Practice Guidelines for the Management of Infectious Diarrhea

Richard L. Guerrant,[1] Thomas Van Gilder,[2] Ted S. Steiner,[3] Nathan M. Thielman,[4] Laurence Slutsker,[2] Robert V. Tauxe,[2] Thomas Hennessy,[2] Patricia M. Griffin,[2] Herbert DuPont,[5] R. Bradley Sack,[6] Phillip Tarr,[7] Marguerite Neill,[8] Irving Nachamkin,[9] L. Barth Reller,[4] Michael T. Osterholm,[10] Michael L. Bennish,[11] and Larry K. Pickering[2]

[1]University of Virginia, Charlottesville; [2]Centers for Disease Control and Prevention, Atlanta; [3]University of British Columbia, Vancouver; [4]Duke University, Durham, North Carolina; [5]St. Luke's Episcopal Hospital, Houston; [6]The Johns Hopkins University School of Public Health, Baltimore; [7]Children's Hospital and Medical Center, Seattle; [8]Memorial Hospital of Rhode Island, Pawtucket; [9]University of Pennsylvania, Philadelphia; [10]Infections Control Advisory Net, Eden Prairie, Minnesota; [11]New England Medical Center, Boston

EXECUTIVE SUMMARY

The widening array of recognized enteric pathogens and the increasing demand for cost-containment sharpen the need for careful clinical and public health guidelines based on the best evidence currently available. Adequate fluid and electrolyte replacement and maintenance are key to managing diarrheal illnesses. Thorough clinical and epidemiological evaluation must define the severity and type of illness (e.g., febrile, hemorrhagic, nosocomial, persistent, or inflammatory), exposures (e.g., travel, ingestion of raw or undercooked meat, seafood, or milk products, contacts who are ill, day care or institutional exposure, recent antibiotic use), and whether the patient is immunocompromised, in order to direct the performance of selective diagnostic cultures, toxin testing, parasite studies, and the administration of antimicrobial therapy (the latter as for traveler's diarrhea, shigellosis, and possibly *Campylobacter jejuni* enteritis). Increasing numbers of isolates resistant to antimicrobial agents and the risk of worsened illness (such as hemolytic uremic syndrome with Shiga toxin–producing *Escherichia coli* O157:H7) further complicate antimicrobial and antimotility drug

use. Thus, prevention by avoidance of undercooked meat or seafood, avoidance of unpasteurized milk or soft cheese, and selected use of available typhoid vaccines for travelers to areas where typhoid is endemic are key to the control of infectious diarrhea.

INTRODUCTION

Two converging factors highlight the growing need for clear guidelines for the diagnosis and management of infectious diarrhea. First, there is increasing recognition of a widening array of enteric pathogens associated with illnesses of the gastrointestinal tract. Agents such as enterohemorrhagic *E. coli,* referred to here as Shiga toxin–producing *E. coli* (STEC), *Salmonella, Shigella, Cyclospora, Cryptosporidium, Giardia, Campylobacter jejuni, Clostridium difficile,* caliciviruses, and other enteric viruses cause >200 million cases of diarrheal illnesses in the United States each year. Many of these organisms are easily transmitted through food or water or from one person to another, and some are devastating to individuals with compromised immune systems or structural abnormalities of the gastrointestinal tract. With the rapid globalization and industrialization of our food supply and with a multiplicity of recognized pathogens and diagnostic tools, the challenges of determining optimal, cost-effective means for appropriate diagnosis, clinical management, and public health control of diarrheal illnesses are great.

The second factor arises from our having entered an era when health care is increasingly managed with an eye to cost containment. Critical to developing a cost-effective approach to the evaluation and management of infectious diarrhea is the selective use of available

Table 1. Categories indicating the strength of recommendations and the quality of evidence on which they are based.

Category	Definition
Strength of evidence	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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diagnostic methods, therapies, and preventive measures. These must be targeted to the clinical scenarios in which they will yield the greatest benefits, and certain factors must be taken into account: the patient's history, exposure, and immune status, and the nature of the illness: its severity and duration and whether the process is inflammatory or hemorrhagic.

Clear guidelines are needed for the application of diagnostic methods to identify enteric infections that require specific therapy or are responsive to control measures. The six recommendations are summarized in table 2 and in figure 1. The recommendations address the following: oral rehydration, clinical and epidemiological evaluation, performance of selective fecal studies, administration of selective antimicrobial therapy, contraindicated antidiarrheals, and available immunizations. These guidelines will continue to evolve as improved understanding of pathogenesis and development and use of inexpensive, rapid tests improve diagnosis and management of infectious diarrheal illness, one of the most common clinical syndromes in our society.

GOALS

These recommendations are intended to provide clinicians and public health practitioners with a consensus-based document that will aid in the management of acute diarrhea by addressing which patients to test, what tests to order, what medical treatments to use, and what steps to take to ensure that appropriate public health actions are implemented. The authors include internists, pediatricians, public health leaders, and laboratory directors with recognized expertise in enteric infectious diseases. Discussions of clinical features and rec-

ommendations are based on extensive MEDLINE searches, and specific citations are given throughout.

Wherever possible these recommendations are evidence-based and provide indications regarding the quality of available evidence (on a scale of I to III) and the degree of certainty for a given recommendation (on a scale of A to E; table 1) [1, 2].

This document identifies areas where key research questions relating to the diagnosis, treatment, and prevention of diarrheal diseases remain unanswered. These guidelines will need to be updated as additional information becomes available, and a process of periodic revisions will be needed to maintain the timelines of this document. The information provided herein is intended to provide a working framework for clinicians and public health providers and should not override or be construed as a substitute for sound clinical decision-making.

DEFINITIONS

"Diarrhea" is an alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency of stools. A decrease in consistency (i.e., soft or liquid) and an increase in frequency of bowel movements to ≥ 3 stools per day have often been used as a definition for epidemiological investigations. "Infectious diarrhea" is diarrhea due to an infectious etiology, often accompanied by symptoms of nausea, vomiting, or abdominal cramps. "Acute diarrhea" is an episode of diarrhea of ≤ 14 days in duration. "Persistent diarrhea" is diarrhea of >14 days in duration. Although we will not categorize persistent diarrhea further here, some experts refer to diarrhea that lasts >30 days as "chronic."

Table 2. **Summary of recommendations for managing infectious diarrhea.**

Recommendation	Ranking[a]
Initiate rehydration (oral whenever possible)	A-I
Perform a thorough clinical and epidemiological evaluation for any significant diarrheal illness (profuse dehydrating, bloody or febrile diarrhea, or illness in infants, elderly, or immunocompromised patients). That is, ascertain how the illness began; stool characteristics (frequency and quantity); symptoms or signs of hypovolemia; travel history; whether the patient attends a day care center; whether the patient has ingested raw or undercooked meat, raw seafood, or raw milk; whether the patient's contacts are ill; the patients sexual contacts, medications, and other medical conditions, if any.	A-II
Perform selective fecal studies (as shown in figure 1)	B-II
Institute selective therapy for	
Traveler's diarrhea	A-I
Shigellosis	A-I
Campylobacter infection	B-II
Avoid administering antimotility agents with bloody diarrhea or proven infection with Shiga toxin–producing *Escherichia coli*	E-I
Selectively administer available vaccines[b] and, for travelers to (or residents of) areas where typhoid is endemic, administer typhoid vaccine (parenteral Vi or oral Ty21A)	B-II

[a] Letters indicate the strength of the recommendation and Roman numerals indicate the quality of evidence supporting it, respectively (see Table 1).
[b] Oral live (103 HgR) and killed (WCBS) cholera vaccines are available outside the United States for travelers to areas where cholera is endemic, although diarrhea is uncommon in careful travelers (B-II).
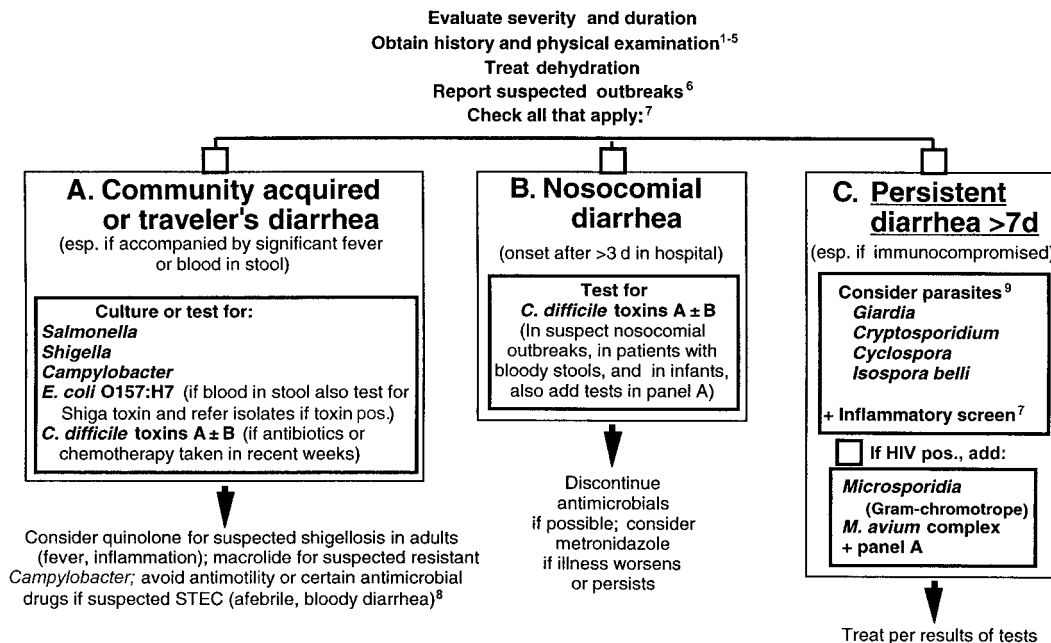
BACKGROUND

Infectious diarrheal diseases are the second leading cause of morbidity and mortality worldwide [3–5]. In the United States alone, an estimated 211–375 million episodes of diarrheal illness occur each year, resulting in 73 million physician consultations, 1.8 million hospitalizations, and 3100 deaths. Foodborne illnesses alone account for 76 million illnesses, 325,000 hospitalizations, and 5000 deaths each year [6–8]. In addition to acute morbidity and mortality, some causes of infectious diarrhea result in serious long-term sequelae such as hemolytic uremic syndrome (HUS) with renal failure following STEC infection (also known as enterohemorrhagic *E. coli* infection), Guillain-Barré syndrome following *C. jejuni* infection [9], and malnutrition with or without diarrhea following infection with enteroaggregative *E. coli*, *Cryptosporidium* species, or perhaps other enteric infections [10–13].

There is also a growing awareness of the potentially huge impact, in the developing world, of long-term disability caused by repeated early childhood enteric infections [5, 14]. The economic costs of infectious diarrheal diseases are considerable also. In the United States an estimated $6 billion each year is spent on medical care and lost productivity due to foodborne diseases, most of which cause diarrhea [15, 16]. Another report estimated that in 1988 alone, $23 billion was spent for 99 million cases of diarrhea, 250,000 of which required hospitalization [17]. Despite the economic and societal burdens of diarrheal illnesses, few clinical guidelines exist for the diagnosis and treatment of persons with suspected infectious diarrhea. The considerable geographic and interspecialty variability in clinical practice has been recently observed to demonstrate a clear need for such clinical diagnostic guidelines that are evidence-based and cost effective [18].

Clinical health care providers and public health practitioners have overlapping interests in the recognition and treatment of infectious diarrhea. For clinicians, early diagnosis of an acute episode of diarrhea can lead to interventions that alleviate symptoms and prevent secondary transmission. For public health practitioners, prompt notification of pathogen-specific diagnoses and subtyping of bacterial isolates through public health surveillance can lower rates of transmission and lead to timely detection and control of outbreaks. Because both clinicians and public health practitioners share overlapping responsibilities for the diagnosis, management, and prevention of infectious diarrheal diseases, these guidelines contain recommendations for both groups. To reduce the morbidity and mortality associated with infectious diarrhea, the clinical and public health practitioner communities must work closely together to identify optimal diagnostic, treatment, and prevention methods.

Diarrheal illness is a problem worldwide, with substantial regional variation in the prevalence of specific pathogens, the availability of means of diagnosis and treatment, and the degree

Evaluate severity and duration
Obtain history and physical examination[1-5]
Treat dehydration
Report suspected outbreaks[6]
Check all that apply:[7]

A. Community acquired or traveler's diarrhea
(esp. if accompanied by significant fever or blood in stool)

Culture or test for:
Salmonella
Shigella
Campylobacter
E. coli O157:H7 (if blood in stool also test for Shiga toxin and refer isolates if toxin pos.)
C. difficile toxins A ± B (if antibiotics or chemotherapy taken in recent weeks)

Consider quinolone for suspected shigellosis in adults (fever, inflammation); macrolide for suspected resistant *Campylobacter;* avoid antimotility or certain antimicrobial drugs if suspected STEC (afebrile, bloody diarrhea)[8]

B. Nosocomial diarrhea
(onset after >3 d in hospital)

Test for
C. difficile **toxins A ± B**
(In suspect nosocomial outbreaks, in patients with bloody stools, and in infants, also add tests in panel A)

Discontinue antimicrobials if possible; consider metronidazole if illness worsens or persists

C. Persistent diarrhea >7d
(esp. if immunocompromised)

Consider parasites[9]
Giardia
Cryptosporidium
Cyclospora
Isospora belli

+ Inflammatory screen[7]

If HIV pos., add:
Microsporidia
(Gram-chromotrope)
M. avium complex
+ panel A

Treat per results of tests

Figure 1. Recommendations for the diagnosis and management of diarrheal illnesses. Pos., positive. [1]Seafood or seacoast exposure should prompt culture for *Vibrio* species. [2]Traveler's diarrheal illnesses that have not responded to empirical therapy with a quinolone or trimethoprim-sulfamethoxazole should be managed with the above approach. [3]Persistent abdominal pain and fever should prompt culture for *Yersinia enterocolitica* and cold enrichment. Right-side abdominal pain without high fever but with bloody or nonbloody diarrhea should prompt culture for Shiga toxin–producing *Escherichia coli* (STEC) O157. [4]Proctitis in symptomatic homosexual men can be diagnosed with sigmoidoscopy. Involvement in only the distal 15 cm suggests herpesvirus, gonococcal, chlamydial, or syphilitic infection; colitis extending more proximally suggests *Campylobacter, Shigella, Clostridium difficile,* or chlamydial (LGV serotype) infection, and noninflammatory diarrhea suggests giardiasis. [5]Postdiarrheal hemolytic uremic syndrome (HUS) should prompt testing of stools for STEC O157 and for Shiga toxin (send isolates to reference laboratory if toxin-positive but STEC-negative). [6]Outbreaks should prompt reporting to health department. Consider saving culture plates and isolates and freeze whole stools or swabs at −70°C. [7]Fecal lactoferrin testing or microscopy for leukocytes can help document inflammation, which is often present in invasive colitis with *Salmonella, Shigella,* or *Campylobacter,* with more severe *C. difficile* colitis, and with inflammatory bowel disease. [8]Some experts recommend avoiding administration of antimicrobial agents to persons in the United States with bloody diarrhea. [9]Commonly used tests for parasitic causes of diarrhea include fluorescence and EIA for *Giardia* and *Cryptosporidium;* acid-fast stains for *Cryptosporidium, Cyclospora, Isospora,* or *Mycobacterium* species (as well as culture for *Mycobacterium avium* complex); and special chromotrope or other stains for microsporidia, as noted in the text.

of prevention achieved. The focus of these recommendations is on the industrialized world, in particular the United States, where diagnostic capacities are widespread and the major epidemic enteric infections such as cholera and typhoid fever have long been controlled. For an excellent approach to the diagnosis and management of diarrheal illness in the developing world, the reader is referred to the guidelines published in 1993 by the World Health Organization [18a].

The magnitude of the problem. Common gastrointestinal illness rates measured in extensive prospective studies conducted over the past 50 years range from 1.2 to 1.9 illnesses per person annually in the general population (table 3). Some populations in the United States have diarrhea rates (and living conditions) that approach those seen in developing areas [19–21]. The age-specific rates are highest for young children: 2.46 illnesses per year per child <3 years old, with a seasonal peak in winter, at which time rotavirus and other enteric viruses predominate, as shown in the Charlottesville, Virginia, family

study (table 4 and figure 2) [19]. Attack rates are even higher (5 illnesses per child per year) for children <3 years old who attended child care centers in a study in Arizona [22]. Studies comparing different types of child care settings have found that there is a 2.2- to 3.5-fold greater relative risk of diarrhea among children <3 years of age associated with attendance in child care centers than among children cared for at home (table 5) [22–24]. Illness rates among young children in tropical, developing areas may exceed 6–10 illnesses per child per year. Because these are critical developmental years, there may be a lasting impact on physical and cognitive development [14, 25–27].

Data from a population survey conducted by random selection from a population of 14.3 million people served by 5 Centers for Disease Control and Prevention (CDC) Food Net sites revealed an average of 1.4 diarrheal episodes per person per year in 1997 (0.75 of these episodes per person per year were "diarrheal illnesses," defined as diarrhea lasting for >1 day

Table 3. Attack rates of diarrheal illnesses, from 3 large multiyear family studies and from the FoodNet population survey.

Location or survey [reference]	Dates	Attack rate[a] (study size)
Cleveland [204]	1948–1957	1.5 (443 py; 85 fam)
Tecumseh, Michigan [205]	1965–1971	1.2 (4095 py; 850 fam)
Charlottesville, Virginia [19, 206]	1975–1977	1.9 (169 py; 45 fam)
FoodNet [6, 8, 18]	1997	1.4 (5 sites; 14.3 m pop)

NOTE. Py, person-years; fam, family; m pop, million population.
[a] Episodes per person per year.

or causing significant impairment of daily activities; CDC, unpublished data). Of the persons affected, an estimated 28 million (8%) visited a physician's or other provider's office, (of whom 1.8 million [7%] were hospitalized); 45 million (12%) telephoned the physician or provider's office; 116 million (31%) received an antidiarrheal medication; and 19 million (5%) received an antimicrobial agent. In addition, an estimated 6 million fecal specimens were submitted from these patients for stool culture and 3 million fecal specimens were submitted for examination for ova and parasites. Estimates of the number of deaths per year associated with diarrhea in the United States range from 500 children [28] to >10,000 persons (of whom 5000 had foodborne infection), with most deaths occurring in the elderly [8, 29–31].

Lew et al. [32] reviewed 28,538 diarrheal deaths (in ICD-9 codes, diarrhea was listed as the immediate or underlying cause) from National Center for Health Statistics data for a 9-year period (1979–1987). There were an average of 3171 deaths per year, of which 51% were elderly patients (>74 years old); 27% were 55–74 years old and 11% were <5 years old [32]. A similar skew, in which 25% of all hospitalizations and 85% of mortality associated with diarrhea involved the elderly (⩾60 years old), was seen in the McDonnell-Douglas Health Information System database reviewed by Gangarosa et al. [30]. It is estimated that, worldwide, there are 3.1 million deaths due to diarrhea per year (>8400 per day), mostly of young children in developing areas [3, 5]; thus, annual deaths due to diarrhea globally occur mainly in young children, and the number of deaths is 1000-fold higher than in the United States, where most of those who die of diarrheal illness are elderly.

Inconsistency in evaluation of acute diarrheal illnesses. One goal of a clinical guideline is to summarize concisely the best available information for practitioners. Although information about diagnosis and management of acute diarrheal diseases is scattered among disease-specific articles and textbooks, we know of no single reference that comprehensively addresses both clinical and public health issues dealing with management of diarrheal diseases. A high degree of variability in health care providers' practices for a given disease has often been cited as evidence of a need for guideline development.

In a recent survey of physicians who see patients with di-

arrhea, a significant variability in the likelihood of a stool culture request was observed among physicians in different geographic areas and in different specialties, even after patients' clinical characteristics were controlled for [18]. There are various interpretations of what is considered medically indicated for evaluating persons with diarrhea. Stool cultures are often viewed as tests with a high cost per relative yield [33–37]. Because the results of stool culture or examination for ova and parasites are often available only after a delay, and because most diarrheal illnesses are self-limited, these tests may provide little information directly relevant to clinical care and seem an unnecessary expense to many clinicians [38]. However, this information may have great public health importance.

One notable example of this importance was a 1994 outbreak of illnesses due to *Salmonella* serotype *enteritidis*. In this outbreak, the results of diagnostic stool cultures for individual patients had little impact upon clinical management decisions, because supportive care without antibiotics is generally recommended for infections with this organism [39]. However, from one region of Minnesota, clinical laboratories submitted an elevated number of *Salmonella* isolates to the state public health laboratory, which led to the detection of an ongoing, nationwide outbreak of *Salmonella* serotype *enteritidis* infections due to contaminated commercially distributed ice cream. This outbreak ultimately affected >220,000 people [40]. Removal of the contaminated product from the marketplace prevented many thousands of additional illnesses. Illnesses in this outbreak were widely dispersed over 41 states, and except for the initial cluster, they were not concentrated in any one dem-

Table 4. Age-specific diarrhea attack rates for acute gastrointestinal illnesses in families in Charlottesville, Virginia, 1975–1977.

Age of patients, y	Person-years	Attack rate[a]
0–3	39	2.46
4–9	33	1.95
10–16	9	1.73
>16	93	1.69

NOTE. Data are from [19, 206].
[a] No. of episodes per person-year.
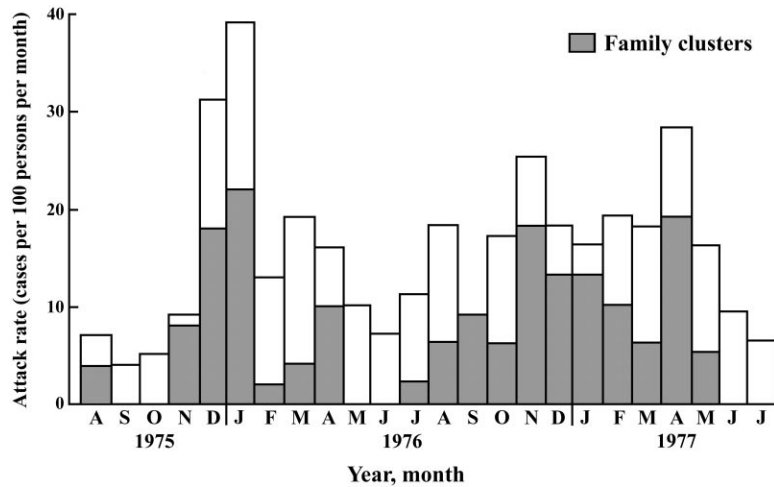
Figure 2. Monthly attack rates for acute gastrointestinal illnesses in Charlottesville, Virginia [19]

ographic group or geographic area that would have allowed easy recognition of the outbreak.

The initial case-control study that determined the source of this outbreak included only 15 matched case-control pairs. If the clinicians who evaluated those ill persons had treated their illnesses empirically and not ordered stool cultures, then the outbreak might not have been recognized. Subsequent investigations determined that only 0.3 percent of the cases associated with this outbreak were culture-confirmed and subsequently reported to health authorities. This degree of underdetection is common and demonstrates the insensitivity of our surveillance system for enteric diseases [41]. Each positive stool culture can be important for public health investigators attempting to detect and control outbreaks. Thus, these guidelines also emphasize the public health value of stool-specimen testing and isolation or identification of specific pathogens in the decision-making process.

IMPACT OF INCONSISTENT TESTING AND TREATMENT

The lack of a specific diagnosis can hinder appropriate management and treatment of many infections. Although the patient's history and clinical findings may provide important clues to likely etiologies, for some pathogens an organism-specific diagnosis is required. A decrease in the proportion of persons with diarrhea who submit stools for testing will likely result in a higher proportion of patients treated empirically and, in some cases, inappropriately. Appropriate antimicrobial therapy can shorten illness and reduce morbidity in some bacterial and parasitic infections and can be life-saving in invasive infections.

The emergence of microbe strains that are resistant to many commonly used antimicrobial agents means that treatment failures may become more common and that determinations of antimicrobial susceptibility may be made more often. Knowledge of the local patterns of susceptibility can guide the initial choice of antibiotic but depends on isolation of pathogens from recent clinical specimens. When empirical therapy is undertaken with broad-spectrum antibiotics or when treatment fails because of resistance to the antimicrobial used, it may facilitate the emergence of drug resistance among some bacterial enteric pathogens that spread easily from person to person, such as *Shigella* species [42, 43]. Empirical therapy also results in courses of unnecessary antibiotics. In addition, outcomes of some bacterial diarrheal illnesses may be worsened by the use of antibiotics.

In these situations, an organism-specific diagnosis is an important guide for appropriate therapy. For example, the likelihood of HUS in patients with *E. coli* O157:H7 infections may be increased when certain antibiotics are used to treat the initial diarrhea [44–58]. Treatment of salmonellosis with antibiotics (including quinolones) can prolong the carrier state [59] and lead to a higher clinical relapse rate [60].

In addition to its impact on the infection itself, antimicrobial therapy can increase susceptibility to other infections, such as infection with a resistant *Salmonella* species, because of selective pressure that converts silent carriage into overt infection and symptomatic illness [61, 62]. Recent antimicrobial use is an established risk factor for subsequent infection with a susceptible *Salmonella* species, perhaps because of changes induced in native flora [63]. Use of metronidazole or vancomycin for possible *C. difficile* diarrhea in hospitals is also a major factor in enhancing colonization with and spread of vancomycin-resistant enterococci [64, 65].

Organism-specific diagnosis of infectious diarrheal diseases allows clinicians to administer antimicrobial therapy most judiciously [63]. Furthermore, negative studies for potential pathogens also have value. This is especially true with documented

Table 5. Relative risk or odds ratio for diarrhea, by type of child care.

| | | | Type of setting | | | |
| | | | Child-care center | | Child-care home | |
Reference	Study design	Study dates	RR or OR	95% CI	RR or OR	95% CI
[22]	Cohort	9/81–9/83	2.2	1.3–3.5	1.3	0.7–2.4
[23]	Case-control	1981	3.5	1.0–4.8	<1.0	—
[24]	Case-control	9/85–3/87	2.4	1.6–3.7	2.0	1.3–3.1

NOTE. Study compared 2 child-care settings: commercial child-care centers vs. small child-care homes.

inflammatory diarrhea—for example, when a diagnosis of inflammatory bowel diseases is greatly aided by a thorough microbiological assessment that is negative [66]. Organism-specific diagnosis also can prevent unnecessary procedures or treatments. For example, a diagnosis of *E. coli* O157:H7, *C. jejuni,* or *Entamoeba histolytica* infection in a patient with severe abdominal cramps or bloody stools can prevent unneeded or dangerous colonoscopy, surgery, or corticosteroid treatment for presumed ulcerative colitis.

Lack of suspicion of an infectious etiology can lead to secondary transmission to others, including health care workers. A noteworthy example of this occurred in an outbreak of *E. coli* O157:H7 in a nursing home, in which several of the staff members became infected [67]. Thus, individual patient care may be adversely affected if laboratory diagnostics are not used appropriately in cases of diarrheal diseases. Finally, an organism-specific diagnosis allows the clinician and public health authorities to provide the appropriate follow-up recommendations for patients who are ill with infectious diarrhea. Examples include communicating to ill food-handlers and health care workers that they need to stay home from work and need to submit follow-up stool samples after infection with a particular pathogen has been diagnosed, as well as ensuring follow-up to detect HUS in persons with *E. coli* O157:H7 infections and providing information about preventing the infection from spreading among family and day-care contacts.

Lack of specific diagnosis can also impede disease surveillance, outbreak detection, and other critical measures that protect the public health. Identification of a case of *E. coli* O157 in a child attending a day-care center or of shigellosis in a person working in a restaurant is critical to protecting others to whom the infection might spread, both through direct clinical advice and management and by prompt notification of public health authorities and subsequent public health actions. This loss of public health surveillance data used to detect and control outbreaks can be minimized by appropriate laboratory testing of persons with diarrhea.

The nature of foodborne diseases in this country is changing; the increasing trend toward mass-produced, minimally processed, and widely distributed foods has been accompanied by more nationwide and international outbreaks of foodborne diarrheal diseases [40, 68, 69]. Outbreaks from low-level contamination of foods can affect thousands of people over a wide geographic distribution but may not exhibit the classic temporal and geographic clustering seen in point-source outbreaks, such as those arising from a shared meal [70]. The detection of outbreaks that involve widely separated human cases and the resultant control effects are critically dependent on reliable surveillance data, including serotyping and molecular subtyping of isolates; a decrease in stool culturing or reporting would have serious negative consequences for public health and safety [70]. In addition, new and emerging diarrheal pathogens are likely to be detected first among outbreak-associated cases, and decreased rates of diagnostic testing of ill persons could seriously hamper our ability to detect such pathogens. For example, monitoring of the antimicrobial resistance of *Salmonella* isolates submitted to health departments has led to detection and characterization of an emerging pathogen, multidrug-resistant *Salmonella typhimurium* DT 104 [71].

YIELD AND COST EFFECTIVENESS OF STOOL CULTURE

Although stool cultures are commonly requested, their usefulness has been questioned [33, 72–78] and the yield of such cultures is often thought to be quite low. In 1997, the Foodborne Diseases Active Surveillance Network (FoodNet) surveyed the 264 clinical laboratories in the five FoodNet sites that collected incidence data in 1996. The laboratories reported processing 233,212 stools tested for *Salmonella* and *Shigella*; these laboratories reported 2,069 *Salmonella* isolations and 1272 *Shigella* isolations, giving crude yield estimates of 0.9% for *Salmonella* and 0.6% for *Shigella*. Similar calculations for *Campylobacter* and *E. coli* O157 give crude yield estimates of 1.4% and 0.3%, respectively. Other reports [18, 33, 35, 76, 77, 79] noted stool culture yields from 1.5% to 2.9% (figure 3; table 6), although a study at the Puget Sound Health Maintenance Organization from May 1985 through April 1986 showed that 5.8% of stool specimens submitted were positive for enteric pathogens [80].
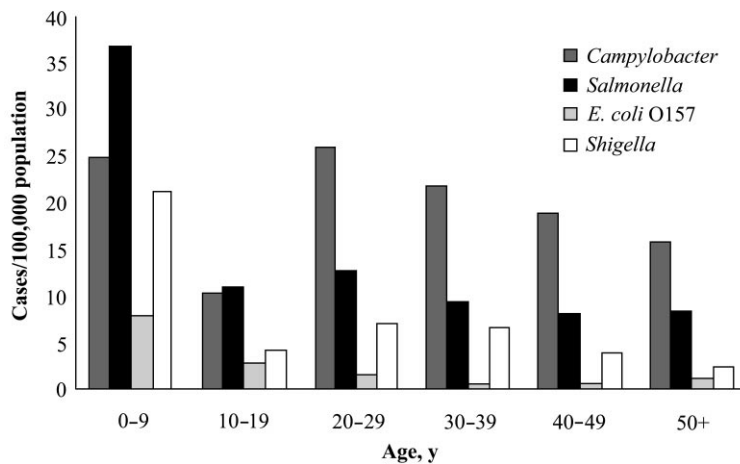
Figure 3. Rates of enteric infection revealed in the Foodborne Diseases Active Surveillance Network (FoodNet) survey, 1998 [18]

Similarly, a report by Slutsker et al. [79, 81] noted a yield of 5.6% from 10 United States hospital laboratories culturing all stools for STEC O157 (table 7). *C. jejuni* was typically the most common organism detected, followed by *Salmonella, Shigella,* and STEC. Of 30,463 specimens submitted to laboratories in the 10 United States hospitals, of specimens that yielded STEC O157, 63% had gross blood and 91% were from patients with a history of bloody diarrhea; such specimens tended to be from patients with less severe fever but more abdominal pain than specimens that yielded *Campylobacter, Salmonella,* or *Shigella* species (table 7) [79].

If one calculates from the yield and price of stool cultures a cost per positive result, as initially done by Koplan et al. in 1980 [33], the cost can be US$952 to $1200 [33–35]. This impressive cost derives from (1) the relative insensitivity of the test for the most likely pathogens and (2) the poor selection of specimens being cultured for what can be sought [34, 35].

Although the costs associated with testing are an important consideration, the cost per positive stool culture is an incomplete and misleading measure of the value of diagnostic testing. Because diagnostic stool testing is a method of obtaining information for both individual patient care and public health purposes, better predictive factors for ordering tests should also be used.

APPROACHES TO IMPROVING THE COST EFFECTIVENESS OF STOOL CULTURE

Selective testing. Selective testing can improve the yield and usefulness of stool testing. For example, the CDC has recommended that *E. coli* O157 be considered for all persons with acute bloody diarrhea or HUS and that stool specimens should be specifically tested for this organism [79, 83]. Because no specific media have been developed to detect non-O157 species of STEC, testing for these organisms is more difficult, and toxin testing of stool or culture supernatants can be used for patients with severe bloody diarrhea or HUS from whom a pathogen has not been isolated [84]. In cases of bloody diarrhea or HUS, testing stool samples after broth enrichment with an EIA kit for Shiga toxin is an excellent way to detect STEC [46]. When this test is positive, it is very important for public health purposes to confirm the serotype of the STEC. This can be done by testing on sorbitol-MacConkey (SMAC) agar (to detect *E. coli* O157) or by sending *E. coli* isolates to the state public health laboratory for testing. Other examples of selective testing of diarrheal stools that could be adopted include performing cultures for *Vibrio* on thiosulfate-citrate-bile salts (TCBS) medium for persons who have ingested shellfish within the 3 days before illness began and performing cultures for *Yersinia enterocolitica* in fall or winter for certain at-risk populations (e.g., Asian-Americans in California and African-American infants) [85].

The "3-day rule" for hospitalized patients. One approach to reducing testing on specimens that have a very low yield has been the "3-day rule" [43, 73–75]. Fecal specimens from patients with diarrhea that develops after 3 days of hospitalization have a very low yield when cultured for standard bacterial pathogens (*Campylobacter, Salmonella, Shigella,* etc.) or examined for ova and parasites. On the basis of this finding, several groups have suggested that unless overriding circumstances prevail, fecal specimens from patients hospitalized for >3 days should not be submitted for routine stool culture. These specimens account for 15%–50% of all specimens submitted, and it has been estimated that implementing this rule would have saved $20–$73 million in the United States in 1996 [43, 74, 77]. Likewise, multiple stool examinations for ova and parasites are of low yield (especially for hospitalized patients with nosocomial diarrhea) [75]. Of course, appropriate cultures should be performed for any patient admitted for diarrheal illness, irrespective of the date of hospital admission, if the

Table 6. Isolates recovered from stool cultures performed in the United States, 1980–1997.

| Reference, study | No. of cultures performed | Isolates recovered, % of cultures | | |
		Total	Salmonella; Shigella; Campylobacter jejuni	STEC
[33]	2468	2.4	2.4[a]	—
[34]	2020	1.5	1.5[a]	—
[77]	1964	2	0.6; .2; 1.2	—
Ova and parasites	1423	3	—	—
Clostridium difficile	2668	21	—	—
[78]	1800	2.9	—	—
[80]	30,463	5.6	1.8; 1.1; 2.3	0.4
[18]	233,212	3.2	0.9; 0.6; 1.4	0.3
Ova and parasites	217,886	2.1[b]	—	

NOTE STEC, Shiga toxin–producing *Escherichia coli*.
[a] Cumulative percentages for isolates of all 3 organisms.
[b] *Cryptosporidium,* 1.7%; *Cyclospora,* 0.4%.

patient has not had specimens collected to perform cultures for all indicated pathogens or if the patient seems to be involved in a nosocomial outbreak of diarrheal illness (e.g., due to *Salmonella*). A multicenter study from Europe suggests that age ≥65 years, comorbid disease, neutropenia and HIV infection may warrant cultures despite onset ≥3 d after hospitalization [76].

Conversely, specimens from patients who have been in the hospital for ≥3 days may yield *C. difficile* in 15%–20% of cases, suggesting that patients developing diarrhea in the hospital (or who have taken antimicrobial agents recently) should have specimens tested for *C. difficile* toxin(s); this pertains especially to patients who are severely ill or who have inflammatory diarrhea.

Screening for inflammatory diarrhea. In addition to the above approach of limiting specimens processed in the laboratory, several groups have suggested that it is more useful to screen for the relative minority of diarrheal illnesses that are inflammatory or invasive [29, 86, 87], since these are the most likely to be caused by the invasive pathogens for which culture (*Salmonella, Shigella, Campylobacter, Yersinia*) or toxin testing (toxigenic *C. difficile*) is usually available. An inflammatory etiology can be suspected on the basis of fever, tenesmus, or bloody stools and can be confirmed by microscopic examination for fecal polymorphonuclear leukocytes or simple immunoassay for the neutrophil marker lactoferrin (Leukotest; TechLab). The disadvantages of microscopy are that the yield is best with fresh-cup specimens and that specimens must be examined by an experienced microscopist [88]. Some studies, however, suggest that testing for fecal lactoferrin may be more sensitive [43, 78, 89]. Disadvantages of lactoferrin testing include its cost ($3.75 per test, for kit) and its false-positive results for breast-fed infants. Evidence of an inflammatory response

is often not present in noninvasive toxin-mediated infections such as those due to STEC or enterotoxic *E. coli*.

Use of more refined diagnostic algorithms and screening tests is an area in need of active research; improved algorithms are a potential source of cost-savings without sacrifice of diagnostic specificity. For example, several studies suggest that when fecal specimens are screened for evidence of an inflammatory process, the yield of culture for invasive pathogens can be increased substantially [34, 35, 78].

RECOMMENDATIONS

As suggested by the above approaches, a rational synthesis can be offered that is appropriate for the optimal care of the individual patient and for the needs of the community. These recommendations are consistent with and update published practice guidelines in the pediatric [36, 90], gastroenterology [29], and clinical laboratory literature. We have divided the recommendations into 2 sections, which give separate recommendations for clinical practice and for public health management.

The complete public-health management of the variety of diarrheal illnesses is beyond the scope of these guidelines and have been well-summarized for each infection [91]. The following general principles define the need for specific fecal testing, pathogen isolation, and patient intervention for optimal clinical care and to protect the public health.

Clinical Recommendations

Initial rehydration. The most common risks with diarrheal illnesses are dehydration and, in developing countries, malnutrition. Thus, the critical initial treatment must include rehydration, which can be accomplished with an oral glucose

Table 7. Clinical characteristics of patients from whose stool selected bacterial pathogens were recovered at 10 hospitals in the United States ($n = 30{,}463$ specimens).

	Stool specimens, %			Patients, %		
Pathogen isolated	Total	Visible blood	Occult blood	History of blood in stool	Fever	Abdominal tenderness
Camplyobacter jejuni	2.3	8	52	37	59	45
Salmonella	1.8	5	43	34	72	29
Shigella	1.1	15	59	51	79	34
STEC O157	0.4	63[a]	83	91	35	72
Total	5.6	3		22		

NOTE. Data are from [80].

[a] Of visibly bloody stool specimens, 39% contained Shiga toxin–producing *Escherichia coli* O157.

or starch-containing electrolyte solution in the vast majority of cases (A-I). Although many patients with mild diarrhea can prevent dehydration by ingesting extra fluids (such as clear juices and soups), more severe diarrhea, postural light-head-edness, and reduced urination signify the need for more re-hydration fluids. Oral rehydration solutions approaching the WHO-recommended electrolyte concentrations (e.g., Ceralyte, Pedialyte, or generic solutions) can be purchased at local phar-macies or obtained from pediatricians. WHO-recommended oral rehydration solutions can also be prepared by a pharmacy by mixing 3.5 g of NaCl, 2.5 g of NaHCO$_3$ (or 2.9 g of Na citrate), 1.5 g of KCl, and 20 g of glucose or glucose polymer (e.g., 40 g of sucrose or 4 tablespoons of sugar or 50–60 g of cooked cereal flour such as rice, maize, sorghum, millet, wheat, or potato) per liter (1.05 qt) of clean water. This makes a solution of approximately Na 90 m*M,* K 20 m*M,* Cl 80 m*M,* HCO$_3$ 30 m*M,* and glucose 111 m*M.*

The evidence supporting this recommendation for all pa-tients with dehydrating diarrhea is well documented [92–94]. Because oral rehydration therapy has been shown to be widely applicable throughout the world, it was hailed in 1978 as "po-tentially the most important medical advance of this century" [95]. Administration of this solution is not only lifesaving in cases of severe diarrhea in settings where iv fluids are difficult to administer but is also less painful, safer, less costly, and superior to administration of iv fluids for persons who are able to take oral fluids. The patient's thirst decreases as he or she is rehydrated, which helps protect against overhydration [96]. Stool output can be further reduced with food-based oral re-hydration therapy [97, 98]. Vitamin A and zinc repletion should be considered for patients with likely or documented deficiency. Promising new approaches to oral rehydration and nutrition therapy, incorporating glutamine or its derivatives to further help mucosal-injury repair, are being developed [99].

Patient evaluation. As recommended in widely used al-gorithms with detailed footnotes and in similar tables published elsewhere [78, 87, 100], obtaining a thorough history, including both clinical and epidemiological features, should be the first step in evaluating a patient who presents with any significant diarrheal illness (i.e., profuse, dehydrating, febrile, or bloody diarrhea, especially in infants and elderly or immunocom-promised patients; figure 1) (A-II). Relevant clinical features include: (1) when and how the illness began (e.g., abrupt or gradual onset and duration of symptoms); (2) stool charac-teristics (watery, bloody, mucous, purulent, greasy, etc.); (3) frequency of bowel movements and relative quantity of stool produced; (4) presence of dysenteric symptoms (fever, tenes-mus, blood and/or pus in the stool); (5) symptoms of volume depletion (thirst, tachycardia, orthostasis, decreased urination, lethargy, decreased skin turgor); and (6) associated symptoms and their frequency and intensity (nausea, vomiting, abdominal pain, cramps, headache, myalgias, altered sensorium).

In addition, all patients should be asked about potential ep-idemiological risk factors for particular diarrheal diseases or for their spread. These include the following: (1) travel to a developing area; (2) day-care center attendance or employment; (3) consumption of unsafe foods (e.g., raw meats, eggs, or shellfish; unpasteurized milk or juices) or swimming in or drinking untreated fresh surface water from, for example, a lake or stream; (4) visiting a farm or petting zoo or having contact with reptiles or with pets with diarrhea; (5) knowledge of other ill persons (such as in a dormitory or office or a social function); (6) recent or regular medications (antibiotics, antacids, anti-motility agents); (7) underlying medical conditions predispos-ing to infectious diarrhea (AIDS, immunosuppressive medi-cations, prior gastrectomy, extremes of age); and (where appropriate) (8) receptive anal intercourse or oral-anal sexual contact and (9) occupation as a food-handler or caregiver. For persons with AIDS, a modified algorithm has been published with recommendations for initial diagnosis and therapy as well as more invasive evaluation [100]. Diarrhea continues to be an important problem for patients with AIDS, even in the era of highly active antiretroviral therapy [101, 102].

A directed physical examination may also give clues as to the appropriate evaluation and treatment of an acute diarrheal illness. It is particularly important to observe for abnormal vital

signs (including fever, orthostatic pulse, and blood pressure changes), other signs of volume depletion (dry mucous membranes, decreased skin turgor, absent jugular venous pulsations), abdominal tenderness, and altered sensorium.

The predominant clinical features associated with the most common infectious diarrheal illnesses are given in table 8. With few exceptions, the predictive value of any of the features listed is relatively low for any particular enteric pathogen [80, 82]. However, some of the diseases that are diagnosed by stool culture (shigellosis, salmonellosis, and campylobacteriosis) share certain inflammatory features such as fever, abdominal pain, bloody stools, and the presence in stools of leukocytes, fecal lactoferrin, and/or occult blood (II) [78, 103–113].

Fecal testing. Developing better algorithms combining clinical and epidemiological features is an area for future research. For example, any diarrheal illness lasting >1 day, especially if accompanied by fever, bloody stools, systemic illness, recent use of antibiotics, day-care center attendance, hospitalization, or dehydration (defined as dry mucous membranes, decreased urination, tachycardia, symptoms or signs of postural hypotension, or lethargy or obtundation), should prompt evaluation of a fecal specimen, as noted below and in figure 1. Additional diagnostic evaluations, such as serum chemistry analysis, complete blood cell count, blood cultures, urinalysis, abdominal radiography, anoscopy, and flexible endoscopy may be considered for selected cases in which disease severity or clinical and epidemiological features suggest the need for such testing.

We recommend a selective approach to fecal studies, such as that shown in figure 1. The enteric illness is profiled to place it in ≥1 categories, and for each of these tests are suggested. The categories include community-acquired or traveler's diarrhea, especially if accompanied by fever or blood in the stool; nosocomial diarrhea that occurs 3 days after the start of hospitalization; and persistent diarrhea (B-II).

Although the presence of fecal leukocytes or lactoferrin further suggests an inflammatory diarrhea illness, such as those listed in panels A and B, experts differ regarding the routine use of screens for inflammatory infection for the initial testing of patients with community or nosocomial diarrhea (figure 1 A and 1B). However, a positive screen for patients with unexplained persistent or recurrent diarrhea suggests that consideration should be given to a diagnosis of possible inflammatory bowel disease (i.e., ulcerative colitis or Crohn's disease) and that a gastroenterologist should be consulted [66]. Patients infected with STEC often have bloody diarrhea and negative or low levels of lactoferrin, indicating the need for a specialized approach for such patients [114] (R. L. Guerrant, C. Park, T. S. Steiner, et al., unpublished observation).

Hospitalized patients (except, as noted above, those patients admitted for a diarrheal illness whose initial workup was in-complete or those patients whose diarrhea is suspected to be nosocomial in origin), especially those with abdominal pain, should be tested for *C. difficile* toxin. Any illness that persists for >7 days (especially in an immunocompromised patient) should prompt further testing of fecal specimens, as indicated in panel C in figure 1. In suspected outbreaks of gastroenteritis, special studies of stool specimens and *E. coli* isolates may be needed [115]. New methods that involve the use of EIA and DNA probe nonculture techniques are rapidly being developed and hold great promise for improved sensitivity. Routine performance of cultures, the traditional "gold standard," will remain critical for antibiotic resistance testing and for serotype determination and subtyping in outbreaks. Rotavirus infection, a leading cause of diarrhea in young children (especially in winter months in temperate climates) can be diagnosed with commercial assays, and Norwalk-like virus infections can be diagnosed with research assays, but these tests are usually not necessary for managing an individual case.

Noninfectious or extraintestinal causes of diarrhea should be considered when the compendium of diagnostic evaluation has not identified a pathogen. These causes include irritable bowel syndrome, inflammatory bowel disease (if recurring or persistent, with fecal leukocytes or lactoferrin, and unexplained), ischemic bowel disease (if the patient is >50 years old or has peripheral vascular disease), laxative abuse, partial obstruction, rectosigmoid abscess, Whipple's disease, pernicious anemia, diabetes, malabsorption, small-bowel diverticulosis, scleroderma, or celiac sprue [29, 116].

Therapeutic considerations. Because of increasing threats from antimicrobial-resistant infections, side effects of treatment with antimicrobial agents, suprainfections when normal flora are eradicated by antimicrobial agents, and the possibility of induction of disease-producing phage by antibiotics (such as Shiga-toxin phage induced by quinolone antibiotics) [47], any consideration of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences. New nonantimicrobial treatments to block secretory or inflammatory toxins or to enhance electrolyte absorption and intestinal repair are badly needed and are under study.

One situation in which empirical antibiotics are commonly recommended without obtaining a fecal specimen is in cases of traveler's diarrhea, in which enterotoxigenic *E. coli* or other bacterial pathogens are likely causes, and prompt treatment with fluoroquinolone or, in children, trimethoprim-sulfamethoxazole (TMP-SMZ) can reduce the duration of an illness from 3–5 days to <1–2 days (A-I). Some also consider empirical treatment of diarrhea that lasts longer than 10–14 days for suspected giardiasis, if other evaluations are negative and, especially, if the patient's history of travel or water exposure is suggestive [29]. Otherwise, for patients with febrile diarrheal illnesses, especially those believed to have moderate to severe

Table 8. Clinical features and physical and laboratory findings for common infectious diarrheal illnesses.

Feature or finding[a]	Patients infected with indicated pathogen, % [reference]									
	Salmonella species[b]	Shigella species	Campylobacter species	STEC O157	Toxigenic Clostridium difficile	Yersinia species	Entamoeba histolytica	Cryptosporidium parvum[c]	Cyclospora species[c]	Other pathogens
Fever	71–91 [106, 110]	58–100 [103, 106, 110, 111]	53–83 [110, 112]	16–45 [80, 207]	28 [208]	68 [109]	8 [111]	57–85 [110, 209]	54 [210]	
Abdominal pain	55–74 [106, 110]	75–100 [103, 110, 111]	48–100 [110, 112]	84–92 [80, 207]	22 [208]	65 [109]		50–84 [110, 209]	75–84 [210]	
Tenesmus[d]	—	55–96 [103, 107, 110]	—	Rare	—					
Bloody stool	5–34 [106, 110]	25–51 [103, 107, 110]	<1–37 [110, 112]	21–97 [207]	—	26 [109]		≤15 [110]		EAggEC, ≤30 [113]
Vomiting and/or nausea	52–55 [106, 110]	62.5–100 [103, 110]	0–50 [110, 112]	37–49 [207]	—	38.5 [109]		48–69 [110, 209]	27–71 [210]	
Physical or laboratory finding										
Bloody stool	5–15 [106]	77 [108]	8	63	—					ETEC, 11 [108]
Heme-positive stool	7–100 [104]; 29 [80]	46–73 [104]; 34 [80]	38–83 [104]; 45 [80]	83; 72 [80]	—		≤100 [104, 211]			Plesiomonas, 44; Aeromonas, 48 [104, 105]
Fecal WBCs										
>50/HPF	—	60–69 [86]	—	—	—					
Any/HPF	11–82 [43, 80, 86, 129, 214]	85–95 [88]	25–80 [43, 80, 129, 213, 215]	42–65 [213, 216]	28–40 [212]	48 [213]	28 [104]			
Fecal lactoferrin	—	—	—	0 [114]	64–75 [212, 219]					
Titer >1:400		43–78[e]		—						
Titer >1:50		94–100 [78, 89, 217, 218][e]		—						

NOTE. EAggEC, enteroaggregative *Escherichia coli;* ETEC, enterotoxigenic *E. coli;* HPF, high-power field.

[a] Combined features: in 1 study [105], 87% of patients with ≥3 days of diarrhea and fever, vomiting, myalgias or headache had stool cultures with results positive for *Salmonella, Shigella,* or *Campylobacter.*

[b] *Salmonella agona* outbreak, 25%.

[c] *Cryptosporidium* [209] and *Cyclospora* [210] are also often associated with weight loss (75% and 91% of cases, respectively), and *Cyclospora* is associated with striking fatigue in up to 92% of cases [210].

[d] Also a prominent feature of sexually transmitted proctitis.

[e] Combined value for patients infected with *Salmonella, Shigella,* or *Campylobacter* species.

invasive disease, empirical treatment should be considered (after a fecal specimen is obtained for the performance of the studies noted above). This empirical treatment can be with an agent such as a quinolone antibiotic or, for children, TMP-SMZ, which can reduce the duration and shedding of organisms in infections with susceptible *Shigella* species (A-I) [117–121] and possibly in infections with susceptible *Campylobacter* species (B-II) [122, 123].

However, there is a worrisome worldwide increase in quinolone-resistant *Campylobacter* infections (≤10.2% in Minnesota [124]), and such infections may possibly be worsened by quinolone eradication of competing normal flora [124–126]. Quinolone resistance that develops during treatment and is accompanied by symptomatic relapse has been described with regard to *Campylobacter* [127–129]. Erythromycin may reduce the duration of illness and shedding of susceptible *C. jejuni*, particularly when given early in the illness [130, 131]. Salmonella infections may warrant quinolone or other antimicrobial therapy when systemic spread is considered a risk or suspected and for children <6 months of age; however, like other antibiotics, quinolones may prolong shedding of non-*typhi* species of *Salmonella* [29, 59, 60, 132].

A particularly worrisome development is the appearance of multiple-drug resistance, including resistance to quinolones, in clinical *Salmonella* strains [133]. Antibiotics should not be prescribed simply to reduce the likelihood of secondary transmission. Other interventions, such as hand-washing, can achieve the same ends without introducing the risk of selecting for resistance [134].

Suspected or documented STEC infections should not be treated with antimotility agents (E-II) [54, 80, 135–139], and a decision to treat an illness that could be due to STEC O157 with an antimicrobial agent should be considered carefully, as it may worsen the risk of HUS developing. Treatment of STEC O157 infections with antimicrobial agents has not been shown to ameliorate illness, and several retrospective studies have noted a higher rate of HUS in treated patients [44–58], which could be an effect of treatment or a reflection of more aggressive treatment of patients who are more ill. In vitro data indicate that certain antimicrobial agents can increase the production of Shiga toxin, and animal studies have demonstrated harmful effects of antibiotic treatment of STEC infections [47, 140]. In Japan, both nonrandomized studies of patients and in vitro studies suggest that fosfomycin, a non–β-lactam cell wall–synthesis inhibitor (licensed only for urinary tract infections in the United States), may be safe and possibly improve the clinical course [58], but further study is needed (C-III) [44, 46, 47, 58, 59].

Details of diagnosis and treatment of specific infections are summarized in table 9 [29, 100, 141]. Because of changing patterns of antimicrobial resistance, recent local patterns are critical to making decisions about antimicrobial therapy [52, 54–56, 67, 136, 142–191].

An increasing amount of information suggests that *Aeromonas* is an enteric pathogen in the healthy host; it is usually associated with mild, though sometimes chronic and sometimes bloody, diarrhea. TMP-SMZ is the agent of choice if antimicrobial therapy is deemed necessary. The data supporting the pathogenicity of *Plesiomonas* are somewhat weaker; laboratory evidence of its pathogenicity is quite thin. However, particularly in the setting of a diarrheal illness following travel or shellfish consumption, if other pathogens have not been isolated it could be considered in the differential diagnosis. Anecdotal reports suggest that TMP-SMZ might diminish the duration of symptoms.

Table 2 summarizes the major recommendations detailed in these guidelines. Initial rehydration, clinical and epidemiological evaluation, and selecting appropriate fecal studies and therapy are key to optimal diagnosis and management, and reporting suspected outbreaks and cases of notifiable illnesses to local health authorities is vital in order to allow measures to be taken to investigate threats of enteric infection arising from our increasingly global and industrialized food supplies. Parenteral (Vi) or oral (Ty21a) typhoid vaccines are recommended for travelers to areas where typhoid is endemic who are at high risk for infection because they are not staying at the usual tourist hotels; new live and killed oral cholera vaccines are becoming available outside the United States [192–194].

Public Health Recommendations

Diagnostic fecal testing for public health reasons. Diagnostic testing of stool specimens is indicated for certain groups of people who are not themselves patients. Food-handlers in food service establishments and health care workers involved in direct patient care should be tested for bacterial pathogens if they have diarrhea because of their potential to transmit infection to large numbers of persons. Similarly, diarrheal illness in a day-care attendee, day-care employee, or resident of an institutional facility (e.g., psychiatric hospital, prison, or nursing home) should be evaluated for bacterial or parasitic infection because gastrointestinal illnesses in these settings may indicate that a disease outbreak is occurring. Physicians who suspect a disease outbreak is occurring because they have observed an increased incidence of diarrheal disease among a particular group should request the types of diagnostic testing appropriate to the clinical illness in order to facilitate identification of the etiologic agent and to define the extent of the outbreak. The suspected outbreak should also be reported to public health authorities.

Disease reporting. The reporting of specific infectious diseases to the appropriate public health authorities is the cornerstone of public-health surveillance, outbreak detection, and

Table 9. Recommendations for therapy against specific pathogens.

Pathogen	Immunocompetent patients	Immunocompromised patients
Shigella species	TMP-SMZ, 160 and 800 mg, respectively (pediatric dose, 5 and 25 mg/kg, respectively) b.i.d. × 3 d (if susceptible[a]) or fluoroquinolone[b] (e.g., 300 mg ofloxacin, 400 mg norfloxacin [186], or 500 mg ciprofloxacin b.i.d. × 3 d) (A-I) [117–121]; nalidixic acid, 55 mg/kg/d (pediatric) or 1 g/d (adults) × 5 d [220] or ceftriaxone [79]; azithromycin [121]	× 7–10 d
Non-*typhi* species of *Salmonella*	Not recommended routinely (E-I) [59,60], but if severe or patient is <6 mo or >50 y old or has prostheses, valvular heart disease, severe atherosclerosis, malignancy, or uremia, TMP-SMZ (if susceptible) or fluoroquinolone[b] as above, b.i.d. × 5–7 d (B-III) [29, 132, 221]; ceftriaxone, 100 mg/kg/d in 1 or 2 divided doses [222]	× 14 d (or longer if relapsing)
Campylobacter species	Erythromycin, 500 mg b.i.d. × 5 d[c] (B-II) [122, 123]	Same (but may require prolonged treatment)
Escherichia coli species		
Enterotoxigenic	TMP-SMZ, 160 and 800 mg, respectively, b.i.d., × 3 d (if susceptible), or fluoroquinolone[b] (e.g., 300 mg ofloxacin, 400 mg norfloxacin, or 500 mg ciprofloxacin b.i.d. × 3 d) (A-I) [152, 153, 168]	Same (B-III)
Enteropathogenic	As above (B, II) [188]	Same (B-III)
Enteroinvasive	As above (B-II) [171, 178]	Same (B-III)
Enteroaggregative	Unknown (C-III)	Consider fluoroquinolone as for enterotoxigenic *E. coli* [190] (B-I)
Enterohemorrhagic (STEC)	Avoid antimotility drugs (E-II) [136]; role of antibiotics unclear, and administration should be avoided[d] (C-II) [52, 54–56, 67, 181]	Same (C-III)
Aeromonas/Plesiomonas	TMP-SMZ, 160 and 800 mg, respectively, b.i.d. × 3 d (if susceptible), fluoroquinolone[b] (e.g., 300 mg ofloxacin, 400 mg norfloxacin, or 500 mg ciprofloxacin b.i.d. × 3 d) (B-III) [146, 160–162, 172, 179]	Same (B-III)
Yersinia species	Antibiotics are not usually required (C-II) [149, 174, 175]; deferoxamine therapy should be withheld (B-II)[149, 182]; for severe infections or associated bacteremia treat as for immunocompromised hosts, using combination therapy with doxycycline, aminoglycoside, TMP-SMZ, or fluoroquinolone[b] (B-III) [149, 184]	Doxycyclin, aminoglycoside (in combination) or TMP-SMZ or fluoroquinolone[b] (B-III) [149, 184]
Vibrio cholerae O1 or O139	Doxycycline, 300-mg single dose; or tetracycline, 500 mg q.i.d. × 3 d; or TMP-SMZ, 160 and 800 mg, respectively, b.i.d. × 3 d; or single-dose fluoroquinolone[b] (A-I) [142, 144, 158, 163, 164]	Same (B-III)
Toxigenic *Clostridium difficile*	Offending antibiotic should be withdrawn if possible (B-II) [154, 157, 187]; metronidazole, 250 mg q.i.d. to 500 mg t.i.d. × 10 d (A-I) [173, 187, 189]	Same (B-III)
Parasites		
Giardia	Metronidazole, 250–750 mg t.i.d. × 7–10 d (A-I) [143, 165, 166]	Same (B-III)
Cryptosporidium species	If severe, consider paromomycin, 500 mg t.i.d. × 7 d, as with immunocompromised hosts (C-III)	Paromomycin, 500 mg t.i.d. × 14–28 d, then b.i.d. if needed (B-I) [145,154,190]; highly active antiretroviral therapy including a protease inhibitor is warranted for patients with AIDS (A-II) [147, 156]
Isospora species	TMP-SMZ, 160 and 800 mg, respectively, b.i.d. × 7–10 d (B-III)	TMP-SMZ, 160 and 800 mg, respectively, q.i.d. × 10 d, followed by TMP-SMZ thrice weekly, or weekly sulfadoxine (500 mg) and pyrimethamine (25 mg) indefinitely for patients with AIDS (A-I) [150, 177]
Cyclospora species	TMP/SMZ, 160 and 800 mg, respectively, b.i.d. × 7 d (A-I) [159, 167]	TMP-/SMZ, 160 and 800 mg, respectively, q.i.d. × 10 d, followed by TMP-SMZ thrice weekly indefinitely (A-II) [176]

(continued)

Table 9. Continued

Pathogen	Immunocompetent patients	Immunocompromised patients
Microsporidium species	Not determined	Albendazole, 400 mg b.i.d. × 3 w (B-I) [151,169 170]; highly active antiretroviral therapy including a protease inhibitor is warranted for patients with AIDS (A-II) [147, 148, 156]
Entamoeba histolytica	Metronidazole, 750 mg t.i.d. × 5–10 d, plus either diiodohydroxyquin, 650 mg t.i.d. × 20 d, or paromomycin, 500 mg t.i.d. × 7 d (A-II) [183, 185]	Same

NOTE. Letters indicate the strength of the recommendation and Roman numerals indicate the quality of evidence supporting it, respectively (see Table 1).
[a] Because up to 20% of isolates from foreign travelers are resistant to TMP-SMZ and resistance to quinolones is rare, a fluoroquinolone is preferred as initial therapy for travel-related shigellosis [186].
[b] Fluoroquinolones are not approved for treatment of children in the United States.
[c] Antibiotics are most effective if given early in course of illness.
[d] Fosfomycin, not licensed for this use in the United States in 1999, may be safer and possibly effective but requires further study [44, 46, 47, 59].

prevention and control efforts. Clinicians and clinical laboratories have a central role in this process. Although reporting requirements and procedures differ by jurisdictions, in most communities reporting begins when a notifiable infection is diagnosed and reported to the local or state health department. Requirements for the reporting of disease can be obtained from the state or local health department or at the Web site of the Council of State and Territorial Epidemiologists: http://www.cste.org.

If an outbreak is suspected, early reporting can lead to prompt investigations that may result in source detection and, ultimately, prevention of additional illnesses. Local health departments can counsel individual patients, conduct outbreak investigations, assist in contact notification, and provide follow-up for patients involved in disease outbreaks. Health departments can also provide information on disease prevention to the general public or persons at increased risk for diarrheal diseases, and they are usually best suited for handling inquiries from print and electronic media.

Isolate subtyping. For several enteric bacterial organisms, public-health surveillance depends on subtyping the clinical isolates in the state public health laboratory to detect and investigate outbreaks and to define the success of control measures. *Salmonella* isolates are routinely serotyped. Beginning in 1997, state public health laboratories also began performing standardized pulsed-field gel electrophoresis (PFGE) on isolates of STEC O157 and comparing the patterns they identified with a national database maintained at the CDC. PulseNet, as this national network for molecular subtyping is called, has since been expanded to include serotyping of isolates of *Salmonella, Shigella,* and *Listeria,* and it has been critical to the detection, early termination, and even prevention of outbreaks of foodborne illness [195]. Molecular subtyping strategies are being developed for viral pathogens, such as hepatitis A and caliciviruses, and may be available for routine public health practice in the future.

Follow-up testing. In certain situations, assurance should be obtained that a patient with a laboratory-confirmed bacterial or parasitic diarrheal disease has been cured or is no longer a fecal carrier. Because food-handlers and health care workers can transmit bacterial and parasitic diseases even if they are asymptomatic, it is recommended that before returning to their jobs these persons have 2 consecutive negative stool samples taken 24 h apart and at least 48 h after resolution of symptoms. If the patient has received antimicrobial therapy, the first stool specimen should be obtained at least 48 h after the last dose [196]. Furthermore, if food-handlers or health care workers are symptomatic, they should be excluded from directly handling food and from caring for high-risk patients.

Regulations vary by jurisdiction and by pathogen, so providers should contact their local public health office before advising persons in these job categories. Public health officials may be able to assist by obtaining follow-up samples and providing patient education. Diarrheal illnesses in day-care attendees and employees should be managed carefully because of the high likelihood of person-to-person spread of common pathogens, such as *E. coli* O157:H7 and *Shigella sonnei.* Approaches to prevention and control of diarrheal disease in day-care settings have included requiring that ill children stay home, cohorting of convalescent children within the center, and education of the community [197–201]. Cooperation between the physicians who detect diarrheal illnesses among day-care contacts and the local public health personnel is critically important for identifying potential outbreaks and implementing effective control methods.

Preventing illnesses through patient education. Many diarrheal diseases can be prevented by following simple rules of personal hygiene and safe food preparation. Hand-washing with soap is an effective step in preventing spread of illness and should be emphasized for caregivers of persons with diarrheal illnesses. As noted above, human feces must always be considered potentially hazardous, whether or not diarrhea or potential pathogens have been identified. Consequently, microbial studies should not be needed to justify careful attention to hygiene.

Select populations may require additional education about food safety, and health care providers can play an important

role in providing this information. Immunocompromised persons (e.g., HIV-infected patients, cancer chemotherapy recipients, and persons receiving long-term oral steroids or immunosuppressive agents) are more susceptible to infection with a variety of enteric pathogens and often are more likely to develop illness of greater severity and more frequently accompanied by complications. Such persons can reduce their risk by learning and following safe food-handling and preparation practices [202].

Alcoholics and persons with chronic liver disease (hemachromatosis or cirrhosis) are at increased risk for infections due to *Vibrio vulnificus* from raw shellfish and should avoid them. Persons with impaired immune defenses are at increased risk for infection with *Listeria monocytogenes* from soft cheeses, unheated deli meats, and raw dairy products, and therefore they should avoid these foods. Pregnant women should avoid undercooked meats because of the risk of infection with *Toxoplasma gondii* and (like all persons) should avoid raw dairy products (e.g., unpasteurized milk or cheeses), soft French-style cheeses, and unheated deli meats, which carry an increased risk of *Listeria monocytogenes* infection; both organisms are associated with miscarriage.

Among young children and the elderly, illness caused by infection with *Salmonella* or *E. coli* can be particularly devastating but is potentially preventable by following safe food practices. General educational information on food safety is available from a number of sources, including many Web sites, such as the following: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/foodborneinfections_g.htm; http://www.fightbac.org; http://www.foodsafety.gov; http://www.healthfinder.gov; and http://www.nal.usda.gov/fnic/foodborne/foodborn.htm.

Although vaccines are not the focus of these management guidelines, currently available vaccines for typhoid fever in the United States are the parenteral Vi capsular polysaccharide vaccine, oral live-attenuated Ty21a vaccine (intermittently available), and the old (often toxic) heat-phenol-inactivated parenteral vaccine. Since typhoid fever in the United States in recent years has often been imported (i.e., usually acquired during international travel) and is potentially severe and largely preventable, we recommend the Vi or Ty21a (or, only for children <2 years old, the heat-phenol-inactivated) vaccine for those with significant likely exposure [194] (B-II [203]).

With regard to cholera vaccines, only the old parenteral vaccine is licensed for use in the United States at the time of this writing, and it is not recommended because of the extremely low risk of cholera to the traveler and the limited efficacy of the vaccine [193]. New oral live (CVD 103HgR) and killed (whole-cell B-subunit) vaccines are licensed outside the United States and are used by some travelers. The rotavirus vaccine, although effective, has presented complications in the form of rare cases of intussusception; it is no longer marketed and thus is not recommended.

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