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Diarrhea in Developed and Developing Countries: Magnitude, Special Settings, and Etiologies

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Diarrheal diseases are major causes of morbidity, with attack rates ranging from two to 12 or more illnesses per person per year in developed and developing countries. In addition, diarrheal illnesses account for an estimated 12,600 deaths each day in children in Asia, Africa, and Latin America. The causes of diarrhea include a wide array of viruses, bacteria, and parasites, many of which have been recognized only in the last decade or two. While enterotoxigenic *Escherichia coli* and rotaviruses predominate in developing areas, Norwalk-like viruses, *Campylobacter jejuni*, and cytotoxigenic *Clostridium difficile* are seen with increasing frequency in developed areas; and *Shigella*, *Salmonella*, *Cryptosporidium* species, and *Giardia lamblia* are found throughout the world. The rational management of infectious diarrhea requires the highly selective use of laboratory tests for these varied etiologic agents, depending on the clinical and epidemiologic setting. The purpose of this review is to provide an overview of the magnitude, special settings, and etiologies of diarrhea endemic to developed and developing countries. This information permits a practical approach to the diagnosis and management of common diarrheal illnesses in different settings.

Tremendous advances have been made during the past 15–20 years in the recognition of a wide variety of viral, bacterial, and parasitic enteric pathogens that are important causes of diarrhea throughout the world. Indeed, most of the leading etiologies of diarrhea in developed and developing countries include viruses (rotaviruses, Norwalk-like viruses, and enteric adenoviruses), bacteria (enterotoxigenic *Escherichia coli*, *Campylobacter* species, and cytotoxigenic *Clostridium difficile*), and parasites (*Cryptosporidium* species) that have been recognized only since 1970. A review of the relative importance of the various microbial etiologies of diarrhea in these areas requires consideration of the setting in which the illnesses occur. We must first recognize that prospective, community-based studies reveal that acute gastrointestinal (GI) illnesses are extremely common, ranging from one to three illnesses per person per year in developed countries to five to 18 illnesses per person per year in children living in impoverished areas of tropical, developing countries. In the latter areas, diarrheal diseases are a major cause of morbidity, as well as a leading cause of death.

In this review, we will first examine the findings from several community-based studies in developed and developing areas and then focus on four specific settings where diarrheal illnesses are becoming increasingly important: hospitals (nosocomial diarrhea), chronic care facilities for the elderly, child care centers, and among patients with AIDS. We will then provide an overview of the microbiology of diarrhea in developed and developing countries as well as a practical approach to specific etiologic considerations based on epidemiologic clues.

Morbidity Due to Diarrhea in Developed and Developing Areas

As summarized in table 1, acute gastrointestinal illnesses are extremely common throughout the world, second only to acute upper respiratory tract illnesses. In the classic studies of 85 families (with 443 individuals) in Cleveland over a 10-year period from 1948 through 1957, "infectious gastroenteritis," which was defined as diarrhea, vomiting, abdominal pain, or these symptoms in combination or with "minor" GI symptoms, occurred an average of 1.52 times per person per year [1]. Such illnesses represented 16% of all illnesses (total, 9.4 illnesses per person per year)

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Table 1. Diarrhea attack rates in developed and developing areas.

Areas studied [reference]	AR in children <5 y	Peak AR (age-specific)	Age at peak AR
Cleveland [1]	1.9	2.0–2.2	1–10 y
Charlottesville [2]	2.1	2.5	0–3 y
Arizona (22 day care centers) [3]	5.0	5.0	0–3 y
Guatemala [4]	7.9	10.5	18–23 mo
Bangladesh [5]	6.1	7.0 (47 d)	2–11 mo
Brazil			
Rural poor [6]	6.0	9.7 (50 d)	6–11 mo
Urban poor [7]	11.4	16.0	12–17 mo
Indian, urban poor [8]	11.9	18.6	6–11 mo

NOTE. Attack rates (AR) are given in episodes per child per year.

and were second in frequency only to common respiratory tract illnesses, which occurred 5.6 times per person per year. The age-specific attack rates rose from 1.0 illness per child per year in children <1 year of age to 2.0–2.2 illnesses per child per year for children 1–10 years of age, tapering to 1.4 illnesses per child per year after 12 years of age. During the 9-month school year (September through May), attack rates tended to be slightly higher in young schoolchildren and preschool siblings of schoolchildren than in preschool children without school-aged children in their families.

None of 77 illnesses studied in the Cleveland family study revealed *Salmonella* or *Shigella* species in stool cultures. Although these studies preceded successful identification of viral and many other etiologic agents, bacteria-free supernatants of stools from one mother with an afebrile diarrheal illness caused similar symptoms in one of seven young adult male volunteers. This agent was believed to be similar to the "Marcy strain" that had been identified by Gordon [9]. In addition, a fecal supernatant (FS) from another mother with fever, vomiting, and abdominal pain (the "FS inoculum") caused a febrile illness with vomiting and abdominal cramps in four of eight young men 26–30 hours after they had ingested the inoculum [10]. Results of subsequent cross-infection studies suggested that the FS and Marcy agents were not cross-protective and that the FS agent caused febrile illnesses, often with vomiting and systemic symptoms lasting only 24 hours, with a short incubation period of ~27 hours. The FS agent contrasted with the Marcy agent, which caused afebrile diarrheal illnesses lasting ~4 days after a 60-hour incubation period [1].

A similar study was conducted over a 2-year period (August 1975 through July 1977) among 45 families with one to four children (total, 169 individuals) in Charlottesville, Virginia. Daily symptom scores were kept, and each family was visited at least once every 2 weeks [2]. We found 334 acute GI illnesses, for an overall rate of 1.9 GI illnesses per person per year. Acute GI illnesses were defined as vomiting or diarrhea (85% of cases) or a combination of two or more GI and systemic symptoms, including nausea, abdominal cramps, malaise, fever, chills, headaches, myalgia, and anorexia, which accounted for 15% of all acute GI illnesses. Age-specific attack rates (table 2) revealed that children <3 years of age experienced 2.5 acute GI illnesses per person per year and that the attack rates declined with increasing age.

The monthly attack rates of acute GI illnesses (figure 1) in the Charlotteville study reveal that the peak rates—unlike those for illnesses frequently observed with enteroviral infections and with diarrhea in many developing countries, which occur in the summer months—occurred during the winter months, with 38% of all cases occurring in November, December, and January. Further, the attack rates for cases occurring in family clusters (defined as cases occurring within a family with the onsets <8 days apart) followed the same seasonal distribution as the overall attack rates, with peaks in the winter months (53% of attacks in family clusters occurred in November through January).

Extensive microbiologic studies were conducted on 188 (69%) of 274 cases of diarrheal illnesses. Swab specimens were placed immediately into Carey-Blair transport medium and subsequently cultured on McConkey agar for isolation of coliform bacteria; at least four coliform colonies were tested for the heat-labile enterotoxin (LT) in cultures of Chinese hamster ovary (CHO) cells, and at least two coliform

Table 2. Age-specific diarrhea attack rates for acute gastrointestinal illnesses in Charlottesville, Virginia, families.

Age group (y)	Person-years	AR
0–3	39.4	2.46
4–9	32.8	1.95
10–16	8.7	1.73
>16	92.7	1.69

NOTE. Attack rates (AR) are given in illnesses per person-year.

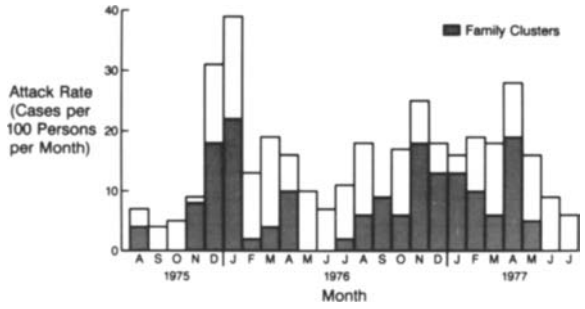


Figure 1. Monthly attack rates for acute gastrointestinal illnesses in Charlottesville, Virginia.

colonies were tested for the heat-stable toxin (ST) in the suckling mouse assay and for invasiveness in the guinea pig conjunctivitis or Sereny test. Specimens were also cultured onto SS agar for isolation of *Salmonella* and *Shigella* species and onto thiosulfate citrate bile salt sucrose (TCBS) agar for isolation of *Vibrio*. In addition, fecal specimens were tested for rotavirus by an ELISA, and selected paired serum specimens were evaluated for antibody to Norwalk-like agents by radioimmunoassay [11, 12] with the help of Drs. R.H. Yolken, H.B. Greenberg, and A.Z. Kapikian (Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland). Positive ELISA tests were confirmed by electron microscopy or by blocking antibody. Control specimens were obtained from 116 of these same study participants when neither they nor any family member had been ill for at least 2 weeks. Although there were no *Salmonella, Shigella, Vibrio* species, or invasive *E. coli* isolated, and 1%–6% of cases and controls had comparable numbers of enterotoxigenic *E. coli* isolated, 8% of cases and only 3% of 116 controls studied had rotaviruses detected, and three (27%) of 11 family clusters studied with paired sera had serologic evidence of infection with Norwalk-like agents (table 3). These findings for community-based studies stand in contrast to those for hospital-based studies, in which *Campylobacter jejuni, Salmonella, Shigella, Cryptosporidium* species, and other agents are found with considerably higher frequencies.

Although the overall attack rates were 1.5 and 1.7 illnesses per person per year in the Cleveland and Charlottesville family studies, respectively, both studies noted higher rates in children, with a peak rate of 2.5 illnesses per child per year in children <3

Table 3. Etiologies of acute diarrhea in Charlottesville, Virginia.

Organism	Percentage with indicated finding: Cases	Controls (n = 116)
Rotavirus	8	3
Norwalk virus (3 of 11 family clusters with paired sera)	27	. . .
LT (*E. coli*)	1	2
ST (*E. coli*)	6	6
Invasive *E. coli*	0	0
Salmonella, Shigella, Vibrio	0	0

NOTE. Of the 274 episodes of diarrheal illness, 188 were sampled for etiologic agent.

years of age in the Charlottesville studies [2]. The latter rates were comparable to the rate of 2.8–3.2 diarrheal illnesses per child per year in children <3 years of age in day care homes and in households not using day care in a report by Bartlett et al. from Maricopa County in Phoenix [3]. These rates nearly doubled, to reach 5.0 illnesses per child per year, in children <3 years of age attending day care centers (table 1).

In contrast to the rates of diarrhea morbidity in developed countries, the rates in developing countries range from 5 to 12 illnesses per child per year, with the peak age-specific attack rates occurring during the first year or two of life, when rates are as high as 18.6 illnesses per child per year in the poorest areas (table 1) [4, 5, 7, 8].

In tropical developing areas diarrhea is not only a major cause of morbidity it also constitutes the leading cause of mortality (table 4), accounting for an estimated 4.6 million deaths per year, or 12,600 deaths per day in children in Asia, Africa, and Latin America [13, 14]. In areas where mortality exceeds 25% in the first 5 years of life, diarrhea accounts for over one-half the deaths, for a mortality due to diarrhea approaching 15% [6, 14–16]. Although the mortality rate from acute diarrhea is being reduced significantly by the increase in use of oral rehydration therapy, prolonged diarrhea (>14–20 days) is emerging as an increasingly important cause of morbidity and mortality. Studies from Indonesia, Guatemala, Addis Ababa, Bangladesh, and Brazil show that 3%–27% of illnesses may extend beyond 14–21 days [5, 7, 17–20], and in areas such as northeast Brazil, prolonged diarrhea may account for

Table 4. Annual morbidity and mortality due to diarrhea.

	Morbidity	Mortality	Reference(s)
Total (Asia, Africa, Latin America)	3–5 billion/y	5–10 million/y	13
Children <5 y (Asia, Africa, Latin America)	1 billion/y (2.2–3 illnesses/child/y)	4–6 million/y (12,600/d)	14
Children <5 y (Northeast Brazil)	6–12 illness/child/y	15% of all children during first 5 y	6, 15, 16

>50% of deaths due to diarrhea [6, 20]. Furthermore, prolonged diarrheal illnesses clearly identify children who are at a high risk for heavy diarrhea burdens—often with malnutrition—and require more intensive treatment [20, 21]. The etiologies of prolonged diarrhea remain unclear; multiple bacterial and viral pathogens often are found, as is frequent colonization of the small intestine with coliform (or other) bacteria that have been shown to cause prolonged diarrhea in an animal model [22–26].

Special Situations in Which Diarrhea Is Increasingly Recognized

There are several settings in developed countries in which diarrhea is recognized with increasing frequency as a special problem. These include nosocomial or hospital-acquired diarrhea, diarrhea in extended care facilities for the elderly and in day care centers, and diarrhea in severely immunocompromised patients, particularly in those with AIDS. These problems are not limited to developed countries, however, and nosocomial diarrhea and diarrhea in patients with AIDS are even greater problems in tropical, developing countries.

Nosocomial Diarrhea

The magnitude and importance of nosocomial diarrhea is just beginning to be appreciated. Of the 223 nosocomial outbreaks reported to the Centers for Disease Control (CDC) between 1956 and 1979, 21% involved the GI tract [27]. Although nosocomial gastroenteritis is reported to the CDC in relatively low numbers (1.3 per 10,000 discharges) [28], nosocomial diarrhea is often not recognized or even considered among nosocomial infections. Yet it poses potentially major logistic problems and may increase patient risk for other nosocomial infections. Welliver and McLaughlin reported that in a pediatric hospital in Buffalo 17% of all nosocomial infections involved the GI tract (second only to respiratory tract infections) in a setting where the overall rate was 4.1 nosocomial infections per 100 children discharged [29]. Even more striking was the rate of nosocomial diarrhea among patients hospitalized in an adult intensive care unit in St. Bartholomew's Hospital in London (81 patients), which reached 41% [30]. Although antibiotics in the latter situation were not significantly associated with nosocomial diarrhea, rates were higher in patients receiving cimetidine (51%) or tube feedings (68%) [30]. In our own prospective surveillance of a medical intensive care unit and two pediatric wards, in which patients were interviewed three times a week and reviews of charts and nursing station and laboratory records were conducted over a 6-month period from October 1985 through March 1986, we found diarrhea to be one of the most common nosocomial illnesses (table 5) [31]. In the medical intensive care unit and the younger pediatric ward, nosocomial diarrhea was the most commonly recognized nosocomial illness by at least two- or threefold (7.7 and 2.3 illnesses per 100 admissions, respectively).

Although little information is available on the etiologies of nosocomial diarrhea, *Salmonella* species

Table 5. Nosocomial infections, by site, at University of Virginia Hospital, October 1985–March 1986.

		No. of cases/100 admissions					
Unit	No. of admissions	Nosocomial diarrhea	UTI	P	SWI	BSI	Other
MICU	260	7.7	2.7	3.9	0	2.7	3.9
Pediatric (<5 y)	609	2.3	0.8	0.9	0.5	0.9	3.6
Pediatric (≥5 y)	545	0.7	1.1	0.5	0.9	0.5	0.9

NOTE. Data are from [31]. MICU = medical intensive care unit; UTI = urinary tract infection; P = pneumonia; SWI = surgical wound infection; BSI = bloodstream infection.

is the most commonly reported cause of outbreaks in the United States [27]; however, limited etiologic studies suggest that viral agents and cytotoxigenic *C. difficile* are more common causes of sporadic (or endemic) nosocomial diarrhea. Data from the CDC between 1980 and 1984 showed that *C. difficile* was responsible for 45.1% of cases of nosocomial diarrhea with identified etiologies, followed by *Salmonella* species, which accounted for 11.8% of infections [28]. In addition, cytotoxigenic *C. difficile* was noted in 15% (12 of 78) of the bone marrow transplant patients studied by Yolken et al. [32] and in 11 (52%) of 21 of nosocomial diarrheal illnesses we studied [31] (table 6). Welliver and McLaughlin noted that 56% of 117 nosocomial GI infections in hospitalized children had viral etiologies (45 rotavirus, seven adenovirus, two coronavirus, and 11 "other") [29]. Similarly, nine (12%) of 78 neutropenic patients in a bone marrow transplant unit at Johns Hopkins Hospital acquired rotavirus infections, and three (38%) of eight children with nosocomial diarrhea in our pilot study had rotavirus infections [31]. In addition, Yolken described 12 patients (15%) with adenovirus infection and four (5%) with coxsackievirus infection in the bone marrow transplant unit. These infections were associated with diarrheal symptoms (58%) as well as with increased mortality (55%) [32]. An additional concern is that nosocomial diarrhea might predispose patients to other nosocomial infections, such as urinary tract or skin infections [33]. Indeed, most of the *E. coli* that cause urinary tract infections have the large intestine as their reservoir [34]. Better data are needed on the magnitude of nosocomial diarrhea as well as on its impact on other nosocomial infections. The impact of nosocomial diarrhea on duration of hospital stay, morbidity, and costs is probably substantial, but research is needed to document the magnitude of its impact.

Table 6. Etiologies of nosocomial diarrhea.

Organism	Percentage of patients studied with indicated diarrheal etiology	
	Marrow transplant patients*	Medical/pediatric patients†
C. difficile	15% (12/78)	52% (11/21)
Salmonella	0	3% (1/30)
Rotavirus	12% (9/78)	38% (3/8)
Adenovirus	15% (12/78)	ND
Coxsackievirus	5% (4/78)	ND

NOTE. ND = not done.
* At Johns Hopkins Hospital [32].
† At University of Virginia Hospital [31].

Diarrhea in Extended Care Facilities for the Elderly

Approximately one-third of patients residing in chronic care facilities for the elderly experience a significant diarrheal illness each year [35, 36]. Stimulated by the occurrence of cytotoxigenic *C. difficile* diarrhea in another chronic care facility, Bender et al. found that 48 (24%) of 200 surveillance stool specimens studied contained *C. difficile* cytotoxin. One-third of these patients had diarrhea [37]. Of 40 patients followed prospectively for up to 6 months, nine (22%) had fecal cytotoxin on admission and an additional six (19%) of the remaining 31 acquired *C. difficile* during the 6-month follow-up period [35]. In a subsequent report, Treloar and Kalra noted that in 33 (53%) of 62 cases of diarrhea in a chronic care facility *C. difficile* was isolated and that in one-third of these cases (11, or 18% of all 62 cases) *C. difficile* cytotoxin was detected [38]. Diarrhea among the elderly in extended care facilities may occasionally pose a serious, life-threatening problem. Cytotoxigenic *C. difficile* is not only found in a significant number of patients admitted to these facilities, it also is commonly acquired after admission; thus further study is warranted of the etiologies and control of nosocomial diarrhea in this setting.

Diarrhea in Child Care Centers

Outbreaks of diarrhea in child care centers are well recognized and have been associated with numerous viral, bacterial, and parasitic pathogens. These include infections with rotavirus, *Shigella* species, *C. jejuni*, *C. difficile*, *G. lamblia*, and *Cryptosporidium* (table 7). During outbreaks, attack rates

Table 7. Causes of diarrhea in day care centers.

Organism	Attack rate (%)	Secondary attack rate* (%)
Rotavirus	71–100	15–79
Shigella	33–73	26–46
C. jejuni	20–50	?
C. difficile	32	?
G. lamblia	17–90	12–50
Cryptosporidium	to 50–65	14

NOTE. Table is adapted from [39–41].
* In family members.

among children in these day care centers ranged from 17% to 100%. Furthermore, substantial secondary attack rates were noted in family members of these children. Details of outbreaks with these agents have been extensively reviewed elsewhere [39–41]. Rotaviral infections tend to occur in children <2 years old, while *G. lamblia* infections tend to occur in older toddlers [39].

Diarrhea in Patients with AIDS

Patients with AIDS commonly present with diarrhea or develop diarrhea that may become life-threatening during the course of their illness. In the United States, 50%–60% of patients with AIDS have diarrhea at the time of the initial diagnosis, whereas >95% of patients with AIDS in Africa and Haiti present initially with diarrhea [42, 43]. The etiologic agents of diarrhea in patients with AIDS range from parasites such as *Cryptosporidium*, *Microsporidium*, and *Isosopora belli* to cytomegalovirus, mycobacteria, *Salmonella* species, *Candida albicans*, or the AIDS virus itself (table 8) [42–44].

Probably the most commonly recognized enteric infection in patients with AIDS is with *Cryptosporidium*, which occurs in 3%–21% of patients in the United States and in 50% of patients with diarrhea and AIDS in Africa and Haiti [42, 43]. Furthermore, in ~10% of patients with cryptosporidiosis and AIDS the biliary tract may become involved, often with an increase in alkaline phosphatase but with normal bilirubin and transaminase enzymes [43]. *I. belli*, like *Cryptosporidium*, is readily detected with acid-fast stains, and although this infection is relatively uncommon in the United States, it is present in up to 15% of patients presenting with AIDS and diarrhea in Haiti [43]. Other parasites such as *Strongyloides*, *Entamoeba histolytica*, and *G. lamblia* are less common. Even *Pneumocystis carinii* may involve the GI tract in patients with AIDS [45]. Cytomegalovirus infections may be present in 10%–45% of patients with AIDS and diarrhea. *Mycobacterium avium-Mycobacterium intracellulare* (MAI) often involves the GI tract as a part of systemic MAI infection. Infections with nontyphoid *Salmonella* occur not only with increased frequency (2%–4.1%, an estimated 20- to 100-fold or greater increase over that in the general population) but also with an increased severity, with an estimated 15-fold increase in bacteremic infections [46–48]. *C. jejuni* as well as infections with other *Campylobacter* species have been noted in patients with AIDS as well [49]. Finally, in 15%–50% of patients with AIDS and diarrhea, no etiologic agent can be identified. In fact, an "AIDS enteropathy" with reduced disaccharidases, blunted villi, and an inflammatory infiltrate has been described [49, 50]. Whether this syndrome is related to infection of crypt cells or enterochromaffin cells in the intestinal mucosa with human immunodeficiency virus (HIV)—as has been demonstrated by Nelson et al. [44]—remains to be determined.

Other enteric infections seen in patients with AIDS include esophagitis or stomatitis due to infections with *Candida* or herpes simplex virus. In addition, in homosexual males, proctitis may be caused by *Treponema pallidum*, *Neisseria gonorrhoeae*, herpes simplex virus, or *Chlamydia trachomatis* [42, 43, 49–52].

Table 8. Agents causing diarrhea in patients with AIDS.

Cryptosporidium, *Microsporidium*
Isospora belli
Pneumocystis, *Strongyloides*, *Entamoeba*, *Giardia*
Cytomegalovirus
Mycobacterium (*M. avium-M. intracellulare* and *M. tuberculosis*)
Salmonella
Campylobacter
AIDS "enteropathy"
Esophagostomatitis (*Candida*, herpes simplex virus)
Proctitis (syphilis, gonorrhea, herpes simplex virus, *C. trachomatis*)

Summary of Infectious Etiologies of Acute Diarrhea in Developed and Developing Countries

The wide range of viral, bacterial, and parasitic agents that are most commonly associated with diarrhea in developed and developing areas are summarized in table 9 [41, 53]. As noted above, illnesses in the winter or dry season are characteristically associated with viral agents [54, 55]. Although immunity usually develops by 2 years of age, younger infants and children are often infected by rotaviruses, while older children and adults appear to remain susceptible to a growing family of Norwalk-like viruses. In addition, the importance of enteric adenoviruses is increasingly appreciated, particularly in young children.

Among bacterial pathogens, the most common on a global scale are probably enterotoxigenic *E. coli* that make either the cholera-like LT toxin or the ST enterotoxin. Enterotoxigenic *E. coli* are present in 15%–30% of illnesses in the community or in hospi-

Table 9. Infectious etiologies of acute diarrhea.

Organism	Percentage of patients with diarrhea infected with indicated organism	
	Developed areas	Developing areas
Viruses		
Rotaviruses*	8–50	5–45
Norwalk-like virus	10–27	1–2
Enteric adenoviruses	2 (<2 y)	5–10 (<4 y)
Bacteria		
Enterotoxigenic *E. coli*	1–7 (16)†	7–50
Enteropathogenic *E. coli*	<5	4–8
Campylobacter	1.7–1	2–14
Shigella	1–25 (39)†	5–16
Salmonella	2–4	0–15
Yersinia, Vibrio, Aeromonas, C. difficile, B. fragilis	1–3	1–6
Parasites		
Cryptosporidium	2.8–4.1	4–11
Giardia	3.7	1–44‡
Strongyloides	0.2	5
E. histolytica	0.6	2–15

* Higher rates reflect hospital-based studies of children <2 years old.

† Numbers in parentheses are from studies of summer diarrhea on Indian reservations of the southwestern United States.

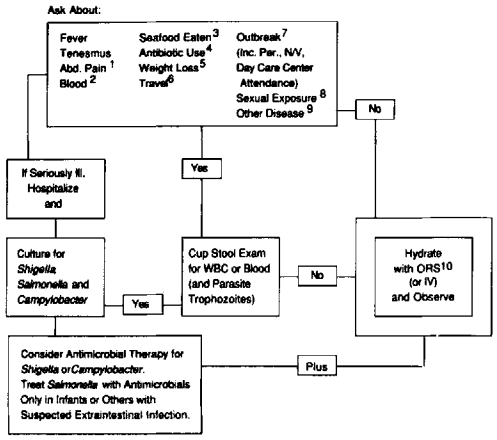
‡ In children <4 years old, the rates were 5%–20%.

tals, particularly in children in tropical, developing areas. These organisms continue to be associated with diarrhea in adult residents in these areas [56–58] and represent the most common, recognized causes of noninflammatory diarrhea in travelers to tropical, developing areas. While not a major cause of diarrhea in developed countries such as the United States or Canada, other types of *E. coli*, including enteropathogenic *E. coli*, enteroinvasive *E. coli*, and enterohemorrhagic *E. coli*, occasionally cause characteristic types of diarrhea throughout the world. Probably the most common cause of inflammatory diarrhea in developed countries is *C. jejuni* [59, 60], an organism that is also found with watery diarrhea and in asymptomatic controls in some tropical developing areas. Shigella infections are particularly common in developing countries and in developed areas where sanitation is poor, such as on Indian reservations and in child care centers. Salmonella infections, while increasingly common in the United States and in other developed countries, are relatively infrequent in developing countries. The roles of *Yersinia, Vibrio, Aeromonas* species, and *Bacteroides fragilis* vary in different clinical settings. Cytotoxin-producing *C. difficile* is well established as a cause of antibiotic-associated colitis and may occasionally cause nonantibiotic-associated diarrhea in certain settings, such as day care centers or extended care facilities [36–39]. Another cytotoxin-producing clostridial infection, that with β-toxin-producing *Clostridium perfringens* type C, is responsible for a dramatic necrotizing colitis seen following pig feasts in the highlands of New Guinea. The role of the β-toxin and protease inhibitors in this impressive illness is demonstrated in an animal model and in its prevention by active immunization against the β-toxin [61–63].

Among parasitic causes of diarrhea, *Cryptosporidium* is increasingly recognized in both developed and developing areas in immunocompetent as well as immunocompromised patients [64–69]. *G. lamblia* infections are common and are sometimes associated with weight loss and diarrhea that may last longer than 10 days. However, giardia cysts are often found in the stools of asymptomatic children after a few years of life. Whether strain differences or immunity may play a role in asymptomatic giardia infections remains to be clarified. Amebiasis may be associated with bloody or invasive diarrhea in which fecal leukocytes are often absent. Finally, the helminthic infection that is most clearly associated with enteric symptoms is *Strongyloides stercoralis*, which may persist for many years via perianal or intestinal infection and may cause the life-threatening hyperinfection syndrome in immunocompromised patients.

Selective Clues to the Microbial Etiologies of Diarrhea: A Practical Approach to Diagnosis and Management

As shown in the algorithm (figure 2), the wide variety of etiologic agents need not be exhaustively sought in every instance of the common problem of diarrhea [70, 71]. Nevertheless, specific clues should be sought for special etiologic considerations. It is both diagnostically and therapeutically useful to consider whether a diarrheal illness is inflammatory or noninflammatory, a distinction often readily made by a simple, rapid methylene blue examination for fecal leukocytes. If present, fecal leukocytes suggest an inflammatory process that may be caused by *Salmonella, Shigella* species, or *C. jejuni*, organisms that are most often sought in routine bacteriology laboratories, and may require specific antimicrobial



1. If unexplained abdominal pain and fever persist or suggest an appendicitis-like syndrome, culture for *Yersinia enterocolitica* with cold enrichment.
2. Bloody diarrhea, especially if without fecal leukocytes, suggests enterohemorrhagic (shiga toxin-producing) *E. coli* 0157 or amebiasis (where leukocytes are destroyed by the parasite).
3. Ingestion of inadequately cooked seafood should prompt consideration of *Vibrio* infections or Norwalk-like viruses.
4. Associated antibiotics should be stopped if possible and cytotoxigenic *C. difficile* considered.
5. Persistence (> 10 days) with weight loss should prompt consideration of giardiasis or cryptosporidiosis.
6. Travel to tropical areas increases the chance of enterotoxigenic *E. coli* as well as viral (ex. Norwalk-like or rotaviral), parasitic (ex. *Giardia, Entamoeba, Strongyloides, Cryptosporidium*), and, if fecal leukocytes are present, invasive bacterial pathogens as noted in the algorithm.
7. Outbreaks should prompt consideration of *S. aureus, B. cereus, Anisakis* (incubation period < 6h), *C. perfringens* (inc. per. 12-18h), ETEC, *Vibrio, Salmonella, Campylobacter, Shigella* or EIEC infection. Short inc. period also suggests metal or MSG poisoning; neurologic symptoms suggest botulism, fish, shellfish, mushrooms, pesticide. If unexplained, consider saving *E. coli* for LT, ST, invasiveness, adherence testing and serotyping, and save stool for rotavirus and stool + paired sera for Norwalk-like virus testing.
8. Sigmoidoscopy in symptomatic homosexual males should distinguish proctitis in the distal 15 cm only (caused by herpes virus, gonococcal, chlamydial or syphilitic infection) from colitis (with *Campylobacter, Shigella, C. difficile* or *Chlamydia* infections) or noninflammatory diarrhea (due to giardiasis).
9. Immunocompromised hosts should have a wide range of viral (ex. CMV, HSV, coxsackie, rotavirus), bacterial (ex. *Salmonella, Mycobacterium avium-intracellulare, Listeria*), fungal (ex. *Candida*) and parasitic (ex. *Cryptosporidium, Strongyloides, Entamoeba* and *Giardia*) agents considered.
10. ORS (oral rehydration solution) can be prepared by adding 3.5 g NaCl (or 3/4 tsp. table salt), 2.5 g NaHCO3 (or 1 tsp. baking soda), 1.5 g KCl (or 1 cup orange juice or 2 bananas) and 20 g glucose (or 4 tbsp. sugar) per liter (1.05 qt.) of clean water. This makes approximately Na 90, K 20, Cl 80, HCO3 30, glucose 111 mmol/L.

Figure 2. Approach to diagnosis and management of acute infectious diarrhea.

therapy. Other special considerations can be based on a careful history. Abdominal pain—mimicking appendicitis—may suggest *Yersinia enterocolitica* infection. The presence of unexplained bloody diarrhea should warrant the consideration of *E. histolytica* or enterohemorrhagic *E. coli* (O157 or others). A history of ingestion of raw or inadequately cooked seafood should prompt consideration of vibrio infection and of culturing the stool on TCBS agar. Diarrhea, particularly if inflammatory, that follows antibiotic use should prompt the discontinuation of antibiotic therapy, if possible, and the consideration of *C. difficile* cytotoxin as the cause. Diarrhea that persists for >10 days, particularly if weight loss occurs, suggests infection with *Giardia* or *Cryptosporidium*. Acute noninflammatory diarrhea in travelers is most likely due to enterotoxigenic *E. coli*, which usually requires diagnosis by a research laboratory. Outbreaks should be characterized in terms of incriminated food, characteristic syndrome, and incubation period to prompt specific diagnostic considerations (figure 2). Proctitis in a homosexual male should be documented by sigmoidoscopy, and if it is present in only the distal 15 cm of the colon, herpesvirus, gonococcal, chlamydial, or syphilitic infection should be suspected, in contrast to the more proximal involvement of colitis, which suggests infection with *Campylobacter, Shigella, C. difficile*, or *Chlamydia*. Noninflammatory diarrhea in this setting suggests giardiasis [72]. Finally, an immunocompromised condition should prompt consideration of viral, bacterial, parasitic, and even fungal infections, as discussed in the sections on nosocomial infections and causes of diarrhea in patients with AIDS. In any case, oral rehydration therapy is a simple, inexpensive means of managing the dehydration that occurs with practically all cases of diarrhea and may be life-saving if dehydration is severe.

In conclusion, the microbial causes of diarrhea have been elucidated to a great extent during the past two decades, and this information raises exciting opportunities for improved control of this common and often severe problem found throughout the world. Further improvements in the understanding of these microbial agents, their epidemiology, and the derangements in physiology that they cause hold promise for the development of improved therapy, epidemiologic control, and immunologic or pharmacologic control aimed at the microorganism or its virulence traits.

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