animal sources. These cysts survive well at cold temperatures. Outbreaks, particularly in the Rocky Mountain areas, have occurred because of inadequate

**TABLE 1.** Food-borne outbreaks: Common food and beverage causes, associated gastrointestinal pathogens, prevention strategies

| <b>Food/<br/>Beverage</b> | <b>Associated pathogens</b>   | <b>Prevention strategy</b>   |
|---------------------------|---|--|
| Water                     | <i>Giardia</i> , <i>Cryptosporidium</i> , Cyanobacterium, Norwalk virus | Chlorination, filtration, flocculation, sedimentation, boiling                       |
| Milk                      | <i>Salmonella</i> , <i>Campylobacter</i> , <i>Yersinia</i>              | Pasteurization   |
| Chicken                   | <i>Salmonella</i> , <i>Campylobacter</i>                                | Thorough cooking (irradiation and vaccination under investigation)                   |
| Eggs                      | <i>Salmonella</i>   | Avoid raw or undercooked eggs, consider the use of pasteurized eggs for institutions |
| Fish                      | <i>Vibrio</i> , Norwalk virus, paralytic shellfish poisoning            | Thorough cooking (may not be totally effective)                                      |

treatment of this surface water before it is consumed. Chlorination alone is adequate to eradicate *Giardia* cysts. However, flocculation, sedimentation, and filtration of public water supplies are also recommended for added safety. Appropriate precautions for wilderness campers and travelers to areas without adequate treatment facilities include boiling water for at least 10 minutes (longer at higher altitudes), chemical treatment (chlorine or iodine), or filtration with pore sizes of 2  $\mu\text{m}$  or less. Campers should be reminded that careful treatment of drinking water is not enough. The water used to wash fruits and vegetables and that used for tooth brushing should be similarly treated to avoid infection. Ice made of contaminated water remains a risk. Ice has been a documented source of infection with *Escherichia coli*, Norwalk virus, and *Vibrio cholera*.<sup>12,13</sup> Travelers frequently make the mistake of drinking bottled water with ice that is locally available and made from inadequately treated water. Even when water meets all current treatment requirements, it may still contain pathogens. To test the hypothesis that further treatment would decrease the incidence of diarrhea, Payment et al<sup>14</sup> added water filters to 299 households and compared the incidence of diarrhea to 307 households drinking regular tap water. People from the households with the added filter had less diarrhea ( $P < .01$ ). It was estimated that, even in this setting, 35% of all diarrhea was water-related.

Poultry products are also associated with a high rate of contamination with organisms that cause infectious diarrhea. In particular, chicken has frequently been identified as the vehicle for infection with *Salmonella* and *Campylobacter*. Evans et al<sup>15</sup> recently reported an outbreak that illustrated several points. The authors found that in Cardiff, Wales, *Campylobacter* was isolated from 5 people who were

among 29 customers that visited a restaurant with a Hawaiian theme. Twelve of these patrons became ill with gastroenteritis. Food-specific attack rates implicated chicken as the vehicle (relative risk 4.81, 95% confidence interval), and all *Campylobacter* isolates were of the same serotype (HS50 phage type 49). As is the case with most food-borne outbreaks, all individuals who ate the contaminated food did not become ill. Sometimes this is because the contaminated food was eaten at different times, and those that ate the food later ingested a larger dose of organisms because of the organisms' continued growth on the food. Alternatively, differences among individuals make some more prone to infection than others (see Pathophysiology below). The authors postulated that the food implicated in this outbreak might have been inadequately cooked because large pieces of chicken were being stir-fried. Also reported in that study is that there were 6 additional *Campylobacter* isolates of the same serotype identified in Cardiff during the months immediately preceding the outbreak, suggesting that this occurrence may have not been an isolated event. Serotyping of outbreak isolates can be a valuable tool that may help explain the occurrence of disease beyond the outbreak investigation.

Because poultry is so frequently a vehicle for *Campylobacter*, the method and timing of the contamination of poultry flocks with *Campylobacter* is important because it may lead to improved prevention strategies. Wallace et al<sup>16</sup> have shown that turkey chicks are born without the organism but that colonization begins by day 7 and is 100% by day 14. *Campylobacter* was found throughout the length of the bird's gastrointestinal tract, with the highest concentration found furthest from the beak. Flocks of laying hens and uncooked chickens from grocery stores are also frequently colonized with *Salmonella*. This has led to several strategies for preventing the spread of the organism, ranging from the use of antibiotics in the animals to the irradiation of the food products that come from them. Thorough cooking of poultry is a more effective and cost-efficient approach. However, it should be noted that even with thorough cooking, any surface (such as a cutting board) where the raw birds are prepared might be a source for the cross-contamination of other food.<sup>17</sup>

Given the high rate of the contamination of flocks of laying hens with *Salmonella* and *Campylobacter*, it should not be surprising that eggs are frequently contaminated with these organisms. In 1978, the New England area experienced an increase in cases of *Salmonella enteritidis*. However, it wasn't until an outbreak in 1986 that involved 3000 people across 7 states that *Salmonella* in flocks of laying hens was clearly linked

to subsequent sporadic and outbreak cases.<sup>18,19</sup> By 1986 the number of *S enteritidis* cases was markedly increased in the entire mid-Atlantic area and, by 1994, this increased incidence had spread along the length of the country to the Pacific Coast.<sup>20</sup> Infected eggs will not necessarily have visible cracks or be of inferior quality in any measurable way. An outbreak in Tennessee demonstrated that chickens that are colonized with the bacteria can transmit infection to humans even when their eggs are inspected as Grade A and are completely intact.<sup>21</sup> Today, *S enteritidis* accounts for approximately 25% of all *Salmonella* infections. The consumption of raw eggs in cake batter, Caesar salad dressing, mousse, and sunny-side up or soft-boiled eggs is clearly a risk. The use of pasteurized egg products is recommended for institutions as a means of decreasing this risk.

Milk was the vehicle of the largest outbreak of *Salmonella* in the United States. In 1984 in Chicago, approximately 200,000 cases of *Salmonella typhimurium* were traced to contaminated milk.<sup>22</sup> Although the milk had been pasteurized, it was postulated that the pasteurized milk became contaminated with unpasteurized milk later in the process. Unpasteurized milk has also been the source of infections with *Campylobacter*, other *Salmonella* species, and *Yersinia*. Another dairy product, cheese, has been linked to infection with *Listeria monocytogenes*.

Fish has been associated with a wide variety of infections. The consumption of shellfish includes the risk of the acquisition of *Vibrio* species, neurotoxic shellfish poisoning, paralytic shellfish poisoning, and Norwalk virus, and thorough cooking of the shellfish may not significantly reduce the risk. During an outbreak of oyster-associated gastroenteritis in Florida in 1995, McDonnell et al<sup>23</sup> interviewed 223 oyster eaters. Those who said that they ate only thoroughly cooked oysters (grilled, stewed, or fried) were as likely to have developed diarrhea as those who ate raw oysters (relative risk 0.68, 95% confidence interval). The oysters had presumably become contaminated as a result of the users of small boats, including fishing boats, dumping human waste in the water over the oyster beds.

In a recent review of food-borne diseases,<sup>20</sup> recent key changes in the types of food-borne outbreaks now seen in the United States were described. For example, an increasing number of outbreaks have involved fresh fruits and vegetables as the vehicle of transmission. Because of large distribution areas, outbreaks may begin as a multistate or even a nationwide problem. At times an outbreak may only be detected above background baseline levels of infection because of the

predominance of an unusual serotype or susceptibility pattern. New pathogens are being identified as important causes of human diseases. An optimal response to these pathogens requires a coordinated approach that involves both local and national public health officials and industry. Although final inspection of products and goods was the main quality strategy of the past, hazard analysis and the determination of critical control points is now preferred. This approach attempts to identify and correct potential contamination points throughout the journey of food from farm to table. Future strategies will include reductions in the contamination of food and water given to animals and the soil and water used to grow and transport produce.

## **Pathophysiology**

### *Host Factors*

Once a diarrhea-causing organism is ingested, it must successfully avoid a number of host defenses to reach the site of action in the small bowel or colon. The main host defenses against the acquisition of enteric disease are (1) gastric acidity; (2) small bowel motility; (3) local antibody formation; and (4) the colonic microflora. The normal fasting gastric pH of less than 4 is a very effective barrier to infection with ingested organisms. At this pH level there is a greater than 99% eradication of most diarrhea-causing bacteria within 30 minutes. Many viruses and parasites are similarly affected. Neutralization of this pH barrier with antacids or gastric resection or neutralization that is caused by achlorhydria greatly decreases the number of organisms necessary to cause disease. This also explains why many people may eat the same contaminated meal and only some become ill. Even if all individuals ate the specific item that was contaminated, they may have significant differences in their gastric pH at the time of ingestion. For example, if gravy on meat was contaminated and this was eaten first, that individual would have maximum stomach acidity to combat this infection. However, if several rolls were eaten before the contaminated gravy, stomach acidity would be buffered, which would allow for a greater susceptibility to infection by a smaller number of organisms.

The small bowel is in constant motion. This motion makes it difficult for organisms that act by attachment and invasion to attach themselves. Patients with decreased peristalsis caused by diabetes or antimotility medications have a resultant increase in the contact time of the organism and the mucosa in the small bowel. This facilitates attachment and increases the chance that

diarrhea symptoms will develop. In a study of patients with *Shigella* infections, therapy with the antimotility drug diphenoxylate hydrochloride with atropine (Lomotil; G. D. Searle & Co, Chicago, Ill) was associated with a more prolonged period of fever and positive cultures.<sup>24</sup> Impaired motility also increases the concentration of anaerobic bacteria in the proximal gastrointestinal tract, which can cause malabsorption.

Local antibodies appear to provide some protection against the acquisition of diarrheal pathogens, although their role is relatively minor. The main secretory antibody class is immunoglobulin A. Patients with immunoglobulin A deficiency may have an increased incidence of giardiasis, and patients with hypogammaglobulinemia may also have an increased risk of malabsorptive diarrhea.

The normal microflora of the colon is a significant host defense. Of the approximately  $10^{11}$  organisms per gram of feces, over 99% are anaerobes. These organisms protect the host by competing with invading pathogens for nutrients and attachment sites. They also produce chemicals, such as short chain fatty acids, that may be toxic for some organisms.

### Organism Factors

Gastrointestinal pathogens cause disease by means of a number of different mechanisms. The most common virulence factor is the production of a toxin by the organism. Diarrheal pathogens produce several types of toxins. Enterotoxins may be produced on the food before it is ingested and act at the level of the small bowel. There the enterotoxin increases local cyclic adenosine monophosphate and, through a series of chemical reactions, leads to changes in sodium and potassium absorption and a net movement of fluid into the gut lumen. This secretory diarrhea can produce voluminous fluid loss, many liters per day. Enterotoxin production is the main mechanism of diarrhea produced by *Cholera*, enterotoxigenic *E coli*, *Clostridium perfringens*, and *Bacillus cereus*. Neurotoxins contribute to the symptoms of gastroenteritis with the use of a different mechanism. They act on the autonomic nervous system and cause hyperperistalsis, and they may also act centrally as a stimulant to emesis. *Staphylococcus* food-poisoning toxin and one of the toxins associated with *B cereus* act in this manner. These toxins also are frequently formed on the contaminated food before it is ingested. Cytotoxins represent a third type of toxin that is associated with gastrointestinal pathogens. Unlike enterotoxins and neurotoxins, cytotoxins cause direct mucosal damage. These toxins are usually formed inside the body by the ingested organism and act at the level of the colon.

Toxins within these classes have more similarities than just mechanism of action. For example, the heat-labile toxin of enterotoxigenic *E coli* has great antigenic and molecular similarity to the enterotoxin of *V cholera*. Other heat-labile toxins found in some *Klebsiella*, *Salmonella*, and *Citrobacter* organisms also have similar antigenic structures. Another example is the similarity seen between the cytotoxin of enterohemorrhagic *E coli* and Shiga's toxin, a cytotoxin produced by *Shigella*. Here the likeness is so close that the toxin found in *E coli* is considered to be a "Shiga-like toxin." Many of these toxins are found on plasmids, which are bits of extrachromosomal DNA. These plasmids, with the genetic codes for toxin production, may be transferred among organisms.

Other microbial virulence factors include their motility, chemotaxis, invasiveness, and their ability to attach and adhere to mucosa. These organisms have multiple properties and, sometimes, more than 1 type of toxin. This explains why infection with a single pathogen may begin as a watery diarrhea and progress to fever and to an invasive syndrome. Because some toxins are preformed and act at the level of the small bowel and others are formed in the body after ingestion and act at the level of the colon, the timing of the effects of the various toxins on the host is staggered. Table 2 summarizes the various host and organism factors.

## **A Clinical Approach to the Evaluation of the Patient With Diarrhea**

The evaluation of a patient with an acute diarrheal illness should focus on the aspects of that patient's history, physical examination, and laboratory findings that are most likely to lead to a diagnosis. Important questions in the history include the duration of the illness, previous occurrence of similar symptoms, the presence or absence of fever or sweats, whether blood or pus has been visible in the stool, and whether the patient has any symptoms that suggest of dehydration. Symptoms consistent with dehydration include dizziness when standing, rapid heart rate, and feelings of weakness.

The incubation period is an important clue to the organism causing the symptoms, but it is often very difficult to ascertain this information from most patients because the incriminating meal has not been identified. Patients will often link the illness to a food that "tasted funny" or to the only meal that they ate away from their family because no other family members are ill. However, it is important to remember that contaminated food often smells and tastes normal and that not all people who eat con-



**TABLE 2.** Microorganism virulence factors and host defense factors that interact and affect the development of diarrhea

| Microorganism      |   | Host                 |             |
|--------------------|---|----------------------|-------------|
| Virulence factors  | Organism  | Defenses             | Site        |
| Enterotoxin        | Enterotoxigenic <i>Escherichia coli</i> ,<br><i>Vibrio cholera</i> , <i>Clostridium perfringens</i>                       | Gastric acidity      | Stomach     |
| Neurotoxin         | <i>Staphylococcus aureus</i> ,<br><i>Bacillus cereus</i>  | Small bowel motility | Small bowel |
| Cytotoxin/Invasion | <i>Shigella dysenteriae</i> ,<br><i>Clostridium difficile</i> ,<br><i>Campylobacter</i> , amebiasis,<br><i>Salmonella</i> | Local antibodies     | Colon       |
| Adherence          | Enteroadherent <i>Escherichia coli</i>  | Normal fecal flora   | Colon       |

taminated food will become ill. These conjectures by the patient typically do not help determine the incubation period or the responsible food vehicle. The one instance in which the history alone can fix the incubation period is when multiple persons become ill after eating a common meal. If they have had no other meals together, this strongly implicates the 1 meal they had in common and identifies the incubation period as the time from the meal to the onset of the symptoms.

The physical examination should include focused attention to the findings that might narrow the differential diagnosis or dictate immediate therapy needs. Careful evaluation of the patient's fluid status is paramount because dehydration is the major cause of morbidity and mortality. Orthostatic blood pressure and pulse should be measured. Skin tenting and the observed finding of "sunken eyeballs" are less accurate findings. The presence of fever suggests an invasive pathogen. Fever is not usually associated with organisms that act solely by means of enterotoxin production, so this finding is helpful for narrowing down the number of organisms under consideration. Hypoactive bowel sounds and severe abdominal pain are ominous findings and may precede the more classic findings of a surgical abdomen. When dealing with a case of diarrhea, a patient's progression to hypoactive bowel sounds and distension should raise the consideration of toxic megacolon. An x-ray of the abdomen is helpful in the diagnosis of this condition, and it usually shows dilation of the transverse colon that is 6 cm or more. Toxic megacolon may be seen as a complication of any of the invasive pathogens. Noninfectious causes include inflammatory bowel disease, volvulus, and ischemic colitis. About a third of the cases of toxic megacolon that complicate ulcerative colitis occur during the patient's first episode.<sup>25</sup>

Jaundice is not usually associated with gastrointestinal pathogens and should suggest the possibility of a different primary process. When jaundice is seen in a traveler, malaria should be considered, because a significant percentage of patients with malaria present with diarrhea and other abdominal symptoms in addition to the jaundice more commonly associated with that illness. The presence of a rash is also not typical of most primary gastrointestinal infections and should suggest a primary process outside the gut lumen. Some types of viral gastroenteritis may be associated with a nonspecific erythematous rash, and about a third of *Salmonella typhi* infections are associated with a pink maculopapular rash (rose spots) on the trunk.<sup>26</sup> Hemorrhagic bullae are associated with infection with *Vibrio vulnificus*.<sup>27</sup> Although most patients have diarrhea as part of this syndrome, it is usually an illness characterized by bacteremia and septic shock. Most patients have a preexisting liver disease, such as cirrhosis. Despite these examples, the presence of a rash should direct the clinician to other considerations such as toxic shock syndrome, meningococcal disease, Rocky Mountain spotted fever, viral exanthem, or a drug reaction. Each of these processes can have diarrhea as part of the constellation of presenting symptoms and findings. This underscores the need to broadly evaluate the patient before focusing on the gastrointestinal tract as the main site of infection.

Of the laboratory tests currently available, the microscopic examination of the stool for cells is the most useful. The appearance of white and red blood cells suggests the presence of an invasive pathogen such as *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C difficile*, or *Entamoeba histolytica*.

On the basis of the above information, one can categorize organisms that cause acute diarrhea as having 2 main types of presentations. Type I is a watery diarrhea without fever. Examination of the stool of these patients reveals no white or red blood cells, and the patients have a low risk of bacteremia. The organisms that cause this syndrome usually act by amplifying an enterotoxin or neurotoxin. Because the toxin is often already formed on the food and the site of action is the small bowel, the incubation period is short, usually 6 to 12 hours. Because the organism may not even be present in large numbers at the time of toxin ingestion and because the organism does not have invasive properties, there is rarely a local inflammatory reaction (white blood cells in the stool) or a systemic inflammatory reaction (fever). For these same reasons, bacteremia is rare. Type I organisms include *Staphylococcus aureus*, *C perfringens*, enterotoxigenic *E coli*, enteroaggregative *E coli*, diffusely adherent *E coli*, *Cryptosporidium*, and *Giardia lamblia*.

**TABLE 3.** Typical findings of Type I and Type II diarrhea syndromes

| Characteristic/Finding | Type I            | Type II       |
|------------------------|-------------------|---------------|
| Fever                  | Rare              | Common        |
| Incubation period      | 6-12 hours        | 1-3 days      |
| Bacteremia             | Rare              | Moderate risk |
| Blood cells in stool   | Usually not found | Usually found |

Type II is a diarrhea characterized by fever and by the finding of cells when the stool is microscopically examined. The organisms that cause this type of diarrhea act at the level of the colon and, once there, attach to and invade tissue. This explains their longer incubation of 1 to 3 days. Type II organisms frequently augment a cytotoxin or have other invasive properties that lead to a local and inflammatory host reaction (eg, blood cells in the stool, fever). Organisms in this group include *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, enteroinvasive *E coli*, and *E histolytica*.

The differences between Type I and Type II diarrhea syndromes are summarized in Table 3. It should be noted that, for the parasitic organisms in each group, the incubation period is longer than for the other group members. It is important to realize that many diarrheal illnesses progress from one type of presentation to the other. For example, some *Salmonella* and *Shigella* strains may also contain an enterotoxin. They may begin with an afebrile watery diarrhea syndrome and then progress to fever and bacteremia. As long as the clinician modifies the differential diagnosis to reflect the evolving clinical picture, appropriate diagnostic and treatment strategies should follow.

## A Review of Select Organisms

### Bacterial Diarrhea

*Escherichia coli*. *E coli* is one of the most commonly identified members of the bowel flora. This facultative bacterium, although frequently living in symbiosis with the human host, is also among the most common causes of infectious diarrhea worldwide. *E coli* organisms that cause diarrhea are indistinguishable morphologically from nonpathogenic organisms, and this presents a real challenge to the microbiology laboratory. There are 4 main types of *E coli* organisms that have been associated with diarrhea. These include (1) enterotoxigenic *E coli* (ETEC); (2) enteropathogenic *E coli* (EPEC); (3) enteroinvasive *E coli*; and (4) enterohemorrhagic *E coli* (EHEC). Two additional types of *E coli* organisms have also been associated with diarrhea. Enteroaggregative *E coli* is named for its tendency to adhere and aggregate to specific cells in culture, and diffusely adherent

*E coli* also adheres to these cells in culture. Although these 2 types of *E coli* have been associated with diarrhea in children in developing countries, the pathogenic potential for these organisms has not been fully established.

ETEC was first recognized as a cause of diarrhea in the 1960s. It has since been identified as the cause of nearly 50% of travelers' diarrhea,<sup>28</sup> and it has also been found to be a common cause of diarrhea in infants. ETEC organisms cause diarrhea by the amplification of 1 or more enterotoxins, and these enterotoxins have been characterized as a heat-stable toxin and a heat-labile toxin. Genes that have been found on transferable plasmids code for these toxins. An *E coli* organism may have one, both, or neither of these toxins. The heat-labile toxin has antigenic similarity to the cholera enterotoxin.<sup>29</sup> As with other enterotoxin-mediated infectious diarrhea, the main syndrome that develops is a watery afebrile diarrhea that is usually self-limited and lasts 1 to 4 days. ETEC is not usually considered to be a cause of diarrhea that is acquired in the United States. Because most microbiology laboratories do not routinely screen for this organism, the incidence of this disease is difficult to estimate. A recent report about a food-borne outbreak demonstrated that ETEC was also a cause of diarrhea in patients who had not been traveling.<sup>30</sup> ETEC organisms were isolated from 5 people who had attended a labor union banquet in Milwaukee with attendees from throughout the United States. An estimated 61% of the 1240 attendees met the case definition of 3 or more loose stools within a 24-hour period, with the first occurring within 3 days of the event. Because attendees had dispersed back to their home states only a small number were available for testing, but the isolation of ETEC from 5 of the attendees and the fact that no other pathogen was identified confirmed it as the cause. As newer methods of identifying these toxin-producing pathogens are developed, it is likely that part of the relatively large percentage of diarrhea illnesses that are "culture negative" will be diagnosed.

EPEC causes diarrhea by means of a different method. These organisms adhere to the brush border of the small intestine and efface the surface. There is no enterotoxin or cytotoxin production, but a watery diarrhea is produced. A similar pattern of focal adherence can be demonstrated in cell culture.<sup>31</sup> Both plasmid-mediated and chromosomal-derived genes code for this pathogenic mechanism. EPEC causes diarrhea mainly in children in developing countries. Although the diarrhea is usually self-limited, a prolonged diarrhea caused by EPEC has also been described.<sup>32</sup> EPEC had been associated with outbreaks of diarrhea in nurseries in the past, but with improvements in sanitation, this is rare today.

Enteroinvasive *E coli* produces a dysentery syndrome that is indistinguishable from that produced by *Shigella*. These organisms act at the level of the large bowel, where they invade and cause cell death. Both the genes that code for this invasive property and the genes that code for invasion in *Shigella* are located on a large plasmid. *E coli* harboring this plasmid have other similarities to *Shigella*. They are less motile and do not ferment lactose. The clinical syndrome produced is a febrile diarrhea with severe abdominal cramping. Fecal leukocytes and occasional gross blood and pus are seen in the stool.

EHEC produce an unusual syndrome of gross blood per rectum and only about a third of patients experiencing fever. Fecal leukocyte examination is typically negative. Inflammatory bowel disease and ischemic colitis are considered as diagnostic possibilities because of the severity of onset. Stool examinations of patients with this clinical picture often revealed *E coli* 0157:H7. This serotype accounts for the majority of diagnosed cases of enterohemorrhagic colitis, but serotypes such as 026:H11 and 0113:H21 can also cause this disease. The cause of this syndrome is a cytotoxin. The organism has been associated with several different cytotoxins, each of which can cause the same syndrome. The toxins are so similar to the Shiga-toxin of *Shigella* dysentery they are called "Shiga-like toxins." A review by the Centers for Disease Control and the Washington State Department of Social and Health Services demonstrated that this organism was also associated with a nonbloody diarrhea and asymptomatic carriage.<sup>33</sup> EHEC organisms are associated with hemolytic uremic syndrome (HUS). This syndrome includes the triad of thrombocytopenia, acute renal failure, and hemolytic anemia. HUS is also seen in children with severe *Shigella* infection and therefore may be related to some effect of the Shiga-like toxin. Unlike *Shigella*, HUS caused by EHEC is not confined to children but may be seen in patients of all ages. Thrombotic thrombocytopenic purpura is also associated with preceding EHEC infection. About half of the patients diagnosed with HUS will require dialysis, and most will need transfusions.<sup>34</sup> There is no evidence that antibiotic treatment during the diarrhea infection will decrease the incidence of subsequent HUS or thrombotic thrombocytopenic purpura. In fact, some investigators have suggested that antibiotic therapy could increase the risk of these conditions by altering protective gut flora and increasing toxin production.<sup>35</sup> Outbreaks of EHEC have been associated with eating undercooked hamburger meat, drinking apple cider, and swimming water contaminated with feces.<sup>36,37</sup> Recent hamburger ingestion is also a risk factor for sporadic cases.<sup>38</sup> Because

**TABLE 4.** *Escherichia coli*-induced diarrhea: Names of pathogens, mechanisms of illness, locations of genes that code for virulence

| Organism                        | Mechanism of illness                             | Location of gene that codes for virulence |
|---------------------------------|--|---|
| Enterotoxigenic <i>E coli</i>   | Enterotoxin (heat-stable and heat-labile toxins) | Plasmid                                   |
| Enteropathogenic <i>E coli</i>  | Adhere and efface brush border of small bowel    | Plasmid, chromosome                       |
| Enteroinvasive <i>E coli</i>    | Tissue invasion                                  | Plasmid                                   |
| Enterohemorrhagic <i>E coli</i> | Cytotoxin (Shiga-like toxins 1 and 2)            | Plasmid                                   |

handling raw beef is a risk, careful handwashing and cleaning of preparation surfaces are important prevention strategies. Table 4 summarizes the characteristics of the various *E coli* diarrhea pathogens.

***Campylobacter jejuni.*** *C jejuni* is the most common bacteria isolated from patients with diarrhea. This organism is a curved gram-negative rod that can occasionally be identified during careful microscopic examination of the stool because the normal flora does not contain curved rods. The other curved gram-negative rods that cause diarrhea belong to the *Vibrio* species. However, the epidemiology and clinical picture of *Vibrio* infections are different (see *Vibrio cholera* below). *C jejuni* grows best at 42°C in an atmosphere of 5% to 10% oxygen. This microaerophilic atmosphere has to be created in the laboratory with the use of special gas tanks, chemical packs, or a candle jar. These special growth requirements explain why *Campylobacter* has only recently been recognized as such a common pathogen.

*Campylobacter* is acquired from animals. The organisms are commonly found in the gastrointestinal tracts of cattle, fowl, dogs, cats, sheep, and rodents. Undercooked chicken, unpasteurized milk, and domestic pets are common sources of infection. Person-to-person spread also occurs. *Campylobacter* is an invasive organism that acts at the level of the colon. The incubation period is usually 2 to 4 days, and the clinical syndrome is one of fever, abdominal pain, and diarrhea. Microscopic examination of the stool usually discloses fecal leukocytes and red blood cells. Other *Campylobacter* and related organisms associated with diarrhea include *Campylobacter coli*, *Campylobacter upsaliensis*, *Helicobacter cinaedi*, and *Helicobacter fennelliae*. The last 2 organisms have mainly been isolated from homosexual men with diarrhea.<sup>39</sup>

***Shigella.*** *Shigella* species are divided into 4 main groups: *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, and *Shigella boydii*. The *Shigella* organism is a small gram-negative rod that has been a known cause of diarrhea for approximately the last century. *Shigella* infections

have played a major part in times of war, with a greater number of casualties attributed to this infection than to bullets and explosives. *Shigella* causes an invasive syndrome in the colon, and it includes fever. In a study of experimental infection with *Shigella sonnei*, the height of the fever correlated with the severity of the illness.<sup>40</sup> *Shigella* bacteremia is relatively rare but does occur. Risk factors are an age of less than 1 year and protein malnutrition.<sup>41</sup> *Shigella* may also cause chronic vulvovaginitis in children.<sup>42</sup> The recognition of this diagnosis is important because it may otherwise be wrongly diagnosed as a sexually transmitted disease. Finally, as noted previously, *Shigella* has been associated with the subsequent development of HUS in children.<sup>43</sup>

***Yersinia enterocolitica.*** In many parts of the world, *Y enterocolitica* rivals *Salmonella* in the frequency of the number of times it is isolated from the stool of patients with diarrhea. The Scandinavian countries, Belgium, Canada, and Japan have the highest rates of isolation of this organism. In these countries, serotype O:3 and O:9 are the most common isolates. In the United States, serotype O:8 predominates. *Yersinia* grows at room temperature, body temperature, and 4°C (refrigeration temperature). This ability to grow at cold temperatures has proved useful in the microbiology laboratory for the selective growth of *Yersinia* from a specimen; it also may be a factor in the food-borne outbreaks where small amounts of contamination may become more significant even when the food has been adequately refrigerated. *Yersinia* has been isolated from animals, lake and stream water, and a variety of foods, and person-to-person spread does occur. Pigs are a particularly important reservoir. *Yersinia* has been isolated from pig tonsils and intestines,<sup>44</sup> and an outbreak in Atlanta in 1988 was traced to the household preparation of chitterlings (pig intestines).<sup>45</sup> Transfusion-associated *Yersinia* has also been reported. In 1991, the Centers for Disease Control reported that 10 cases of transfusion-associated *Y enterocolitica* occurred between 1987 and 1991. These cases were reported from 9 different states, and 7 of these 10 patients died from the infection. The transfusions they had received were packed red blood cells that had been stored at 4°C for a mean of 33 days.<sup>46</sup> Patients developed fever and hypotension within 50 minutes of transfusion. Half of the donors reported a diarrheal illness that had occurred within the 30 days before they had donated blood.

The clinical presentation of *Y enterocolitica* diarrhea is similar to *Shigella* or enteroinvasive *E coli*. An associated pharyngitis may be present. The incubation period is about 4 to 7 days, and ulceration of the mucosa at the level of the terminal ileum may be seen. This syndrome may mimic regional enteritis (Crohn's disease) or appendicitis. *Yersinia*

infections have also been associated with the subsequent development of a reactive polyarthritis in human leukocyte antigen-B27 positive patients. This has also been reported in patients after they have been infected with *Salmonella* or *Campylobacter*. *Yersinia pseudotuberculosis* can also cause diarrhea, particularly in children. It is a rare isolate and, like *Y enterocolitica*, it is acquired from animals.

**Salmonella.** *Salmonella* are gram-negative motile rods that do not form spores. As is the case with many other enteric pathogens, animals are important sources of infection. Poultry, beef, milk, and eggs have all been documented vehicles in outbreaks and in cases of person-to-person spread. There are over 2000 serotypes of *Salmonella*, many of which are named for the animal from which the organism was first isolated or for the city in which it was first identified. Not all of these serotypes are pathogenic for humans. *S typhimurium*, *S enteritidis*, and *Salmonella heidelberg* are common isolates in the United States. Enterotoxins and cytotoxins have been isolated from *Salmonella* species, but the main mechanism of diarrhea appears to be a combination of the penetration of the mucosa and of an inflammatory/immune response. *Salmonella* can survive inside phagocytes, which provide a protected intracellular site for survival and for the avoidance of other host defense measures. Bacteremia is a more common complication of *Salmonella* infection than other enteric infections, and patients with defects in cell-mediated immunity (eg, AIDS, high-dose steroid therapy, lymphoma) and those with hemolytic illnesses (eg, sickle cell disease) are at increased risk.<sup>47</sup> Persistent bacteremia, often with few gastrointestinal symptoms, has also been reported, and this syndrome is often caused by *Salmonella choleraesuis*. There is a marked increased risk of infection of endovascular surfaces for patients infected with these organisms, particularly for elderly patients with atherosclerotic disease or vascular grafts.<sup>48</sup> Infection of an aortic aneurysm, occasionally with fistula formation to the duodenum, is a well-reported complication. Typhoid fever is caused by *S typhi*, an organism that is only found in humans. Abdominal pain, fever, and bacteremia characterize this infection. Approximately 80% of patients are bacteremic during the first week of illness, and bone marrow cultures can be positive in up to 90% of cases. The bacteria's ability to penetrate the mucosa and survive in Peyer's patches in the ileum is associated with a 2% to 5% risk of intestinal perforation. This complication usually occurs during the second or third week of illness and carries a 40% mortality rate.<sup>49</sup> The enteric fever syndrome (typhoidal syndrome) can also be seen with infection caused by *Salmonella paratyphi*. Patients who have excreted the organism in the stool or urine for 1 year or more are identified as chronic carriers. Most chronic carriers are asymptomatic, but they may



need treatment if they have an occupation, such as a job in food preparation, that poses a risk for transmission to others.

***Vibrio cholera.*** *Vibrio* organisms are curved gram-negative rods that are morphologically similar to *Campylobacter*. *Vibrio* organisms are commonly found in surface water, and inadequate sanitation and water purification methods are the main contributors to proliferation of the bacteria. *V cholera* is the classic enterotoxin-mediated watery diarrhea pathogen. The volume of fluid loss is so significant that a previously healthy person may die within hours of the onset of this type of diarrhea unless appropriate fluid replacement therapy is provided. The World Health Organization's oral rehydration fluid therapy, which contains sodium chloride, sodium bicarbonate, potassium chloride, and glucose, can be life-saving even for severely ill patients.

Infection with *Vibrio* species usually follows exposure to salt water or shellfish. Raw or undercooked clams and oysters in particular are associated with the acquisition of *Vibrio* species. Several *Vibrio* organisms cause disease. *Vibrio parahaemolyticus* is a major cause of diarrhea in Japan. This organism produces an enterotoxin, and it also causes an inflammatory reaction in the bowel, so both syndromes may be seen. *Vibrio mimicus* is a less-commonly isolated diarrheal pathogen. *Vibrio alginolyticus* is a cause of wound infections after exposure to salt water, and *V vulnificus* is a cause of bacteremia and sepsis. For *V vulnificus*, risk factors for acquisition of infection include preexisting liver disease and the ingestion of raw oysters or clams.

***Clostridium difficile.*** *C difficile* is the most common cause of nosocomial infectious diarrhea. Up to 25% of diarrhea acquired in the hospital is caused by this pathogen.<sup>50,51</sup> The most important risk factor for the development of this infection is treatment with antibiotics. The organism is a spore-forming gram-positive anaerobic rod. It is found in the stool of about 3% of healthy persons and in a much higher percentage of newborns. *C difficile* produces an enterotoxin (toxin A) and a cytotoxin (toxin B). Although the organism itself does not invade the mucosa and bacteremia is rare, mucosal ulceration secondary to cytotoxin activity is commonly seen. In severe disease, pseudomembranes can form (pseudomembranous colitis). The incidence of this disease is highest among the elderly. Recently, tube feedings, especially postpyloric feedings, were found to be an additional risk.<sup>52</sup> Numerous strategies to decrease the incidence of this disease have been tried and have including barrier precautions, promotion of handwashing, and training about the use of antibiotics. Nearly every antimicrobial agent has been associated with the subsequent development of this infection, although clindamycin (Cleocin; Upjohn Co, Kalamazoo,

Mich) has been linked most closely. A recent study from the Veteran's Administration Hospital at the Medical College of Virginia and Virginia Commonwealth University demonstrated that the formulary restriction of clindamycin is an effective way of reducing cases in a setting where clindamycin use is identified as risk before intervention.<sup>53</sup>

***Listeria monocytogenes.*** *L. monocytogenes* has, until recently, been thought of primarily as a cause of bacteremia and meningitis in immunocompromised patients. However, several recent studies have demonstrated that in many cases the organism can be acquired through the consumption of contaminated food. Soft cheeses and foods such as cold cuts from a deli counter have been shown to be the most common vehicles.<sup>54</sup> Inadequately pasteurized milk has also been associated with foodborne outbreaks. Diarrhea from these sources may affect all hosts, but invasive disease with bacteremia is much more common in the immunocompromised host. Risk factors include pregnancy, extremes of age, and defects in cell-mediated immunity.

### ***Viral Gastroenteritis***

It is estimated that viral pathogens account for 30% to 40% of diarrheal disease in the United States.<sup>55</sup> The main viruses that cause diarrhea in the immunocompetent patient are rotavirus, Norwalk virus (and other calciviruses), enteric adenovirus, astrovirus, and enteric coronavirus. Clinical viral gastroenteritis is similar to an enterotoxin-mediated diarrhea with the sudden onset of watery diarrhea that does not include fecal cells. However, unlike bacterial enterotoxin illnesses, viral gastroenteritis is more commonly associated with fever. Rotavirus is usually a wintertime illness that is worse in young children; it accounts for about half of hospital admissions for diarrhea in children. The incubation period is 1 to 3 days, and the illness may last a week or more. Norwalk virus has a shorter incubation period (< 24 hours) and involves all age groups, and community outbreaks account for a significant percentage of the cases of the illness. Commercially available enzyme-linked immunosorbent assays have now made the diagnosis of viral gastroenteritis possible in hospital laboratories.

### ***Diarrhea Caused by Parasites***

A number of protozoal parasites are important infectious causes of diarrhea. These organisms are larger than viruses or bacteria and, therefore, are usually diagnosed by staining a stool specimen and observing it under a microscope. In the United States, the most commonly isolated of the parasites is *G lamblia*. The exact mechanism of diarrhea in giardiasis

is not known. *Giardia* does not produce an enterotoxin or cytotoxin, and it is not invasive. Deconjugation of bile salts by an associated bacterial overgrowth may play a role. The syndrome is a noninflammatory malabsorptive diarrhea. After an incubation period of 1 to 3 weeks, patients develop bloating, steatorrhea, and nausea. Patients are afebrile, and examination of the stool for blood cells is negative. If left untreated, symptoms may wax and wane, but they often persist for weeks or months. The cyst is the infectious form of the organism, and the ingestion of only a small number of cysts can cause disease.

*E histolytica* is the causative agent of amebiasis. Unlike giardiasis, amebiasis is an invasive illness, and it affects the large bowel. Patients experience a gradual onset of illness, but once it has fully developed, the clinical picture is similar to that of *S dysenteriae* or enteroinvasive *E coli*. Fever and gross blood and pus in the stool are common. Extraintestinal disease may complicate amebic colitis. The most common sites of infection include the liver (liver abscess), the peritoneal cavity, the brain, and the pericardial sac.

*Cryptosporidium parvum*, a cause of persistent diarrhea in patients with AIDS, can also cause self-limited diarrhea in immunocompetent patients.<sup>56,57</sup> Watery diarrhea associated with nausea and low-grade fever are included in the most typical presentation. A recent 2-year longitudinal study in Peru showed that infection early in life (first 17 months) led to a decreased rate of growth and that children who had been infected did not catch up with their peers.<sup>58</sup> Outbreaks have been associated with contaminated drinking water and swimming in a contaminated pool.

*Cyclospora cayetanensis* is a protozoan that has been recently recognized as a cause of diarrhea. This organism, like *Cryptosporidium*, can be detected by an acid-fast stain of the stool. *Cyclospora* causes a watery and malabsorptive diarrhea that may last 2 to 3 weeks. In a study of 1465 cases that occurred in 1996, food histories strongly suggested raspberries as the vehicle for the majority of these illnesses.<sup>59</sup> *Cyclospora* can be treated with trimethoprim-sulfamethoxazole.

## Diagnosis

Unfortunately, the clinical presentation of a person with diarrhea usually does not suggest a specific causal agent. There is significant overlap, and one organism can cause several different syndromes.<sup>60</sup> The laboratory work-up of a patient with diarrhea may therefore be necessary. In general, a complete blood count and a metabolic profile may be required if the patient appears to be septic or dehydrated. In addition, if the patient appears septic, blood cultures drawn at 2 different sites may be useful.

The question of whether to obtain stool cultures for a patient with diarrhea is not always a simple one. In general most people with diarrhea do not have a bacterial pathogen, and even when they do, stool cultures are often negative.<sup>61</sup> Nevertheless it may be important from a public health standpoint, as well as for the treatment of the individual patient, to determine if that patient has a bacterial pathogen. An approach used to distinguish those patients who are more likely to have a pathogen from those not likely to have a pathogen has been to look for white blood cells in the stool. Microscopic examination of stool samples that have demonstrated the presence of fecal leukocytes suggests that the diarrhea has an inflammatory cause and that it is caused specifically by organisms such as *Shigella*, *Salmonella*, *Campylobacter*, or *C difficile*.<sup>62,63</sup> However, the use of fecal leukocyte detection has several limitations.<sup>64-66</sup> First of all, the smear must be performed on a fresh specimen; a delay in processing the sample results in lysis of the fecal leukocytes. Even if fresh specimens are examined, accurate microscopy is very dependent on the skill and expertise of the microscopist. Some have questioned whether the presence of white blood cells in the stool has proved to be of any clinical use.<sup>64-66</sup>

Choi et al<sup>66</sup> have developed a fecal lactoferrin latex agglutination assay to help determine if fecal leukocytes are indeed present in the stool. This, in general, appears to be much more sensitive than fecal leukocyte microscopy, and it may help to determine which people should have fecal cultures obtained.<sup>67</sup>

Although stool cultures are considered to be the gold standard for the diagnosis of bacterial causes of gastroenteritis, their clinical use is limited to organisms that are routinely cultured. Most laboratories only attempt to culture for *Salmonella*, *Shigella*, and *Campylobacter*. Common organisms that can cause diarrhea, such as enteroinvasive *E coli* and enterotoxigenic *E coli*, are not routinely looked for. Unusual organisms such as *Yersinia* species and *Vibrio* species, which may be important in certain locations, are not routinely tested for. Therefore it is important to obtain information from the patient about recent travel and to know the local epidemiology of diarrhea-producing pathogens. For example, if a person has recently traveled to the states along the Gulf of Mexico and eaten oysters, examining the stool for *Vibrio* may be important. If a person presents with gross blood in the stool, then enterohemorrhagic *E coli* may be a possible cause. The laboratory must be informed of these concerns so that appropriate testing can be performed. Routine culture for these organisms is otherwise not indicated.<sup>67</sup> Stool examination for ova and parasites should be performed if a patient has

recently traveled outside of the United States and also if a patient is potentially immunosuppressed; these tests should also be performed for male homosexuals with acute diarrhea. Otherwise stool examination for ova and parasites should not be routinely obtained unless the diarrhea persists despite negative bacterial cultures.<sup>64</sup> Stool examination for *C difficile* should only be performed in hospitalized patients and only for patients who have been on antibiotics during the preceding 30 days<sup>68</sup>; it is not cost-effective to check stool for *C difficile* in any other patient population. As a corollary, it is not cost-effective to routinely test for stool pathogens or for ova and parasites in a patient in the hospital or in a patient who has been on antibiotics during the preceding 30 days.<sup>64,65</sup> Diarrhea in these situations is almost always related to *C difficile*. Stool examination for ova and parasites and for enteric pathogens should be limited to patients who are otherwise immunosuppressed, to those who have a negative result despite continued symptoms, and to times of a known outbreak of a bacterial pathogen in the hospital or the community.

Unfortunately, a study that proves the optimal method for diagnosing diarrhea caused by *C difficile* has not yet been performed. The use of fecal leukocytes or stool lactoferrin in the screening for *C difficile* diarrhea has not been great enough for these studies to serve as good screening tools<sup>66,68</sup>; neither a positive nor a negative result of a fecal leukocyte test will replace specific testing for *C difficile* or *C difficile* toxin. Currently the cell cytotoxin assay is the most specific test, and the stool culture is the most sensitive test. However, neither one of these studies has a rapid turnaround, and both are associated with excessive cost and time commitments. More rapid assays such as the enzyme immunoassay for detecting toxin A and B are specific, but they are much less sensitive than the cell cytotoxin assay. A latex agglutination assay does not distinguish toxigenic from nontoxigenic *C difficile*; it is neither sensitive nor specific, and it should not be routinely used. Testing the stool of asymptomatic patients for *C difficile* to test a cure is not recommended except for epidemiologic or research purposes.<sup>68</sup>

## Treatment

Effective treatment of bacterial gastroenteritis is important on an individual basis, and it also has potential public health implications. Because most of these organisms are spread by person-to-person contact, it is important to eliminate reservoirs of these bacteria whenever possible. Unfortunately there are few data that support the routine use of anti-infective antibiotics for most patients with bacterial gastroenteritis. More

than half of the patients who develop bacterial gastroenteritis improve within 2 days even without specific therapy.<sup>60</sup> It has also been shown that antibiotics do not reduce the duration of diarrhea or fever in patients with *Salmonella* gastroenteritis, and they may increase the risk for bacterial relapse.<sup>69</sup> The typical goal of the treatment of gastroenteritis is supportive therapy with hydration; this usually involves oral rehydration methods, although intravenous rehydration may be necessary in certain situations. Nonspecific treatment to decrease bowel motility and improve symptoms is another option. In the past, drugs that decrease bowel motility have been discouraged because of the possibility that they might worsen symptoms or decrease the clearance of the bacteria. The use of loperamide in the setting of travelers' diarrhea that is primarily caused by enterotoxigenic *E coli* has shown that use of loperamide with ciprofloxacin was the most effective treatment.<sup>70</sup> However, similar studies are not available for infections caused by an invasive organism such as *Salmonella*, *Shigella*, or *Campylobacter* or for *C difficile*-associated diarrhea. Until more data are available, the routine use of loperamide should be avoided for patients who potentially have invasive pathogens causing their diarrhea.

As noted above, most patients with diarrhea do not require antimicrobial therapy. However, antimicrobial therapy may be beneficial independent of culture or fecal leukocyte test results. Goodman et al<sup>60</sup> compared the use of ciprofloxacin with the use of trimethoprim-sulfamethoxazole and placebo in a randomized, double-blind study. A causal organism was isolated in only 34% of patients, and only 77% of patients with a positive culture had a positive fecal leukocyte smear. The smear was positive in 37% of patients with negative cultures. These data suggest that neither culture nor fecal leukocyte testing may be very useful for most patients with community-acquired diarrhea. However, antibiotic treatment—especially with ciprofloxacin, as compared with placebo—resulted in a reduction in the duration of symptoms of approximately 1 day. Another study by Dryden et al<sup>70</sup> about the empiric treatment of severe community-acquired gastroenteritis with ciprofloxacin had similar conclusions.

Nonetheless, routine antibiotic therapy for all patients with diarrhea may be a problem in the future. A major potential problem is the increasing incidence of antimicrobial resistance in organisms such as *Salmonella*, *Shigella*, and *Campylobacter*.<sup>71,72</sup> *Campylobacter* are routinely resistant to most antibiotics, with the exceptions of macrolides and quinolones, and an increasing incidence of quinolone resistance has been noted in several countries, which has been attributed to the use of

quinolones in animal feed.<sup>73-75</sup> In addition, *Salmonella* that produce extended-spectrum beta-lactamases have been reported. These organisms are also often quinolone-resistant, and quinolone-resistant *Shigella* have recently been described.<sup>75</sup> Many of these organisms were also resistant to unrelated classes of antibiotics such as tetracyclines, cephalosporins, chloramphenicol, and trimethoprim-sulfamethoxazole. Because of all of this information, the routine empiric use of antibiotics—including quinolones—for the treatment of bacterial gastroenteritis needs to be reevaluated.

Unlike those with community-acquired gastroenteritis, most patients with *C difficile*-associated diarrhea will require specific therapy. Metronidazole and vancomycin are effective agents that are currently available in the United States. Metronidazole is currently considered the drug of choice because its clinical efficacy is comparable with that of vancomycin<sup>69</sup>; it is also much less expensive than oral vancomycin, and there is some concern about the development of glycopeptide resistance in enterococci with the use and overuse of oral vancomycin. Metronidazole in doses of 250 mg 4 times day or in doses of 500 mg 3 times a day can be useful. An alternative choice is a 125 mg dose of vancomycin 4 times a day. There is no need to obtain a stool sample from patients with *C difficile*-associated diarrhea at the end of treatment unless symptoms recur. Approximately 5% to 30% of patients will develop recurrent symptoms, regardless of initial therapy. These patients usually respond to the same drug that was used to treat them initially. A very small percentage of patients will have multiple relapses of *C difficile*-associated diarrhea. The optimal management of such patients is not known at this time. Some physicians recommend the combination of vancomycin and rifampin for 10 days, but there are no comparative data currently available.<sup>68</sup>

Making a diagnosis of cause in cases of bacterial gastroenteritis remains a difficult prospect. The treatment of most cases of bacterial enteritis is usually supportive, but the use and overuse of antibiotics may result in an increased incidence of resistance, which could continue to be problematic in the future.

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