

## Practice guidelines

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# Guidelines on Acute Infectious Diarrhea in Adults

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**Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by the interpretation and collation of scientifically valid research, derived from an extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines are also approved by the governing boards of the American Gastroenterology Association and the American Society of Gastrointestinal Endoscopy. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the Committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time. The following guidelines are intended for adults and not for pediatric patients.**

### INTRODUCTION

In developing the guidelines for evaluation and management of the patient with acute diarrhea, the following material is divided into eight subheadings: importance of diarrhea, patient evaluation, noninfectious and extraintestinal causes, empiric therapy in selected patients, laboratory eval-

uation, management, the international traveler, and the immunocompromised patient.

### IMPORTANCE OF DIARRHEA

In the United States acute diarrhea is one of the most common diagnoses in general practice. Acute diarrhea can be defined as the passage of a greater number of stools of decreased form from the normal lasting less than 14 days. It is generally associated with other signs or symptoms suggesting enteric involvement including nausea, vomiting, abdominal pain and cramps, increase in intestinal gas-related complaints, fever, passage of bloody stools (dysentery), tenesmus (constant sensation of urge to move bowels), and fecal urgency. When diarrhea lasts as long as 14 days, it can be considered persistent. Many restrict the term *chronic diarrhea* to indicate illness lasting at least 1 month. In this review, diagnosis and treatment of acute and persistent diarrhea will be considered because both tend to be short-term illnesses, infectious agents characteristically produce both, and the tests procedures and treatments of both forms of diarrhea show similarities.

The annual rate of diarrheal illness in the United States and western Europe among adults averages about one episode per person per year (1, 2). In one study, it was estimated that for a single year, 99 million cases of gastroenteritis or acute diarrhea occurred among adults in the United States (1). In this study, half of the persons with gastroenteritis or diarrhea had restriction of their activities for more than a full day, a physician was consulted in 8.2 million of the cases, 250,000 persons were hospitalized, 7.9 million persons saw a physician yet were not hospitalized, and more than 90 million experienced illness without seeking medical attention. In a second study, it was found that gastroenteritis and acute diarrhea accounted for 1.5% of hospitalizations of adults  $\geq 20$  yr of age in the United States (3). Sixty-two percent of the admissions for diarrhea were in adults greater than 20 yr of age. In this study and others most of the deaths associated with diarrheal illness in the United States occurred in the elderly (3–5).

Although statistically the rate of diarrhea in adults in the United States and other industrialized regions is approximately one episode per person per year, diarrhea actually does not occur in all persons annually. Food- and waterborne outbreaks involving a relatively small subset of the general population and recurrent bouts of illness in others make up the bulk of the cases of the illness. Diarrhea is a special problem among adults who are exposed to children and nontilet-trained infants particularly in a day care setting, travelers to tropical and semitropical regions, homosexual males, persons with underlying immunosuppression, and those living in an unhygienic environment and having exposure to contaminated water or foods.

### PATIENT EVALUATION

Most cases of diarrhea are managed by the affected patient or by a family member without need for medical attention.

#### *Recommendation*

1. Medical evaluation should occur for a subset of patients with more severe illness. Specific indications for medical evaluation include: profuse watery diarrhea with dehydration; dysentery, passage of many small volume stools containing blood and mucus; fever (temperature  $\geq 38.5^{\circ}\text{C}$ ,  $101.3^{\circ}\text{F}$ ); passage of  $\geq 6$  unformed stools/24 h or a duration of illness  $> 48$  h; diarrhea with severe abdominal pain in a patient above the age of 50 yr; diarrhea in the elderly ( $\geq 70$  yr of age) or the immunocompromised patient (AIDS, after transplantation, or receipt of cancer chemotherapy).

*Indications for medical evaluation.* Dehydration, defined as dry mucous membranes, decreased urination, and tachycardia, is the most common complication of a small bowel secretory diarrhea and should be promptly evaluated and treated (6). Osmotic diarrhea seen in patients with small intestinal injury due to an infectious agent who attempt to ingest carbohydrates or other substances (magnesium, salts, fiber) may present with watery diarrhea and dehydration. Patients with dysentery will have more intense and prolonged illness without antimicrobial therapy (7). Fever is usually a finding associated with an invasive pathogen that produces intestinal inflammation. These cases optimally will be studied for etiologic agents and many will benefit from antimicrobial therapy (8). Similarly more intense diarrhea ( $\geq 6$  unformed stools/24 h) and that lasting more than 48 h should be evaluated for cause of illness or treated empirically (8, 9). Patients with severe abdominal pain particularly if above the age of 50 yr may have a complicating illness such as ischemic bowel disease (10). Diarrhea in the elderly is more likely to be severe and possibly fatal (4, 11), and patients who are immunocompromised usually have complicated and difficult to manage diarrhea (12).

#### *Recommendation*

2. The clinical and epidemiologic history is central to patient medical evaluation and management.

*The history.* From the standpoint of functional impairment from the illness, diarrhea may be categorized as mild (no change in normal activities), moderate (forced change in activities), or severe (disability generally with confinement to bed). In Table 1 the clinical syndromes seen in enteric infections are detailed along with suspected cause and anatomic location of the disease process. Assessment of the severity of illness, presence of dehydration, character of stool pattern, presence of fever, vomiting, or dysentery often will help to focus the evaluation to determine the likely cause of the illness. When diarrhea lasts as long as 2 wk, a different list of etiologic agents and conditions should be considered when compared with the person with acute diarrhea. When fever (oral temperature  $> 38.5^{\circ}\text{C}$ , or  $101.3^{\circ}\text{F}$ ) is present, the patient has intestinal inflammation characteristically due to invasive bacteria (*Shigella*, *Salmonella*, *Campylobacter*), one of the enteric viruses, or a cytotoxic organism resulting in mucosal histologic damage and inflammation (*C. difficile* or *Entamoeba histolytica*). Finally, in taking a history epidemiologic factors and associations should be considered (Table 2).

In the homosexual male with diarrhea, three disease transmission or clinical scenarios may explain the enteric disease (13). First, because of the sexual practices of many homosexual men, there is an increased rate of fecal oral transmission of all agents showing this route of spread. This includes *Shigella*, *Salmonella*, *Campylobacter*, and the intestinal protozoa. Second, in homosexual males who have been the recipients of anal intercourse, direct rectal inoculation of a pathogen (see Table 1) may lead to proctitis (13) associated with rectal pain and tenesmus and passage of small volume stools often containing blood and mucus. The third setting of diarrhea in a homosexual male is when the individual has developed AIDS (12) (see Management of the Immunocompromised Patient with Diarrhea section).

Foodborne or waterborne outbreaks of diarrhea are becoming more common (14–16). The incubation period of resultant illness and the predominant symptoms often will help the clinician to determine the cause of the outbreak based on clinical grounds. When diarrhea and vomiting occurs within 6 h of exposure to a food item, food poisoning secondary to the ingestion of preformed toxin of *Staphylococcus aureus* or *Bacillus cereus* should be suspected. When the incubation period of an outbreak of diarrheal disease is 8–14 h, *Clostridium perfringens* enteric infection should be suspected. When the incubation period is greater than 14 h and vomiting is the prominent feature of the diarrheal disease, viral agents should be suspected. When fever and/or dysentery is present in a majority of cases during an outbreak, the invasive pathogens should be considered such as *Shigella*, *Salmonella*, or *Campylobacter*. Other pathogens can produce the same clinical features of an invasive patho-

TABLE 1  
Clinical Syndromes Associated with Diarrhea

Syndrome	Anatomic Location	Clinical Features	Suspected Etiology
Gastroenteritis	Stomach and small intestine	Nausea, vomiting and watery diarrhea	Viral agents or preformed toxin produced by <i>S. aureus</i> or <i>B. cereus</i> , any enteric pathogen
Acute watery (often secretory) diarrhea	Small intestine, colon may be involved	Voluminous stools, upper abdominal pain and cramps	Any enteric pathogen
Colitis and proctitis	Colitis: colonic inflammation documented beyond 15 cm;  Proctitis: inflammation confined to distal 15 cm of colon	Many small volume stools, fecal urgency, tenesmus, and dysentery	<i>Shigella</i> , <i>Campylobacter</i> most common, also consider <i>Salmonella</i> , Shigatoxin producing <i>E. coli</i> (e.g. 0:157 H:7) invasive <i>E. coli</i> , <i>E. histolytica</i> , <i>Aeromonas</i> spp, noncholera <i>Vibrios</i> , <i>Chlamydia trachomatis</i> , inflammatory bowel disease; in a recipient of anal intercourse consider <i>Neisseria gonorrhoeae</i> , herpes simplex, <i>Chlamydia trachomatis</i> , <i>Treponema pallidum</i>
Persistent, $\geq 14$ days, diarrhea	Small intestine, colon may be involved	Clinical features will depend upon intestinal location of disease process	Parasitic infection ( <i>Giardia</i> , <i>Cryptosporidium</i> , <i>Cyclospora</i> , <i>Microsporidium</i> ), bacterial infection, small bowel bacterial overgrowth syndrome, lactase deficiency, Brainard syndrome, malabsorption syndrome

TABLE 2  
Epidemiologic Factors Important in the Evaluation of the Patient with Acute Diarrhea

Epidemiologic Consideration	Etiologic Agent to Consider
Travel to a developing region, to mountainous areas or recreational bodies of water of North America or to Russia	Bacterial agents are considered among those who travel to developing regions, <i>Giardia</i> for travel to mountainous areas and recreational waters associated with wildlife and <i>Cryptosporidium</i> or <i>Giardia</i> for those visiting Russia
Recent antimicrobial therapy (past 2 months)	<i>Clostridium difficile</i>
Male homosexual	All enteric pathogens showing fecal oral route of transmission; those spread by receptive anal intercourse or a variety of agents if AIDS is present (see Table 1 and text)
Day care center contact	Any agent spread by fecal oral route, commonly <i>Shigella</i> spp, <i>Giardia</i> , or <i>Cryptosporidium</i>
Foodborne or waterborne outbreak	The incubation period and clinical features of the illness often will give clues as to etiology, the laboratory will be important to identification of enteric pathogen (see text)

gen such as invasive *Escherichia coli*, *Aeromonas* spp, and noncholera *Vibrios*. Enterohemorrhagic *E. coli* infection often is associated with the passage of bloody stools, but fever is generally absent or low grade.

## NONINFECTIOUS AND EXTRAINTESTINAL CAUSES

Noninfectious and extraintestinal processes may present as acute diarrhea. In all patients with diarrhea, particularly persistent or chronic diarrhea or when there is severe abdominal pain or underlying disease processes, a noninfectious cause of the illness should be considered. Some of the important diagnoses to consider include irritable bowel syndrome, inflammatory bowel disease, ischemic bowel disease (particularly in someone older than 50 yr of age with other evidence of peripheral vascular disease), partial bowel obstruction, and pelvic abscess in the area of the rectosigmoid colon. Pernicious anemia, pellagra, malaria, Whipple's disease, diabetes mellitus, small bowel scleroderma, small bowel diverticulosis, and various malabsorption syndromes may present as acute or persistent diarrhea resembling infectious diarrhea.

## EMPIRIC THERAPY OF SELECTED PATIENTS

There are two types of patients who might be considered for empiric antimicrobial therapy without additional evaluation. They include patients in whom bacterial diarrhea is suggested by clinical features and/or by the presence of occult blood or fecal leukocytes in stool samples, or patients in whom diarrhea has persisted for 2 wk or longer and *Giardia* is suspected. Patients not treated empirically should be studied to determine the presence of etiologic agents by using laboratory tests and procedures (Table 3).

TABLE 3  
Selected Laboratory Tests and Procedures Used in the Etiologic Diagnosis of Patients with Diarrhea

Test or Procedure	Indications	Likely Etiologic Agents
Stool culture for enterohemorrhagic <i>E. coli</i> (e.g. Shigatoxin producing O157:H7)	Epidemic foodborne dysentery especially hamburger-associated diarrhea or bloody diarrhea with few or no fecal leukocytes or diarrhea in a case(s) of hemolytic uremic syndrome	Cytotoxigenic <i>E. coli</i> (O157:H7, O26:H11, etc.)
Stool culture for <i>Vibrios</i>	Severe and profuse watery diarrhea in a cholera-endemic area or seafood associated diarrhea or diarrhea after consumption of inadequately cooked seafood, including sushi or ceviche	<i>V. cholerae</i> and noncholera <i>Vibrios</i>
Stool culture for <i>Yersinia</i> including cold enrichment	Febrile dysentery or diarrhea and severe abdominal pain or pseudoappendicitis-like symptoms	<i>Y. enterocolitica</i>
<i>C. difficile</i> toxin assay	In a patient with diarrhea who has received an antimicrobial in the past 2 months	<i>C. difficile</i>
Virus examination (see likely etiologic agents)	Waterborne or foodborne illness with incubation period >12 h in which vomiting is the predominant symptom	Rotavirus, enteric adenovirus (type 40, 41), Norwalk virus,* and other small round structured viruses
Duodenal intubation or 14-c-d-xylose breath test	In a patient with persistent diarrhea not responding to empiric therapy	<i>Giardia</i> , <i>Cryptosporidium</i> , rarely <i>Strongyloides stercoralis</i> , small bowel bacterial overgrowth syndrome
Flexible sigmoidoscopy with biopsy of abnormalities	Homosexual male with moderate to severe diarrhea, any patient with persistent diarrhea and clinical colitis (see Table 1) not responding to antimicrobial therapy or without diagnosis after laboratory evaluation	See causes of colitis and proctitis (Table 1 above)
Flexible sigmoidoscopy and upper endoscopy with biopsy of abnormalities	Any patient with persistent diarrhea without evidence of colitis (see Table 1) and without response to empiric therapy	Causes of colitis and proctitis (Table 1 above) as well as upper intestinal infection by <i>Giardia</i> , <i>Cryptosporidium</i> , <i>Cyclospora</i> , <i>Microsporidium</i> , cytomegalovirus, HIV, <i>Mycobacterium avium intracellulare</i> complex

\* Norwalk virus detection is presently done only in a research laboratory.

### Recommendation

3. In patients with fever (oral temperature > 38.5°C, or 101.3°F) plus either leukocyte-, lactoferrin-, or hemocult-positive stools or in patients with acute dysentery or in patients with moderate and severe travelers' diarrhea, antimicrobial therapy may be given empirically (Table 4).

**Empiric therapy for presumed bacterial diarrhea.** In patients with fever and either fecal leukocyte-, lactoferrin-, or hemocult-positive stools, infection with invasive bacterial pathogens such as *Shigella*, *Salmonella*, and *Campylobacter* should be considered (17, 18). A majority of patients with numerous fecal leukocytes will respond favorably to antimicrobial therapy (19–21). Finding hemocult-positive stool in patients with acute diarrhea has the same clinical significance as finding numerous fecal leukocytes (18, 22). The same pathogens associated with the presence of numerous fecal leukocytes will generally be found in patients with acute dysenteric disease (23, 24). Patients with travelers' diarrhea, particularly those with moderate to severe illness are characteristically infected with bacterial pathogens and their illness is shortened by antimicrobial therapy (25–27).

### Recommendation

4. Patients with diarrhea lasting 2 to 4 wk without systemic symptoms or dysentery may be studied for cause of

illness or may be treated empirically with anti-*Giardia* therapy (Table 4).

**Empiric treatment of presumed giardiasis.** While many clinicians would prefer to evaluate the patient with persistent diarrhea for cause of illness some elect to treat empirically for presumed giardiasis. This approach is reasonable in view of the importance of *Giardia* in this syndrome (28) and because at least half of studied stools of patients with giardiasis will be negative for the parasite (29, 30). Work-up of those failing to respond to empiric therapy for *Giardia* (usually stool enzyme immunoassay) may then be indicated. The most frequently used empiric therapy of presumed giardiasis is metronidazole (see Table 4), which also may be effective against a small bowel bacterial overgrowth syndrome associated with persistent diarrhea, a problem occasionally seen after an enteric infection (31).

## LABORATORY EVALUATION

Laboratory tests and procedures may be used to evaluate patients with illness calling for medical evaluation (see above) and for other patients in whom a definable pathogen is suggested by the history (Tables 1 and 2).

TABLE 4  
 Indications for Empiric and Specific Antimicrobial Therapy in Infectious Diarrhea

Indication for Antimicrobial Therapy	Suggested Antimicrobial Therapy
Fever (oral temperature >38.5°C or 101.3°F) together with one of the following: dysentery (grossly bloody stools) or those with leukocyte-, lactoferrin-, or hemocult-positive stools	Quinolone:* NF 400 mg, CF 500 mg, OF 300 mg <i>b.i.d.</i> for 3–5 days (see text)
Moderate to severe travelers' diarrhea	Quinolone:* NF 400 mg, CF 500 mg, OF 300 mg <i>b.i.d.</i> for 1–5 days (see text)
Persistent diarrhea (possible <i>Giardia</i> infection)	Metronidazole 250 mg <i>q.i.d.</i> for 7 days
Shigellosis	If acquired in the U.S. give TMP/SMX 160/800 mg <i>b.i.d.</i> for 3 days, if acquired during international travel treat as febrile dysentery (above); check to be certain of susceptibility to drug employed
Intestinal salmonellosis	If healthy host with mild or moderate symptoms, no therapy; for severe disease or that associated with fever and systemic toxicity or other important underlying condition (see text) use TMP/SMX 160 mg/800 mg or quinolone:* NF 400 mg, CF 500 mg, OF mg bid for 5 to 7 days depending on speed of response
Campylobacteriosis	Erythromycin stearate 500 mg <i>b.i.d.</i> for 5 days
Enteropathogenic <i>E. coli</i> diarrhea (EPEC)	Treat as febrile dysentery
Enterotoxigenic <i>E. coli</i> diarrhea (ETEC)	Treat as moderate to severe travelers' diarrhea
Enteroinvasive <i>E. coli</i> diarrhea (EIEC)	Treat as shigellosis
Enterohemorrhagic <i>E. coli</i> diarrhea (EHEC)	Antimicrobials are generally withheld except in particularly severe cases in which usefulness of these drugs is uncertain (see text)
<i>Aeromonas</i> diarrhea	Treat as febrile dysentery
Noncholera <i>Vibrio</i> diarrhea	Treat as febrile dysentery
Yersiniosis	For most cases, treat as febrile dysentery, for severe cases give ceftriaxone 1 g <i>q.d.</i> IV for 5 days
Giardiasis	Metronidazole 250 mg <i>q.i.d.</i> for 7 days or (if available) tinidazole 2 gr in a single dose or quinacine 100 mg <i>t.i.d.</i> for 7 days
Intestinal amebiasis	Metronidazole 750 mg <i>t.i.d.</i> for 5–10 days plus a drug to treat cysts to prevent relapses: diiodohydroxyquin 650 mg <i>t.i.d.</i> for 20 days, or paromomycin 500 mg <i>t.i.d.</i> for 10 days or diloxanide furoate 500 mg <i>t.i.d.</i> for 10 d
<i>Cryptosporidium</i> diarrhea	None, for severe cases, consider paromomycin 500 mg <i>t.i.d.</i> for 7 days
<i>Isospora</i> diarrhea	TMP/SMX 160 mg/800 mg <i>b.i.d.</i> for 7 days
<i>Cyclospora</i> diarrhea	TMP/SMX 160 mg/800 mg <i>b.i.d.</i> for 7 days

\* Fluoroquinolones include norfloxacin (NF), ciprofloxacin (CF), and ofloxacin (OF).

### Recommendation

5. The fecal leukocyte, lactoferrin, or hemocult blood test is a useful screening test in patients with moderate to severe acute infectious diarrhea because they support the use of empiric therapy in the febrile patient (see above) and when negative may eliminate the need for stool culture in some cases of diarrhea.

**Laboratory screening.** Fecal leukocytes, lactoferrin, or occult blood are found in diarrhea patients with diffuse colonic inflammation (17, 18). The most commonly identified pathogens in patients with a positive test result include: *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas*, *Yersinia*, noncholera *Vibrios* (17, 18), and *Clostridium difficile* (32). Low numbers of fecal leukocytes are found in patients with intestinal amebiasis.

### Recommendation

6. A stool culture should be obtained in a patient with one of the following: severe diarrhea; a temperature  $\geq 38.5^{\circ}\text{C}$ , or  $101.3^{\circ}\text{F}$ , (orally); passage of bloody stools; stools contain leukocytes, lactoferrin, or hemocult blood; or, the patient with persistent diarrhea has not been treated with antibacterial agents empirically.

**Routine stool culture.** The bacterial enteropathogens identified by normal stool culture are *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas*, and *Yersinia*. Severe (intense) diarrhea, moderate to high fever, dysentery, finding fecal leukocytes, lactoferrin, or hemocult blood positive stools all are predictive of finding an identifiable bacterial enteropathogens when fecal samples are submitted to the laboratory for culture. The bacterial pathogens may cause more

prolonged diarrhea when compared with pathogen-negative nonspecific diarrhea (25, 33, 34).

Studies in the United States have found that stool studies are frequently inappropriately ordered resulting in excessive medical costs (35). In two studies, stool cultures as obtained routinely in selected locations were found to have a positivity rate of 2% or less, making the cost of the test between \$900 and \$1200 per pathogen detected (35, 36). Stool cultures should not be ordered routinely but reserved for the appropriate patient and setting.

#### Recommendation

7. Patients not treated with empiric antiparasitic therapy should be studied for parasitic causes of diarrhea if they have persistent diarrhea; diarrhea has followed travel to Russia, Nepal, or mountainous regions; they have been exposed to infants attending day care centers; diarrhea has occurred in a homosexual male or a patient with AIDS; diarrhea is part of a community waterborne outbreak; or has bloody diarrhea with few or no fecal leukocytes.

*Laboratory evaluation for parasites.* Although less well studied than the value of routine stool culture, the common obtaining of "O and P's" (ova and parasites) in patients with acute diarrhea is not cost effective (37). As indicated above, patients with giardiasis often have persistent diarrhea. The diarrheal illness associated with *Cryptosporidium* (28) and *Entamoeba histolytica* (38) may be protracted. Infection by *Cryptosporidium*, *Giardia*, or both, should be suspected whenever diarrhea follows trips to Russia (28, 39); *Cyclospora* should be considered in travelers to Nepal (40); and *Giardia* should be suspected in persons who have recently traveled to mountainous areas or to recreational waters of North America (41). Among infants in day care centers, *Giardia* (42) and *Cryptosporidium* (43) are common causes of diarrhea and may be spread to adult contacts because of the low inoculum required for human infection (44, 45). Homosexual males may be infected with a variety of parasites including *Giardia* and *Entamoeba histolytica*. In patients with AIDS-associated diarrhea, parasites represent the major definable pathogens (46). The specific agents to consider in this setting are mentioned below. Both *Giardia* (47) and *Cryptosporidium* (16) may cause extensive community waterborne outbreaks. Numerous leukocytes are not usually found in the stools of patients with intestinal amebiasis because of the presence of uninflamed mucosa between ulcerations and because of the lytic effect of exotoxins produced by the organism (48). Therefore when a patient with diarrhea is passing bloody stools and there are few leukocytes, amebiasis should be considered. Stools may be studied by routine microscopic techniques for parasitic enteropathogens by a well-trained parasitologist or in the case of *Giardia* and *Cryptosporidium*, by a commercially available immunofluorescent antibody tests (49) or by diagnostic enzyme immunoassays (50), which may be more sensitive than microscopic studies (51, 52).

#### Recommendation

8. In patients with certain epidemiologic findings, fecal samples should be collected and sent to the laboratory for specific enteropathogens including *enterohemorrhagic E. coli*, *Vibrio cholerae*, noncholera *Vibrios*, and *Yersinia*. Selected patients may be studied for the presence of *C. difficile* toxin, or viruses or they may be studied by endoscopy (see Table 3).

*Special bacterial enteropathogens.* A number of bacterial enteropathogens will not be detected by routine stool culture. These pathogens include enterohemorrhagic colitis producing *E. coli* O157:H7 and other Shigatoxin producing *E. coli* (53), *V. cholerae*, other noncholera *Vibrios* (54), and *Yersinia* (55), although routine stool cultures will identify most of the strains of *Yersinia*. Except for *E. coli* O157:H7, which is readily detected by stool culture using specialized media, the other diarrheagenic *E. coli* are presently only detected by research laboratories. Stool assays for *C. difficile* toxin by tissue culture assay or enzyme immunoassay should be carried out in the patient who is currently receiving antimicrobials or who has received antimicrobials in the last 2 wk. In the case of food- or waterborne outbreaks, in which the illness is associated with vomiting as the major clinical feature and the incubation period is > 12 h, viral agents should be considered (see Table 3). Homosexual males with diarrhea and any patients with persistent diarrhea not responding to empiric therapy may be evaluated by endoscopy.

## MANAGEMENT

### Fluid and Electrolyte Treatment

#### Recommendation

9. In all patients with diarrhea requiring medical evaluation, fluid and electrolyte therapy and alteration of the diet should be part of the management.

*Fluid therapy and diet alteration.* For most cases of acute diarrhea, the most important form of therapy consists of fluid combined with electrolytes (56). Whereas such treatment is life saving for young infants in the developing world, in the United States the most important adult groups in which special attention should be given to fluid therapy are the elderly and the immunosuppressed. For these persons solutions containing sodium in the range of 45 to 75 mEq/L are recommended (Pedalyte or Rehydrolyte solutions). In the nondehydrated otherwise healthy person with acute diarrhea, sport drinks, diluted fruit juices, and other flavored soft drinks augmented with saltine crackers and broths and soups can meet the fluid and salt needs in nearly all cases. For dehydrating cholera-like diarrhea more aggressive fluid therapy will be required. Here the ideal formulation of oral fluids is Na 60–90 mEq/L, K 20 mEq/L, Cl 80 mEq/L, citrate 30 mEq/L, and glucose 20 g/L. A home-made version of this form of oral rehydration solution for more severe diarrhea is to prepare two separate glasses that

TABLE 5  
Symptomatic Treatment of Acute Diarrhea

Pharmacologic Agent	Indication/Perspective	Dose and Administration
Loperamide (Imodium)	Acute diarrhea, fever is absent or low grade, dysentery is not present/minimal central opiate effects, the preferred symptomatic drug when used for most nonfebrile, nondysenteric cases	2 tablets (4 mg) initially then 2 mg after each unformed stool not to exceed 8 mg/day (OTC dose) or 16 mg/day (prescription dose) $\leq 2$ days
Diphenoxylate with atropine (Lomotil)	Acute diarrhea, fever is absent or low grade, dysentery is not present/has central opiate effects, with overdose liability, atropine may cause side effects without offering antidiarrheal effects	2 tablets (4 mg) <i>q.i.d.</i> for $\leq 2$ days
Tincture of opium	Acute diarrhea, fever is absent or low grade, dysentery is not present/occasionally useful in HIV-associated diarrhea when the safer loperamide is not	0.5–1 ml <i>p.o.</i> q 4–6 h for $\leq 2$ days
Bismuth subsalicylate (Pepto-Bismol)	Any form of acute diarrhea/in most cases is less effective than loperamide and cannot be combined with antimicrobials; should not be used in HIV-positive patients with diarrhea	30 ml or two tablets each 30 minutes for eight doses, may repeat once again day two
Octreotide	AIDS-associated diarrhea not responding to other treatment/considered last resort therapy for these patients, once symptoms are controlled, the patient should be started on other more convenient preparations	100–500 $\mu\text{g}$ subcutaneously <i>t.i.d.</i>

are consumed alternately. The first contains 8 ounces of orange, apple, or other fruit juice (supplying potassium),  $\frac{1}{2}$  teaspoon of honey or corn syrup, and 1 pinch table salt; the second glass contains 8 ounces clear water plus  $\frac{1}{4}$  teaspoon of baking soda (56).

During a bout of acute diarrhea, calories (energy) should be provided to facilitate enterocyte renewal (56). Diet follows clinical course. Boiled starches/cereals (potatoes, noodles/rice, wheat, oat) with some salt represent ideal foods during episodes of watery diarrhea. Crackers, bananas, yogurt, soup, and boiled vegetables can also be used. When stools are formed, diet may return to normal as tolerated. Many authorities would exclude milk products early in the illness but clinical lactose intolerance is not commonly found in cases of acute diarrhea.

### Nonspecific Therapy

#### Recommendation

10. When nonspecific therapy is desired, loperamide is the drug of choice for most cases of diarrhea.

*Symptomatic treatment of acute diarrhea.* In Table 5 a brief perspective on the use of symptomatically acting drugs is provided. The antimotility drugs (loperamide, diphenoxylate with atropine, and tincture of opium) are the most effective drugs directed to treating symptoms. They work by slowing the intraluminal flow of liquid facilitating intestinal absorption (57). Loperamide is generally the recommended agent for most cases of diarrhea when symptomatic treatment is used because of safety and expected efficacy in which stool number is generally reduced by approximately 80% (58, 59). Diphenoxylate may not be the ideal antimotility drug, although it is less expensive than the preferred loperamide. Diphenoxylate possesses central opiate effects

and may lead to death if a child takes a parent's medication. Also, the atropine added to the drug may lead to objectionable cholinergic side effects without adding antidiarrheal effects. The antimotility drugs should not be used in patients with febrile dysentery in which disease may be prolonged (60). This disease prolongation by antimotility agents is not commonly seen, and most clinicians do not need to worry about use of the drugs in nondysenteric forms of diarrhea caused by invasive colonic pathogens, providing antimicrobial therapy is administered (61). In patients with enterohemorrhagic *E. coli* (EHEC) infection, the hemolytic uremic syndrome (HUS) may be facilitated by administering antimotility agents (62) or these agents may worsen neurologic symptoms (63).

#### Recommendation

11. Bismuth subsalicylate is the preferred agent when vomiting is the important clinical manifestation of enteric infection.

*Bismuth subsalicylate treatment of gastroenteritis.* Bismuth subsalicylate is effective in treating acute diarrhea, reducing the number of stools passed by approximately 50% compared with a placebo (64). The antidiarrheal effect of the drug is through its antisecretory salicylate (65, 66). The drug has antibacterial properties, which may explain its value in prevention of travelers' diarrhea when used as a prophylactic agent (67, 68). Bismuth subsalicylate seems to be the most effective agent in improving the symptom of vomiting associated with enteric viral infection (69). Attapulgit (Kaopectate or Diasorb), a clay-like material, absorbs water and makes stools more formed. The preparation is less effective than loperamide (70). Because it is not absorbed, it is quite safe.

### Recommendation

12. Loperamide is the recommended treatment for immunocompromised patients with diarrhea of uncertain etiology. Bismuth subsalicylate should not be used in these patients.

*Symptomatic treatment of diarrhea in the immunocompromised patient.* A number of immunocompromised patients with diarrhea have persistent diarrhea that is difficult to manage (12). In most of the cases a treatable pathogen is not identified or if a potential agent is found the symptoms of diarrhea continue in the face of specific antimicrobial therapy. Table 5 lists the drugs available. As in the otherwise healthy patient, those with underlying immunosuppression can best be managed with symptomatic therapy (71). Bismuth subsalicylate should not be given to immunocompromised patients with diarrhea to prevent the taking of excessive doses and the occurrence of bismuth encephalopathy (72). In some patients tincture of opium has been used with success in treating patients not responding to loperamide (unpublished observations). In otherwise refractory cases of AIDS-induced diarrhea, octreotide, a synthetic cyclic octapeptide analog of somatostatin, may be effective. Whereas the drug is best used in pathogen-negative diarrhea, it may be useful in some patients with microsporidiosis (73) and possibly other otherwise nontreatable conditions. The drug must be given subcutaneously, and it is quite expensive. It should be considered a last resort to symptomatic management.

### Antimicrobial Therapy

In Table 4 recommendations for antimicrobial therapy in infectious diarrhea are provided.

### Recommendation

13. Specific antimicrobial therapy is given when a treatable pathogen is identified in stool samples submitted to the laboratory.

*Specific antimicrobial therapy.* For specific therapy, the cause of illness is usually determined by laboratory demonstration of a treatable pathogen (see Table 4). Alternatively, a patient may be treated based on epidemiologic evidence and laboratory study of other cases during a well-defined foodborne or waterborne outbreak. A few specific infections will be discussed. Most are listed in tables along with recommendations for therapy without further discussion.

*Shigella*—Recommendation 14: All patients with confirmed shigellosis are treated with an antimicrobial agent: trimethoprim/sulfamethoxazole if acquired in the United States and a fluoroquinolone if acquired outside or if resistant to trimethoprim.

Antimicrobial therapy of shigellosis: In shigellosis, antimicrobial therapy is indicated in all cases for two reasons. First, the illness is shortened by antimicrobials providing the organisms is susceptible to the drug used (74). Second, the dose of *Shigella* required to cause infection is low (75) explaining the potential for infecting strains to be spread

from person-to-person. Therefore, there is a public health reason for treatment of infected patients. The treatments of choice for culture proven shigellosis are TMP/SMX or a fluoroquinolone given for 3 to 5 days. If the *Shigella* infection is acquired in the U.S., TMP/SMX is the preferred initial treatment of choice (76). If the infection is acquired during travel, TMP resistance occurs commonly (77). For these cases a quinolone is indicated.

*Salmonella*—Recommendation 15: Selected patients with intestinal salmonellosis should be treated with a quinolone for possible systemic infection including those with fever and systemic toxicity, those with dysentery or with underlying immunosuppression.

Antimicrobial therapy of intestinal salmonellosis: Nontyphoid salmonellosis is an important form of diarrheal disease occurring in up to 2 million persons in the United States each year (78). The decision to treat patients with intestinal salmonellosis with antimicrobial agents should depend upon the age, underlying health of the host, and severity of clinical illness. In healthy persons with mild symptoms treatment should not be given because therapy may encourage the proliferation of the infecting organism, leading to prolongation of excretion of the strain (79). However, intestinal salmonellosis is associated with bacteremia in between 2 and 14% of cases (80) and systemic complications of the bacteremia may occur. Certain underlying conditions increase the frequency of bacteremia. Bacteremia is common in infants under 3 months of age (81) and in the elderly (>65 yr of age) (11). Other risk factors for bacteremia include HIV infection and AIDS (82); uremia (83); malignancy, including hematologic, lymphatic, and solid tumors (84); after renal transplantation (85); and congenital and acquired immunodeficiencies including corticosteroid use (86). There are other conditions that may predispose patients to localized extraintestinal infection when *Salmonella* gastroenteritis develops. This includes patients with an aortic aneurysm, prosthetic heart valve, vascular graft, or orthopedic prosthesis. Antimicrobials are indicated for cases of intestinal salmonellosis complicated by any one of these conditions as well as for otherwise healthy persons with febrile illness, systemic toxicity or dysenteric disease.

For all practical purposes, all patients with intestinal salmonellosis illness severe enough to lead to hospitalization should be given antimicrobial therapy (Table 4).

*Campylobacter*—Recommendation 16: Patients with culture-proven *Campylobacter* infection are treated with an antimicrobial agent to shorten illness, although development of antimicrobial resistance is becoming a problem.

Treatment of *Campylobacter* diarrhea: *Campylobacter* resembles *Salmonella* in many ways. First they both show an animal, often poultry, reservoir for human infection. Second, antimicrobial resistance occurs commonly during therapy or over time in a population (87). Erythromycin will shorten the duration of *Campylobacter* diarrhea (88). If susceptible to the drugs, the fluoroquinolones (89) are effective against campylobacteriosis. Unfortunately, quin-

TABLE 6  
Prevention of Travelers' Diarrhea

All Travelers	
Diet and Beverage Precautions	
Consume only safe items while in high risk area, including airplane leaving area:	
1) Steaming hot foods and beverages (e.g. cooked foods, coffee, tea)	
2) Acidic foods (e.g. citrus)	
3) Dry foods (e.g. bread)	
4) Foods with high sugar content (e.g. syrups, jellies)	
5) Carbonated drinks (e.g. bottled soft drinks and beer); bottled, uncarbonated water may not be safe	
Selected Travelers	
Those who wish prophylaxis	
BSS* 2 tablets with meals and at bedtime (8 tablets/day) (62% effective in eliminating diarrhea)	
Those who might be encouraged to take prophylaxis include those with underlying illness: AIDS, prior gastric surgery and those taking proton pump inhibitors (omeprazole), or those who cannot afford an 8 hour illness (e.g. politician, honeymoon couple, or weekend scuba diver)	
Antimicrobial agent (same drug used normally for therapy (Table 4) in single daily dose during time at risk (90% effective in eliminating diarrhea)	
Use of prophylactic antimicrobials is controversial	

\* BSS, bismuth subsalicylate.

olone resistance is increasing worldwide among *Campylobacter* isolates (87, 90, 91). It is necessary to confirm *in vitro* susceptibility of infecting strains of *Campylobacter*. In addition to erythromycin, azithromycin may be used in quinolone-resistant *Campylobacter* infections (87).

**Diarrheagenic *E. coli*:** There are four major diarrheagenic *E. coli*: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), and enterohemorrhagic *E. coli* (EHEC). EPEC diarrhea is primarily a problem of infant populations. The related HEp-2 cell adherent *E. coli* are pathogens of both children and adults (33, 92). The diarrhea caused by HEp-2 cell adherent *E. coli* tends to be persistent (33, 93). These strains have been shown to be causes of prolonged diarrhea in patients with AIDS in Zambia (94). EPEC and HEp-2 cell adherent *E. coli* are highly resistant to most antimicrobials except the newer quinolones (95). It is not known whether antimicrobials will shorten the illness.

ETEC diarrhea will respond to antimicrobial therapy (21, 25, 96). This form is the major cause of travelers' diarrhea. TMP/SMX or the quinolones remain standard therapy for infection depending upon susceptibility.

All Take ORT and Alter Diet (See Text)

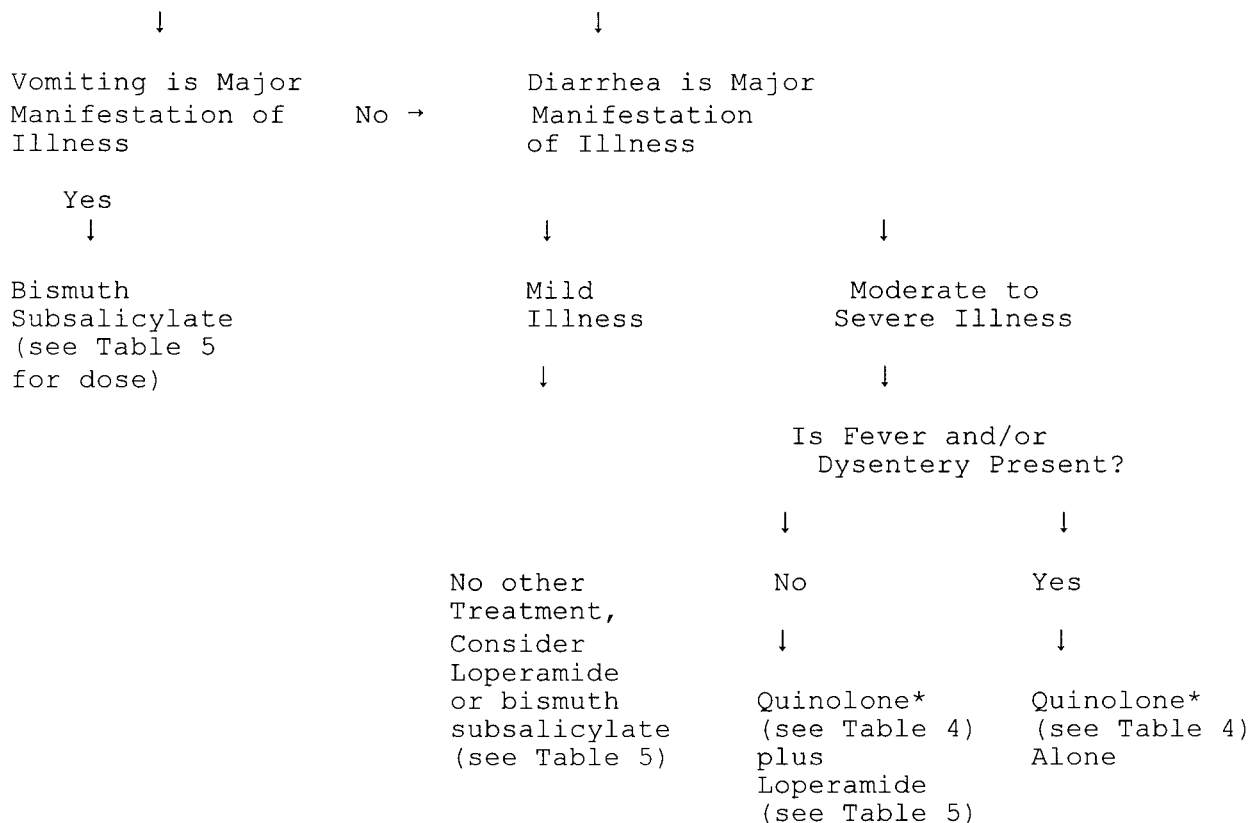


FIG. 1. Self-treatment of gastroenteritis and diarrhea in the international traveler. \*From the interior of Mexico during the summertime, TMP/SMX may be used instead of a quinolone.

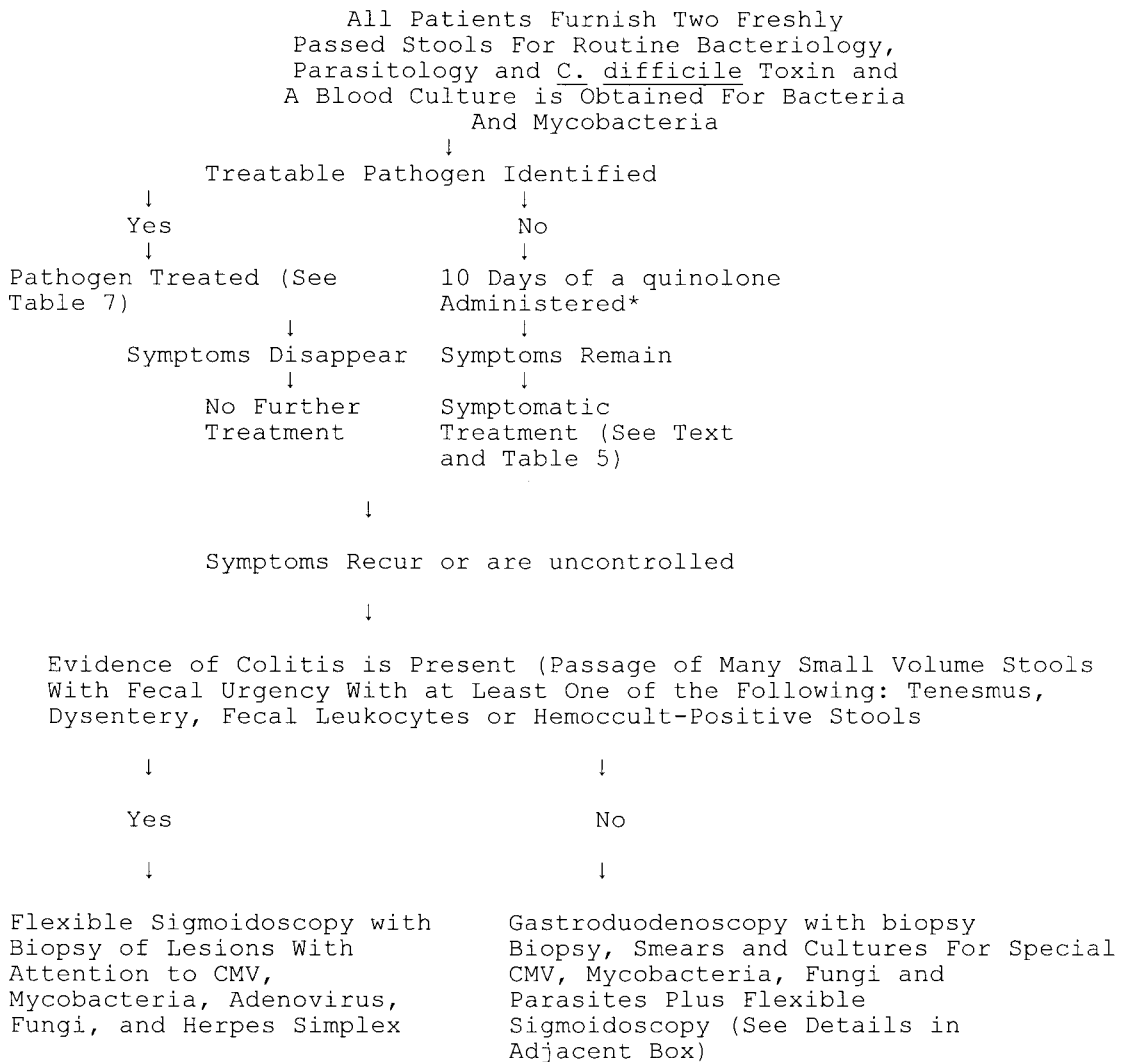


FIG. 2. Approach to the work-up of the immunocompromised patient with acute or persistent diarrhea. Immunocompromised patients include those patients with AIDS, after organ transplantation, and those receiving cancer chemotherapy. \*Quinolones include norfloxacin, ciprofloxacin, or ofloxacin.

### Recommendation

17. Antimicrobial therapy is currently not recommended for patients with diarrhea due to *E. coli* 0157:57 and other Shigatoxin producing *E. coli*.

*Antimicrobial treatment of enterohemorrhagic E. coli diarrhea.* The antimicrobial therapy of EHEC infection is controversial. Administration of antimicrobials early in infection may enhance the release of toxin from killed intracolonic organisms leading to greater absorption and increased propensity to develop the hemolytic uremic syndrome (HUS) (97). Retrospective analyses have furthermore offered suggestive information that prior antimicrobial therapy may in fact be a predisposing factor in the development of HUS (98, 99). In a single prospective study, prior receipt of TMP/SMX late in the illness did not predispose to the development of HUS (100), making the whole issue of therapy uncertain.

### THE INTERNATIONAL TRAVELER

Diarrhea occurs during travel with rates varying according to levels of microbial contamination in the host country and the region of origin. For persons from the United States, diarrhea occurs in 2 to 4% of travelers during travel to another low-risk region [United States, Canada, western Europe, Japan (if raw fish, which may be contaminated with noncholera *Vibrios*, is not consumed), South Africa, Australia, and New Zealand]. For travel from the United States to high-risk areas (most parts of Latin America, Africa, and southern Asia, the rate of diarrhea occurrence is 40%. For travel to intermediate risk regions (northern Mediterranean countries, the Middle East, China, and Russia) the rate of diarrhea is 10 to 15%. The remaining discussion will be for travelers from the United States during travel to high-risk regions. This illness has two unique features. First, more than 80% of the illness is caused by bacterial pathogens. In

TABLE 7

Indications for Specific Antimicrobial Therapy in Infectious Diarrhea in Immunocompromised\* Patients

Indication for Antimicrobial Therapy	Suggested Antimicrobial Therapy
Shigellosis	If acquired in the U.S. give TMP/SMX 160/800 mg <i>b.i.d.</i> for 7–10 days, if acquired during international travel treat as febrile dysentery (above) Check to be certain of susceptibility to drug employed
Intestinal salmonellosis	TMP/SMX 160 mg/800 mg <i>b.i.d.</i> or quinolone:† NF 400 mg, CF 500 mg, OF 300–400 mg <i>b.i.d.</i> for 14 days, repeat stool cultures 1 week after treatment
<i>Cryptosporidium</i> diarrhea	Paromomycin 500 mg <i>p.o. q.i.d.</i> with food for 14–28 days, then 500 mg <i>b.i.d.</i> indefinitely, with treatment failures, may try azithromycin 2.4 g <i>p.o.</i> day 1, then 1.2 g/day for 27 days, then 600 mg/day for maintenance treatment given indefinitely
<i>Isospora</i> diarrhea	320 mg TMP/1600 mg <i>p.o.</i> SMX <i>b.i.d.</i> for 2–4 wk then 160–320 mg TMP/800–1600 mg SMX <i>q.d.</i> ( <i>p.o.</i> )
<i>Cyclospora</i> diarrhea	TMP/SMX 160 mg/800 mg <i>p.o. q.i.d.</i> for 10 days then 160 mg/800 mg once three times a week indefinitely
Microsporidiosis	Albendazole 400 mg <i>p.o. b.i.d.</i> $\geq 4$ wk or metronidazole 500 mg <i>p.o. t.i.d.</i> or atovaquone 750 mg <i>p.o. t.i.d.</i> continued indefinitely
Cytomegalovirus diarrhea	Ganciclovir 5 mg/kg <i>i.v.</i> q 12 h or q 8 h for 14–21 days and foscarnet 60 mg/kg <i>i.v.</i> q 8 h or 90 mg/kg <i>i.v.</i> q 12 h for 14–21 days
<i>Mycobacterium avium intracellulare</i> complex	Clarithromycin 500 mg <i>b.i.d.</i> ethambutol 15 mg/kg/day plus one of the following CF 500–750 mg <i>b.i.d.</i> clofazimine 100 mg/day, rifampin 600 mg <i>q.d.</i> , or rifabutin 300 mg/day <i>p.o.</i> indefinitely

\* Patients with AIDS, after organ transplantation, and those receiving cancer chemotherapy.

† Fluoroquinolones include norfloxacin (NG), ciprofloxacin (CF), or ofloxacin (OF).

contrast, less than one-third of diarrhea occurring in the United States is caused by bacterial enteropathogens. Second, the traveler typically becomes ill while away from home and customary medical help.

### Recommendation

18. Only a small proportion of travelers venturing into high-risk areas should use chemoprophylaxis. All travelers should bring along with them loperamide and an antimicrobial agent and instructed on the self-therapy of diarrhea that may occur.

*Prophylaxis and self-therapy for travelers' diarrhea.* Chemoprophylaxis is not generally recommended for most otherwise healthy persons during travel to high-risk areas unless the traveler has an important predisposing illness or if the purpose of the trip is particularly important (27). If preventive medication is requested by the traveler, bismuth

subsalicylate is recommended (67). For patients with certain serious underlying illnesses (*e.g.*, AIDS, inflammatory bowel disease, hypochlorhydria induced by prior gastric surgery, or treatment with a proton inhibitor such as omeprazole, diabetes mellitus on insulin, and systemic malignancy) prophylactic antimicrobials may be used during travel to high-risk areas. Intermittent use of H<sub>2</sub> antagonists for gastroesophageal disease does not appear to predispose to travelers' diarrhea and is not an indication for use of prophylaxis. In the settings in which antimicrobial prophylaxis is considered, the uncommon risk of developing an adverse reaction to therapy including a superinfection may be outweighed by beneficial effect of the drug in preventing diarrhea. For a subset of persons, a trip is so important that a short (6–10 h) illness would not be tolerated. For these persons an antimicrobial would be more advisable in view of its greater protective efficacy (Table 6). For all travelers exercising care about what one eats or drinks is the cornerstone of prevention of illness (101). Moist foods served at room temperature are generally unsafe including many buffet items and leafy green vegetables. In Table 6 the safe foods are identified.

While TMP/SMX is currently the most cost effective treatment for diarrhea among U.S. persons visiting the interior of Mexico as studied in Guadalajara (102) during the rainy season (our warmer months), for other regions and dry wintertime in the interior of Mexico, TMP-resistant bacteria can be expected (103, 104). The quinolones are the recommended treatment in these settings (27). In Figure 1, a suggested management strategy for travelers' diarrhea is provided. When diarrhea persists after quinolone therapy, the illness should be treated as persistent diarrhea in non-travelers (see Tables 1 and 3).

### THE IMMUNOCOMPROMISED PATIENT

The patient with HIV infection and reduced CD 4 count (<200/mm<sup>3</sup>) and other persons with altered immunity (*e.g.*, patients after organ transplantation or when cancer chemotherapy is being given) are at special risk of developing opportunistic enteric infection. The causes of diarrhea in patients with AIDS have been evaluated and found to be varied. The most common definable agents are the parasitic organisms including *C. parvum*, *I. belli*, *Cyclospora*, *Microsporidia*, the bacterial enteropathogens *S. enteritidis*, *Campylobacter*, *Shigella* spp, and *Mycobacterium-avium-intracellulare*, and the viral pathogens cytomegalovirus, herpes simplex, adenovirus, and HIV itself.

### Recommendation

19. Immunocompromised patients with diarrhea should receive a limited evaluation followed by full evaluation only for patients failing to respond to specific or symptomatic treatment.

*Management of the immunocompromised patient with acute diarrhea.* The initial evaluation of the immunocompromised host with diarrhea is given in Figure 2. A more detailed evaluation is not indicated in view of the low yield for treatable etiologic agents when an expensive work-up is undertaken. As in infections outside the gut in these patients, when a treatable enteropathogen is identified, curative treatment characteristically requires prolonged treatment, and in many of the cases suppressive therapy is required for lifetime. When curative therapy is being attempted, stools should be obtained 1 wk after stopping medication to verify the eradication of the organism. If the organism is present, *in vitro* susceptibility should be performed if feasible, and the drug begun again for a longer period of time, possibly for lifetime. In Table 7 specific management of infectious diarrhea in immunocompromised patients is outlined.

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