The Burden and Etiology of Diarrheal Illness in Developing Countries

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KEYWORDS

• Diarrhea • Rotavirus • *Shigella* • *Cryptosporidium* • ETEC • Gastroenteritis • Developing countries • Burden

KEY POINTS

- Diarrheal disease contributes to one in eight deaths among children younger than 5 years, most of whom reside in developing countries.
- Four pathogens are responsible for most illnesses: rotavirus, *Cryptosporidium*, *Shigella*, and ETEC.
- A single episode of moderate-to-severe diarrhea has a significant impact on mortality and linear growth among survivors during the ensuing 2 to 3 months.
- The interventions available to prevent and treat diarrheal disease in developing countries are rotavirus vaccine, oral rehydration solutions (ORS), zinc, sanitation, hygiene, and targeted antibiotic treatment of dysentery and suspected cholera.

INTRODUCTION

Diarrheal disease is characterized by the onset of loose stools with or without vomiting, which may be associated with systemic manifestations, such as fever and abdominal cramps. The term acute gastroenteritis (AGE) is often used synonymously with diarrheal disease, although it is better suited to viral etiologies, such as rotavirus and norovirus, in which vomiting is a prominent symptom. Manifestations are shaped by the pathogen, the host, and the epidemiologic setting, which lead to a range of acute, subacute, and chronic intestinal and extraintestinal complications and outcomes.

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DISEASE BURDEN

In 2015 an estimated 2.3 billion illnesses and 1.3 million deaths resulted from diarrheal disease worldwide.[1] Children younger than 5 years accounted for 40% of the diarrheal deaths even though they represent less than 10% of the world's population.[2] One in eight deaths in this age group, or a total of approximately 499,000 annually, are attributed to diarrheal disease,[1,2] 90% of which occurs in Sub-Saharan Africa and South Asia. The risk of growth faltering, ill health, and cognitive impairment increases among survivors.[3]

PATHOGENS

Table 1 describes the major viral, bacterial, and protozoal pathogens causing diarrheal disease in children.

Viral

Rotavirus is the most common cause of pediatric diarrhea. In the prevaccine era, greater than 90% of circulating human rotavirus strains globally belonged to the one of five common genotypes: G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]. In developing countries, there is greater genetic diversity and emergence of new and unusual strains.[4,5] The two genera of *Calicivirus* that cause diarrheal disease in humans are norovirus and sapovirus, each of which is further divided into genogroups and genotypes. Genetic drift among *Calicivirus* caused by point mutations and recombination events is common, resulting in emergence of antigenic variants. Since the 1990s, GII.4 norovirus has caused most infections worldwide. Among the more than 50 serotypes of adenovirus, types 40 and 41 are most often associated with diarrhea. Astroviruses that cause disease in humans belong to the *Mamastrovirus* genera (types 1–8).

Bacterial

The major bacterial enteropathogens are *Shigella*, nontyphoidal *Salmonella* (NTS), *Campylobacter*, and *Yersinia*. Four species of *Shigella* cause human disease: *S flexneri* (the major cause of shigellosis in low-resource countries), *S sonnei* (the second most common cause of shigellosis in low-income countries and the major cause in industrialized and transitional countries), and less commonly *S boydii* and *S dysenteriae*. *Salmonella* are classically divided into the human-restricted typhoidal *Salmonella* (*S typhi* and *S paratyphi* A and B), which cause enteric fever, and NTS, which contains most other serovars causing human diarrheal disease. *Salmonella typhimurium* and *Salmonella enteritidis* are the most common human NTS serovars globally. Two species of *Campylobacter* affect humans: *C jejuni* (90%–95% of infections) and *C coli*. Only 2 of the 11 species of *Yersinia* cause diarrhea in humans (*Y enterocolitica* and *Y pseudotuberculosis*). Five pathotypes of *Escherichia coli* infect humans: enterotoxigenic (ETEC), enteropathogenic, Shiga toxin-producing (also known as enterohemorrhagic) (STEC), enteroinvasive, and enteroaggregative. Pathogenic *E coli* are identified according to genotypic or phenotypic features that indicate virulence factors that they produce. There are greater than 200 serogroups of *Vibrio cholerae* but only two (O1 or O139) have been associated with epidemic cholera and cause nearly all sporadic cases. The O1 serogroup is further classified by serotype (eg, Ogawa and Inaba) and biotype (El Tor or classical). The seventh pandemic, which began in 1961 and is ongoing, is caused by *V cholerae* O1 El Tor. El Tor variants have emerged with genetic and phenotypic characteristics of classical biotype and seem more virulent.

Clostridium difficile that produce toxin are pathogenic for humans. Since 2000, a hypervirulent strain, North American Pulsed Field Type 1, polymerase chain reaction (PCR) ribotype 027 (NAP1/B1/027), has produced outbreaks of disease worldwide.[6]

Table 1
Pathogens causing diarrheal disease among children in developing countries

Agent	Clinically Relevant Species or Phenotypic, Antigenic, Serologic, or Genetic Types	
Viruses		
Rotavirus	Genotypes G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] are the predominant strains worldwide, although in low-income countries there is considerable diversity	
Calicivirus	Genera: *Norovirus*, *Sapovirus* Genogroups: *Norovirus*, GI and GII; *Sapovirus*, GI, GII, GIV, GV Genotypes: Many	
Enteric adenovirus	Enteric serotypes 40 and 41	
Astrovirus	Serotypes 1–8	
Bacteria		
Shigella (genus)	Species and number of serotypes:	• *S flexneri* (major species causing endemic diarrhea in developing countries), 15 serotypes and subtypes • *S sonnei* (second most common species causing endemic diarrhea in low-income countries) and major cause in middle and high income countries, 1 serotype • *S boydii* (uncommon), 20 serotypes • *S dysenteriae* (uncommon), 15 serotypes; *S dysenteriae* type 1 can cause pandemics
Salmonella (genus)	Species and subspecies: Serotypes:	*S enterica* • Those mainly causing enteric fever: *S* typhi, *S paratyphi* A, B, and C • Those mainly causing invasive disease in developing countries and diarrhea in middle- and high-income countries (nontyphoidal *Salmonella*): *S typhimurium*, *S enteritidis*
Campylobacter (genus)	Species:	*C jejuni* (90–95%) and *C coli*
Yersinia (genus)	Species:	*Y enterocolitica* and *Y pseudotuberculosis*
Enterotoxigenic *Escherichia coli*	*E coli* with genetic or phenotypic evidence of heat-labile toxin, and/or heat-stable toxin Colonization factor antigens (CFA/I, CFA/II, or CFA/IV)	
Shiga toxin–producing *E coli*[a]	*E coli* detected on sorbitol-MacConkey agar (presumed O157:H7) confirmed serologically, or producing Shiga toxin 1 and/or 2 (by immunoassay or polymerase chain reaction) Shiga toxin–producing serogroups other than O157 occur in 30%–50% of episodes in United States: O26, O111, O103, O121, O45, O145, and recently O104:H4 (detected at reference laboratories)	

(*continued on next page*)

Table 1
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Agent	Clinically Relevant Species or Phenotypic, Antigenic, Serologic, or Genetic Types
Enteropathogenic *E coli*	*E coli* bearing *eae* and *bfpA* (present in typical but not atypical strains), and absent Shiga toxins 1 and 2
Enteroaggregative *E coli*	*E coli* with characteristic adherence pattern to cultured HEp-2 cells or genetic elements associated with virulence (eg, *aggR* regulon, *aatA* and *aaiC*)
Enteroinvasive *E coli*	*E coli* virulence genes: *ipaH* (genes encoding proteins capable of immune modulation)
Vibrio (genus)	Species: V *cholerae* Serogroup (98% of diarrheagenic strains are O type 1 or 139) Biotypes of O1: El Tor and classical (hybrid "altered El Tor" strains have emerged Serotypes of O1: Ogawa, Inaba, and Hikojima
Clostridium difficile[a]	Classified using several molecular methods (eg, toxinotyping, ribotyping, and pulse-field typing) Hypervirulent strain NAP1/B1/027 has caused outbreaks in North America and Europe since 2000
Other[a]	*C perfringens* *Bacillus cereus* (two forms: preformed emetic toxin and enterotoxin-producing) *Staphylococcus aureus* toxin A-E
Protozoa	
Cryptosporidium (genus)	Species: *C hominus* (most common), *C parvum*
Cyclospora (genus)	Species: *C cavetanesis*[a]
Entamoeba (genus)	Species: *E histolytica*
Giardia (genus)	Species: *G intestinalis*[a]

[a] Rare cause of diarrhea or unknown burden in developing countries.

Other bacterial pathogens are common causes of foodborne illness because of their ability to produce emetic and/or enterotoxins. These include *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus.* The burden of these pathogens has not been well-documented in developing countries and they are not discussed in detail.

Protozoal

Cryptosporidium is an oocyst-forming coccidian protozoa. At least 13 of the more than 60 species have been found to cause human disease, but *C hominus*, and to a lesser extent anthroponotic strains of *C parvum*, account for most (~90%) human infections.[7] *Cyclospora cayetanesis* is another coccidian protozoa. The genus *Entamoeba* includes six species that colonize humans; *Entamoeba histolytica* is thought to be the sole pathogen causing intestinal illness. *Giardia intestinalis* (formerly *Giardia lamblia* and *Giardia duodenalis*) is a flagellate protozoan that infects the small intestine and biliary tract.

RECENT DEVELOPMENTS IN ELUCIDATING THE CAUSE AND OUTCOMES OF DIARRHEAL DISEASES IN DEVELOPING COUNTRIES

Etiology of Diarrhea in Developing Countries

Two important studies conducted during the previous decade have advanced the understanding of the burden of diarrheal disease among young children living in

developing countries. The GEMS (Global Enteric Multicentre Study) was a large, 3-year, population-based case-control study of acute, medically attended moderate-to-severe diarrhea (MSD) among children younger than 5 years living in Sub-Saharan Africa and South Asia.[3,8] Three age strata were included: 0 to 11 months, 12 to 23 months, and 24 to 59 months. The second was the MAL-ED (Malnutrition and Enteric Disease) Study of the cause, risk factors, and interactions of enteric infections and malnutrition and the consequences for child health. MAL-ED was a longitudinal community-based study with evaluation and sampling of newborn cohorts during health and acute diarrheal illnesses in eight low- and middle-income countries across Africa, Asia, and South America.[9,10] Children were followed until their second birthday.

Four major differences in the study design between GEMS and MAL-ED are notable. Similarities in study design are also worthy of mention as they allow comparisons of the findings to be made. First, GEMS used a case definition to enroll more severely ill children with blood in stool, evidence of dehydration (sunken eyes or decreased skin turgor), hospitalization, or administration of intravenous fluids. MAL-ED recruited milder cases from the community, with fewer than one-third meeting GEMS enrollment criteria. Together these studies capture the severe and less severe diarrheal diseases, which may have different etiologies. Second, GEMS sites were generally less developed; four of the seven GEMS sites and no MAL-ED sites were located in countries with the 35 highest under-5 mortality rates in 2010, so exposures and host vulnerability might differ. Third, GEMS was a case-control study in which children were visited a second time 2 to 3 months after enrollment to detect adverse outcomes. Although MAL-ED detected fewer adverse outcomes presumably because milder illnesses were captured, the longitudinal design was better suited to assess the sequence of events to determine causality and to measure disease burden over time (incidence). Both studies measured the proportion of diarrheal disease that was attributable to a broad array of pathogens, adjusting for asymptomatic detection of pathogens in controls. The end point, designated attributable fraction (AF), thus represented the proportion of cases significantly associated with diarrhea that could be prevented if an effective intervention were implemented. Finally, GEMS was conducted before introduction of rotavirus vaccine at any site, whereas three MAL-ED sites introduced vaccine before study initiation.

Across sites, most attributable cases in GEMS were caused by four pathogens (rotavirus, *Cryptosporidium*, *Shigella*, and ETEC producing heat-stable toxin [ST] alone or with labile-toxin [LT], herein termed ST-ETEC), and to a lesser extent, adenovirus 40/41.[3] Reanalysis of GEMS data using quantitative PCR (qPCR) substantially increased the AF of pathogens compared with estimates based on culture or immunoassay for key agents, such as *Shigella* and *C jejuni/coli* (two-fold), ST-ETEC (1.5-fold), and adenovirus 40/41 (five-fold).[11]

The public health importance of rotavirus in developing countries is a resounding message in GEMS. Rotavirus was the leading pathogen at every site during the first year of life, and at seven sites during the second year of life. The incidence of rotavirus among infants was more than two times higher than that seen for any other pathogen. GEMS data can be used to predict the public health impact of rotavirus vaccine introduction in developing countries. For example, a vaccine with 60% efficacy would prevent 4.2 episodes of rotavirus MSD per 100 child-years in the first year of life alone. In a low-resource African setting, such as Mali, with a birth cohort of 758,000 in 2016, this means that approximately 31,500 cases of life threatening rotavirus infection during the first year of life would be averted annually.

An unexpected observation in GEMS was the high prevalence of *Cryptosporidum* among episodes of MSD. *Cryptosporidium* ranked second among infants at all sites

regardless of human immunodeficiency virus prevalence, and third among children 12 to 23 months of age. Although recognized as a cause of diarrhea and malnutrition in Sub-Saharan Africa, the importance of this pathogen in Asia had not previously been appreciated. Moreover, children with *Cryptosporidium* in the 12-to-23-month age group had a significantly higher risk of death during the ensuing 2 to 3 months, consistent with observations of excess mortality associated with this pathogen among infants and toddlers from Guinea-Bissau 15 years earlier.[12]

GEMS also illustrated the strong contribution of *Shigella* to the MSD burden at every study site. In contrast to rotavirus and *Cryptosporidium*, whose incidence declined with age, the incidence of *Shigella* increased with age, becoming the second most common pathogen identified among children 12 to 23 months, and the leading pathogen at 24 to 59 months of age. The qPCR analysis demonstrated not only that *Shigella* was the major pathogen associated with dysentery, which was expected (AF, 63.8%), but also the second most common agent associated with watery diarrhea (12.9%). The qPCR used in this analysis was not able to distinguish *Shigella* from enteroinvasive; however, further analysis suggested that most of these strains are *Shigella* (C. Stine and J. Nataro, unpublished data).

Several pathogens were important only in Asia (*Aeromonas*) or in Asia plus Mozambique (*C jejuni/coli* and *V cholerae* O1). Historically, an association between *Aeromonas* and diarrhea has been observed inconsistently, raising the possibility that only certain species or pathotypes were capable of causing diarrhea, or that *Aeromonas* was a cotraveler with pathogens acquired by the same route. Although coinfections involving *Aeromonas* were common in GEMS, particularly with *Shigella*, the association with diarrhea persisted when the analysis controlled for the presence of other pathogens and when *Aeromonas* was the only pathogen identified in a diarrheal episode.[13] In accordance with other reports, 26% of episodes were dysenteric.[14] These provocative data deserve further investigation.

Pathogens significantly associated with MSD at only one or two sites included (1) norovirus GII and *E histolytica* among infants; (2) norovirus GII, NTS, typical enteropathogenic (EPEC), and enteroaggregative *E. coli* among children aged 12 to 23 months; and (3) norovirus GII, NTS, and sapovirus in the 24-to-59-month age group. The paucity of NTS as a cause of diarrhea in developing countries deserves special mention. During the past several decades, distinct clones of NTS that have arisen in Sub-Saharan Africa are a frequent cause of often-fatal bloodstream infection in young children (particularly those with coincident malaria or malnutrition) and in adults infected with human immunodeficiency virus. In contrast to most NTS elsewhere, these strains do not seem to arise from zoonotic reservoirs and seldom cause diarrheal disease. A common feature involves high levels of genetic degradation (a characteristic of *S typhi*), rather than acquisition of new virulence factors.[15]

At least three pathogens are notable for their absence as a cause of MSD. First, STEC, a zoonotic infection that causes sporadic cases and outbreaks of diarrhea and hemorrhagic colitis linked to hemolytic uremic syndrome in high-income countries, was not found in any site. Second, ETEC strains producing LT only were not associated with diarrhea. This may be because LT-only ETEC produce less severe disease.[16] Third, *Yersinia*, generally found in cool climates, has occasionally been reported to occur in developing countries[17] but was not detected in either GEMS or MAL-ED.

Interestingly, *Giardia* was not associated with MSD but instead was found significantly more often in control subjects than in cases 12 to 59 months of age at most sites. This interesting finding has been observed by others[18] and suggests the hypothesis that in developing countries *Giardia* may actually interfere with the pathogenic mechanisms of other enteric pathogens. Along the same lines, one wonders whether

Giardia is a factor associated with suboptimal colonization and immune responses to live enteric vaccines that is commonly seen in developing countries.

In MAL-ED no pathogen exhibited a high AF in all individual sites. When an AF for all sites combined was calculated, the most common agents associated with diarrhea, in descending order, were norovirus GII, rotavirus, *Campylobacter*, astrovirus, and *Cryptosporidium* during infancy and *Campylobacter*, norovirus GII, rotavirus, astrovirus, and *Shigella* during the second year of life.[10] Rotavirus had the highest AF for sites without vaccine introduction and the fifth highest AF fraction for sites with vaccine introduction. During infancy, the AF in sites without vaccine introduction ranged from 3.2% to 9.6% compared with 16.3% to 27.8% in GEMS. These differences may reflect the observed trend for rotavirus to be identified with increasing frequency as the severity of illness increases; the clinical venue where cases are identified (community vs health center or hospital) is thought to be a proxy for disease severity.[19]

At first glance, it seems that norovirus GII played a leading role in MAL-ED, which is at odds with the GEMS results.[20] However, close examination reveals that norovirus GII has the highest AF during infancy in MAL-ED and the second highest during the second year of life for all sites combined. When sites were examined individually, however, norovirus GII was associated with diarrhea at only three sites during infancy and three sites during the second year of life. Two sites where norovirus GII predominated had introduced rotavirus vaccine, thus increasing the relative proportion of norovirus disease. In GEMS, norovirus GII was significantly associated with MSD in The Gambia (all age groups) and India (12–23 months old). The lack of association of norovirus with diarrhea at some sites in GEMS and MAL-ED was caused by high rates of asymptomatic carriage[21]; considerable geographic diversity in the prevalence of norovirus GII also contributed. Factors that might influence this diversity include geographic differences in the prevalence of genetic factors that mediate virus binding, which are less common in certain African and Latin American populations.[22,23] Temporal variations in the prevalence and severity of disease are seen when strains mutate in the hypervariable regions of the capsid genes resulting in emergence of new strains. GEMS and MAL-ED may have underestimated the burden of norovirus by excluding children who present with vomiting alone. Finally, GEMS may have captured less norovirus diarrhea because it produces a less severe illness.

As with norovirus, *Campylobacter* was identified in most children in MAL-ED by 1 year of age.[24] Despite high prevalence and high AFs for diarrhea when all sites were combined, infection was associated with diarrhea at only a few sites. Both norovirus and *Campylobacter* were associated with subsequent linear growth faltering in MAL-ED.

Outcomes of Moderate-To-Severe Diarrhea

An observation in both GEMS and MAL-ED was the geographic heterogeneity of pathogens. Nonetheless, both studies found rotavirus, *Shigella*, *Cryptosporidium*, and ST-ETEC to be associated with diarrhea in multiple sites. The widespread prevalence and high incidence of these four pathogens suggest that they should be prioritized for development and implementation of interventions to reduce the diarrheal disease burden.

EPIDEMIOLOGIC PATTERNS

Insufficient access to adequate hygiene, sanitation, and clean drinking water are the major risk factors for the heavy burden of diarrheal diseases in developing countries. Intrinsic properties of organisms that promote transmission include a low infectious dose, which enables person-to-person spread usually by the fecal-oral route without a food or water vehicle (eg, norovirus, *Shigella*, and *Cryptosporidium*). Other

properties that promote transmission are bioavailability as conferred by a high level and/or prolonged fecal shedding, extended infectivity in the environment, and/or a large environmental or animal reservoir (eg, *Cryptosporidium*, *Giardia*, *Campylobacter*, *S typhi*), resistance to disinfection (eg, norovirus and *Cryptosporidium*), and the ability to circumvent immune surveillance (eg, the frequent antigenic changes of norovirus resulting from recombinational events). Organisms with higher infectious dose (eg, ETEC, *V cholerae*, *S typhi*, NTS) generally require a contaminated food or water vehicle. Exposure to animals or animal products may be important in some settings (eg, NTS in the United States) but not others (eg, NTS in developing countries, where source of transmission is unclear).[25] The more complex the pathogenesis, the longer the incubation period. At one end is AGE resulting from preformed toxin, such as *B cereus* and *S aureus* (12–24 hours), followed by most other viral and bacterial pathogens that generally require epithelial attachment or invasion sometimes followed by elaboration of toxins (1–5 days), and then protozoa that require excystation and phased development (1–4 weeks).

Host characteristics are also important. Most pathogens show an age predilection. The incidence of rotavirus and *Salmonella* are highest in infancy; in unvaccinated populations, nearly all infants experience at least one rotavirus infection by 24 months of age. Endemic shigellosis peaks in 1 to 4 year olds, whereas *Campylobacter* and *Cryptosporidium* show a bimodal distribution with the greatest number of reported cases in infants and young children and in young adults. Pandemic *V cholerae* and *S dysenteriae* type 1 emerge in immunologically naive populations and produce high attack rates and mortality in all age groups, and often affect displaced persons in emergency settings. Some agents (eg, NTS, *Shigella*, *Campylobacter*, *Yersinia*, and *Cryptosporidium*) are more frequent and more severe when the host is immunocompromised or malnourished.

CLINICAL EVALUATION

Diarrhea is usually defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Frequent passage of formed stools is not diarrhea, nor is the passing of loose, "pasty" stools by breastfed babies. Mothers generally know when their children have diarrhea.

Clinical Symptoms According to Etiology

The clinical history is used to categorize a diarrheal episode into one of three clinical syndromes that have different (albeit overlapping) etiologies, outcomes, and treatments: (1) acute (nonbloody) diarrhea, (2) bloody diarrhea or frank dysentery (the frequent passage of scant stools containing blood with or without mucus, often accompanied by fever, lower abdominal cramps, and rectal tenesmus), and (3) persistent diarrhea (lasting more than 14 days). Profuse watery diarrhea is a subset of acute watery diarrhea that should raise suspicion for cholera.

Although there is considerable overlap, high fever greater than 40°C, overt fecal blood, abdominal pain, no vomiting before diarrhea onset, and high stool frequency (>10 per day) are more common with bacterial pathogens. High fever and overt fecal blood are often absent in bacterial enteritis, but when present, there is a high probability of a bacterial cause. Viral illnesses often begin with vomiting followed by frequent passage of watery nonbloody stools, associated with fever in about half the cases. Recovery with complete resolution of symptoms generally occurs within 7 days. Although disaccharide malabsorption is found in 10% to 20% of viral episodes, it is rarely clinically significant. A protozoal cause should be suspected when there is a prolonged diarrheal illness characterized by episodes of sometimes-explosive diarrhea with

nausea, abdominal cramps, and abdominal bloating. The stools are usually watery, but can be greasy and foul smelling because of concomitant malabsorption of fats, which is more likely to occur if the parasite load is high. Occasionally diarrhea may alternate with constipation. Although infection with *E histolytica* causes the typical syndrome of protozoal diarrhea (known as intestinal amebiasis), a range of other syndromes may occur, including amebic dysentery and hepatic amebiasis. Amebic dysentery is characterized by bloody or mucoid diarrhea, which may be profuse and lead to dehydration or electrolyte imbalances or prolonged. Hepatic amebiasis is limited to abscess formation in the liver, which may occur with or without intestinal disease.

Defining Dehydration Severity

Classification of the severity of dehydration is used to guide rehydration therapy. The World Health Organization (WHO) guidelines simply use none, some, and severe dehydration (**Table 2**). Vital signs, weight, and length should be measured. The child's

Table 2
Classification of dehydration

Type of Dehydration	Signs	Fluids and Food Management
No dehydration	Signs of some or severe dehydration are absent	• Extra fluids at home • Continued breastfeeding • Normal diet of foods
Some dehydration	Two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly	• ORS for 4 h at the health center ○ Continued breastfeeding ○ Teach mother how to prepare ORS at home • After 4 h ○ If still some dehydration ■ Repeat ORS ■ Refeed with age-appropriate, unrestricted diet[a] ○ If rehydrated, follow steps for no hydration ○ If severe dehydration develops at any time follow steps below
Severe dehydration	Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly	• Rapid intravenous rehydration • Switch to guidelines for some dehydration when improved

Abbreviation: ORS, oralrehydration.

All children with diarrhea should be treated with zinc for 10–14 days. The daily oral dose is 10 mg for infants ≤6 months and 20 mg for older infants.

[a] Recommended foods are those containing complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables.

Specific guidelines for administration of ORS and intravenous rehydration can be found in World Health Organization. Handbook: IMCI integrated management of childhood illness. 2005. Available at: http://www.who.int/maternal_child_adolescent/documents/9241546441/en/. Accessed March 22, 2012; and World Health Organization. Pocket book of hospital care for children: guideline for the management of common illnesses with limited resources. 2005. Available at: http://whqlibdoc.who.int/publications/2005/9241546700.pdf. Accessed December 11, 2013.

nutritional status should be carefully evaluated and addressed as part of the management plan. The presence of lethargy, level of consciousness, and restlessness or irritability that interferes with feeding should be documented. The child should be offered fluid to see whether he or she is thirsty or drinks poorly. Hyperpnea (deep, rapid breathing) suggests acidosis secondary to dehydration, whereas respiratory distress (tachypnea, grunting, nasal flaring, head bobbing, and retractions) suggests pneumonia. Skin turgor is assessed by pinching a small skin fold on the lateral abdominal wall at the level of the umbilicus. If the fold does not promptly return to normal after release, the recoil time is quantified as delayed slightly or greater than or equal to 2 seconds. Note that excess subcutaneous tissue and hypernatremia may result in a false-negative test and malnutrition can prolong the recoil time.

Other signs of dehydration that have been found to be valuable include capillary refill time and hyperpnea,[26] recognizing that these have not been incorporated into the WHO algorithm. Capillary refill time is assessed by applying moderate pressure for 5 seconds to the nailbed of the child's distal fingertip, with the child's arm above heart level, until blanching occurs. When dehydration is present, the time elapsed until normal color is restored after release usually exceeds 3 seconds. Sunken fontanelle, dry mucus membranes, decreased urination, and crying without tears can also be seen in dehydrated infants and children.

Most episodes of dehydration are isonatremic. Serum electrolyte measurements, if available, should be reserved for children with severe dehydration, or children with some dehydration with suspected electrolyte abnormalities, such as when there is a history of frequent watery stools yet the skin pinch feels doughy without delayed recoil, suggesting hypernatremia, or inappropriate rehydration fluids have been administered at home. A blood culture should be obtained, if possible, for infants and children with fever and/or blood in the stool who are younger than 3 months, are immunocompromised, and have hemolytic anemia or other risk factors for bacteremia. A complete blood count, peripheral smear, serum electrolytes, and renal function tests are indicated when hemolytic uremic syndrome is suspected.

COMPLICATIONS

The major complications of diarrhea from any cause (**Table 3**) are dehydration and electrolyte abnormalities. At the extreme is cholera gravis, manifesting as rice water stools, vomiting, and leg cramps, which can lead to hypovolemic shock and death within hours. Bacterial diarrheal has been associated with a variety of intestinal and extraintestinal complications. The complications included in this category generally represent either end-organ damage that results directly from the infectious process and its extension to other sites, unusual manifestations of infection, or postinfectious immune-mediated events. *Shigella* is likely the major culprit with its ability to cause toxic megacolon, intestinal perforation, rectal prolapse, bacteremia (usually in immunocompromised or malnourished children), seizures, or encephalopathy. Hemolytic uremic syndrome can result from *S dysenteriae* type 1 and STEC.

Immune-mediated complications that are thought to result from immunologic cross-reactivity between bacterial antigens and host tissues are more often seen in adults than children. These include reactive arthritis following infection with the classical bacterial enteropathogens believed to be rare in developing countries at least in part because of the low prevalence of the HLA B27 haplotype,[27] and Guillain-Barré syndrome following *Campylobacter* infection.[28]

Table 3
Intestinal and extraintestinal complications of enteric infections

Complications, by Site and Time Frame	Major Causes
Intestinal complications	
Toxic megacolon	*Shigella*, *Clostridium difficile*, *Entamoeba histolytica*
Intestinal perforation	*Shigella*, *Yersinia*, *C difficile*, *E histolytica*
Rectal prolapse	*Shigella*, STEC, *C difficile*
Persistent diarrhea	All causes
Recurrent diarrhea (usually immunocompromised persons)	*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C difficile*
Extraintestinal complications	
Dehydration and metabolic disturbances, malnutrition, micronutrient deficiency	All causes
Bacteremia with distant infectious foci	*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C difficile*
Pseudoappendicitis (older children and adolescents)	*Yersinia* (rarely *Campylobacter*)
Exudative pharyngitis, cervical lymphadenopathy	*Yersinia*
Postinfectious complications	
Reactive arthritis[a]	NTS, *Shigella*, *Yersinia*, *Campylobacter*
Glomerulonephritis, myocarditis, pericarditis	*Campylobacter*
Guillain-Barré or Miller Fisher syndrome	*Campylobacter*
Hemolytic uremic syndrome	STEC, *Shigella dysenteriae* type 1
Seizure or encephalopathy	*Shigella*
Erythema nodosum or other rash	*Yersinia*, *Campylobacter*, *Salmonella*

Abbreviation: STEC, Shiga-toxin producing *E. coli.*

[a] Arthritis can be seen alone or as part of a constellation of arthritis, conjunctivitis, uveitis, and urethritis and is rare in developing countries.

DIFFERENTIAL DIAGNOSIS

The infectious causes of watery and bloody diarrhea, and the noninfectious causes that should be considered in the differential diagnosis, are shown in **Table 4**. One entity that should be considered in particular when children younger than 3 years of age present with bloody stools is intussusception. The typical presentation of intussusception is the sudden onset of intermittent abdominal pain accompanied by crying and drawing legs up to abdomen, sometimes followed by vomiting. The stools often have the appearance of "currant jelly." Pain may become constant and severe over time. Initially the child is normal between episodes. A sausage-shaped mass may be palpable in the right side of the abdomen. Vigilance for intussuception is important because delay in diagnosis increases mortality, which can exceed 25% in developing country settings.

TREATMENT

Rehydration and Refeeding

The reader should refer to guidelines published by WHO for the management of diarrheal disease in children living in developing countries. The *Integrated Management of Childhood Illness* describes methods for prevention and management of diarrheal

Table 4
Infectious and noninfectious etiologies of diarrheal syndromes in infants and children

Clinical Presentation	Major Causes
Watery diarrhea	
Infections	Viruses (rotavirus, adenovirus 40/41, calicivirus, astrovirus) Bacteria (ETEC, EPEC, STEC, EAEC, EIEC, *Vibrio cholerae*, *Shigella*, NTS, *Campylobacter*, *Yersinia*, *Clostridium difficile*) Protozoa (*Cryptosporidium*)
Noninfectious causes	Metabolic (hyperthyroidism), food intolerance, medications (especially antibiotics), celiac disease
Bloody diarrhea/bloody stools	
Infections	Bacteria (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C difficile*, *Aeromonas*, STEC, EIEC) Protozoa (*Entamoeba histolytica*) Necrotizing enterocolitis (newborns)
Noninfectious causes	Inflammatory bowel disease Meckel diverticulum, intestinal polyps (usually painless rectal bleeding) Intussusception (intermittent crampy pain with "currant jelly" stools)
Chronic or relapsing diarrhea	
Infections	Intestinal protozoa, 10%–20% of all infectious diarrhea
Noninfectious causes	Cystic fibrosis, celiac disease, milk protein intolerance, congenital or acquired disaccharidase deficiency
Vomiting with or without abdominal pain	
Infections	Viruses (norovirus, rotavirus, adenovirus 40/41), astrovirus
Noninfectious causes	Pyloric stenosis, intestinal obstruction, pancreatitis, appendicitis, and cholecystitis

Abbreviations: EAEC, enteroaggregative; EIEC, enteroinvasive; EPEC, enteropathogenic; ETEC, enterotoxigenic; STEC, Shiga-toxin producing *E. coli*.

diseases at home and at outpatient facilities with limited diagnostic tools and medications.[29] Guidelines for inpatient management of children who reach a referral center are found in the *Pocketbook of Hospital Care for Children*.[30] A brief summary of the general principles of rehydration is provided in **Table 2**. Two situations require special attention. Children with severe acute malnutrition and those with persistent diarrhea and signs of dehydration require prompt hospitalization and treatment according to the guidelines that are outlined in the WHO guidelines. Specific feeding regimens are recommended for children with persistent diarrhea with or without associated dehydration.[30]

Zinc and Ancillary Treatments

WHO recommends that all children with diarrhea should be treated with zinc for 10 to 14 days. The daily oral dose is 10 mg for infants less than or equal to 6 months and 20 mg for older infants. Zinc replacement reduces the duration and severity of the episode and lowers the risk of diarrhea in the following 2 to 3 months. The following agents are *not* recommended for use in children: antimotility agents (eg, loperamide, or difenoxylate and atropine), antisecretory agents (eg, bismuth subsalicylate), and agents designed to adsorb toxins and water (kaolin and pectin).

Antibiotics

Judicious use of antibiotics is recommended for specific indications (**Table 5**). For acute diarrheal diseases, these indications are limited to dysentery and suspected

Table 5
Antibiotic treatment of diarrhea

Syndrome/Indication	Management
Dysentery	
Local susceptibility known	Follow local guidelines
Local susceptibility unknown	
First line	Ciprofloxacin, 15 mg/kg PO twice a day for 3 d
Second line (severely ill)	Ceftriaxone, 50–80 mg/kg/d IV or IM for 3 d
Not improved after 2 full days of antibiotics	• Stop first-line treatment • Look for other conditions • Choose one of the following ◦ An antibiotic known to be effective against *Shigella* in the area; OR ◦ Azithromycin, 20 mg/kg PO for 3 d or; OR ◦ Cefixime, 8 mg/kg/d PO for 3 d
Not improved after 2 more days of antibiotics	• Stop the previous antibiotic • Look for other conditions • Metronidazole, 10 mg/kg PO 3 times a day for 5 d if amebiasis is possible
Cholera: if child is 2 y or older, has severe dehydration, and there is cholera in the area	
Local susceptibility known	Follow local guidelines
Local susceptibility unknown	Choose one of the following • Erythromycin estolate, 12.5 mg/kg PO 4 times a day for 3 d; OR • Ciprofloxacin, 15 mg/kg PO twice a day for 3 d; OR • Azithromycin, 20 mg/kg PO for 3 d

Abbreviations: IM, intramuscularly; IV, intravenously.

Adapted from Pocket book of hospital care for children: guideline for the management of common illnesses with limited resources. 2005. Available at: http://whqlibdoc.who.int/publications/2005/9241546700.pdf. Accessed December 11, 2013.

cholera (see **Table 4**). Use outside of these indications is discouraged for several reasons. For one, most episodes of diarrhea are viral and thus self-limited. Second, the increasing prevalence of antibiotic resistance has prompted restrictions in promiscuous use of these drugs. Third, antibiotics may actually worsen outcome in some circumstances, such as in STEC infection antibiotics may increase the risk of hemolytic uremic syndrome, and in NTS they may prolong excretion and increase relapses.

PREVENTION

There are four strategies that are readily implemented by the clinician for prevention of diarrhea and its complications: (1) vaccination, (2) ORS, (3) zinc, and (4) hygiene (particularly handwashing). We are on the cusp of a dramatic shift in the epidemiology of pediatric diarrheal diseases since rotavirus vaccines became available and were recommended for routine immunization of all infants by WHO and the national regulatory authorities of numerous high- and middle-income countries. Three live oral vaccines are now licensed: the three-dose pentavalent G1, G2, G3, G4, P[8] human-bovine vaccine (RotaTeq); the two-dose monovalent human G1P[8] vaccine (ROTARIX); and the three-dose monovalent human-bovine 116E G6P[11] vaccine (Rotavax). In high- and middle-income countries, vaccine introduction has resulted in substantial reductions in rotavirus-associated and all-cause hospitalizations for diarrheal disease in vaccinated infants (direct protection) and unvaccinated individuals

(indirect, or herd protection)[31]; in addition, substantial declines in less severe disease are demonstrated by reductions in office visits for rotavirus diarrhea.[32] Reductions in all-cause diarrhea deaths have been observed in Mexico and Brazil.[33,34] That norovirus has become the most common enteropathogen identified in US children hospitalized with AGE since the introduction of rotavirus vaccine provides a powerful illustration of the impact that rotavirus vaccines will have on the global epidemiology of pediatric diarrheal disease in the decades to come.

Programmatic uptake is lagging in low-resource settings where most severe disease and death occurs; however, Gavi, the Vaccine Alliance, a global health partnership that promotes vaccine access for the world's poorest countries, has supported introduction of rotavirus vaccine into approximately 40 countries. Lower point estimates of vaccine efficacy observed in clinical trials and in vaccine effectiveness during "real life" programmatic use in these settings (51%–64%) demonstrate smaller reductions in disease incidence compared with that seen in wealthier countries (85%–98%)[35,36]; however, with broad coverage, the life-saving potential is predicted to be substantial. The cause of hyporesponsiveness to oral vaccines in less-developed countries is unknown. Several avenues under investigation include small intestinal bacterial overgrowth, intestinal microbiome composition, genetic factors mediating pathogen attachment, coinfection with intestinal helminths or *Helicobacter pylori*, environmental enteropathy often accompanied by undernutrition, and micronutrient deficiency. Recent data on rotavirus vaccine suggest that improved efficacy may result from delaying the first dose to 8 to 10 weeks of age, which presumably minimizes interference of maternal antibody.[37] Investigators at the University of Maryland School of Medicine are assessing the impact of vaccine introduction on the incidence and cause of diarrhea in Sub-Saharan Africa. There is renewed interest in developing other vaccines against other enteric infections, including *Shigella* and ETEC, because the burden of disease has been better defined.

SUMMARY

Diarrheal diseases continue to cause substantial morbidity and mortality in developing countries. Four pathogens (rotavirus, *Shigella*, ST-ETEC, *Cryptosporidium*) contribute to most of the burden of diarrhea in developing countries. Efforts are needed to improve uptake of existing interventions (rotavirus vaccine, zinc, ORS) and to develop new methods that target the major causes of disease.

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