13 Diarrhea and Other Gastrointestinal Diseases

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CONTENTS

KEY POINTS

- Diarrheas and gastrointestinal infections are a leading cause of childhood morbidity and mortality in developing countries.
- Undernutrition increases diarrheal morbidity by increasing the incidence, severity, and duration of infections.
- Increased diarrheal morbidity occurs with undernutrition primarily caused by impaired cellular immunity.
- The pathophysiology of diarrheal episodes is dependent on the infectious agent.
- Micronutrient supplementation, especially zinc and vitamin A, can have an important role in providing adjuvant therapy for diarrhea.
- Infectious gastrointestinal diseases may not cause diarrhea, but can continue to affect the immune system and, therefore, indirectly increase the onset of acute diarrhea.

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- Impaired immune status, particularly cellular immunity, is a major risk factor for persistent diarrhea.
- Probiotics have an important role in the prevention and treatment of diarrheal diseases.
- Only a limited number of vaccines are available against agents that cause infectious diarrhea.

Introduction

Infectious diarrheas and gastrointestinal diseases are leading causes of childhood morbidity and mortality in developing countries. More than 1.4 billion cases of diarrhea occur each year leading to about 3 million deaths, most in children under 2 yr of age living in developing countries. A greater severity of diarrhea is often associated with reduced nutritional status and an impaired immune response. Persistent diarrhea can occur in 3–23% of all diarrheal episodes and accounts for about 40% of diarrheal-related deaths.

This chapter discusses the bidirectional interaction between nutritional status and gastrointestinal infections and the accompanying immune system response. Many intestinal infections are causative agents for diarrhea. However, many of the organisms that infect the intestinal tract do not overtly cause diarrhea, but their presence affects the body's immune system leading to comorbid conditions. The associations between nutritional status and the immune status presented in this chapter relate to those found among children living in developing countries, although they do reflect the physiological responses in all children.

Diarrhea and Gastrointestinal Infections

Various definitions can be used for diarrhea *(1)*. The quantitative definition is a stool volume greater than 10 mL/kg/d. The clinical definition for acute diarrhea is a report of three or more loose or watery stools within a 24-h period. In both cases, the consistency of the stools is not firm. The severity of diarrhea can be determined by an increase in the total volume of stool produced or the number of stool movements in a 24-h period. The presence of steatorrehea (fatty stools), mucus, dysentery (blood), and the degree of dehydration are additional criteria for defining the severity of diarrheas. A diarrheal episode ends when the symptoms have stopped for at least 24 h.

Persistent diarrhea is defined as diarrhea that had an acute start, occurs for 14 or more consecutive days, is presumed to be caused by an infectious agent, and is not responsive to appropriate treatment. Undernutrition, including micronutrient deficiency, particularly zinc and vitamin A, impaired cell-mediated immunity, and not exclusively breastfeeding during the first 4 mo of life are risk factors for developing persistent diarrhea *(2)*. The organisms associated with persistent diarrhea are usually different to those that started the initial

Table 1
Leading Causes of Diarrhea and Gastrointestinal Infections

Viruses	**Protozoa**
Rotavirus	*Entomoeba histolytica*
Adenovirus	*Giardia lamblia*
Astrovirus	Cryptosporidium
Calicivirus	*Isospora belli*
Cytomegalovirus	*Balantidium coli*
Torovirus	Cryptosporidium
Enteric Coronavirus	Microsporidium
Picobirnaviruses	
	Helminthes
Bacteria	*Ascaris lumbricoides*
Escherichia coli	*Trichuris trichuria*
Salomonella typhi	Hookworms
Shigella spp	*Stronglyloides stercoralis*
Clostridium difficle	
Vibrio cholerae	
Campylobacter	
Yersinia	
Aeromonas	
Plesiomonas	
Edwardsiella	

episode of acute diarrhea. This strongly suggests that children whose immune status is compromised during the initial episode of acute diarrhea are vulnerable to other infectious agents becoming established in the gastrointestinal tract. Once this happens, trauma to the intestinal epithelial tissues continues. Nutritional status and the cellular immune response deteriorate further, and persistent diarrhea becomes established.

Many different infections cause diarrhea. The most common include viral, bacterial, and protozoan infections that are normally present in the gastrointestinal tract (*see* Table 1). However, diarrhea can also be caused by infectious agents that are not usually associated with the gastrointestinal tract, such as malaria, and by noninfectious states such as celiac disease, allergic enteropathies, tropical sprue, and hereditary disorders. The epidemiology of infectious agents that cause diarrheas varies throughout the world. Rotavirus is the major viral agent and responsible for about 140 million diarrheal cases and 900,000 deaths/yr *(1)*. The incidence of rotavirus infections peaks between 6 and 24 mo of age. However, other viruses also contribute significantly to diarrheal epi-

sodes and these include Norwalk-like viruses, adenoviruses, caliciviruses, retroviruses, and astroviruses. The toxins produced as a result of viral infections can have a direct effect on the enteric nervous system that control peristalsis and stimulate epithelial cells to secrete more water *(3)*, and it is hypothesized that this mechanism may also occur with bacterial infections such as cholera and infections with *Escherichia coli* (*E. coli*). If so, it may be possible to direct interventions at the enteric nervous system to decrease the amount of water lost in the increased volume of stools that is produced in many diarrheas.

The most common bacterial causes of diarrheas include *Shigella* bacteria and the intestinal toxin producing *E. coli*. Five strains of *E. coli* cause diarrhea: enterotoxigenic *E. coli*, enteroinvasive *E. coli*, enterohemorrhagic *E. coli*, enteropathogenic *E. coli*, and enteroaggregative *E. coli*. Each *E. coli* has its own mechanism of damaging epithelial tissue. The combined infections from *Shigella* and *E. coli* account for nearly 1 billion cases of diarrhea and 1.4 million deaths each year. *Vibrio cholerae* is also a leading cause of diarrhea accounting for 7 million cases and more than 100,000 deaths/yr *(4)*. Although there are often large outbreaks of cholera, the case mortality rates for cholera have decreased during the last decade *(4)*. *Clostridium difficile* is a spore-forming toxigenic bacterium that also causes diarrhea, but the proportion of diarrheas in the world caused by its occurrence is unknown as it most often occurs after a course of broad-spectrum antibiotics.

Protozoa and helminthes are the major intestinal parasitic infections associated with diarrhea. Protozoa are more commonly associated with diarrhea, but helminthes independently affect nutritional status and alter the anatomy and physiology of the gastrointestinal tract, making them important comorbid infections that increase the risk for diarrhea. Other parasitic infections that do not harbor in the gastrointestinal tract can also cause diarrhea, such as visceral leishmaniasis. The modes of action of intestinal parasitic infections are very different to those of viruses and bacteria, and they can also differ among each other. For example, *Entomoeba histolytic*, the infectious agent for amebic dysentery, is more likely to invade the intestinal epithelium causing traumatic damage to the intestinal lining and disrupting intestinal functions. In contrast, the protozoan *Giardia lamblia* is less invasive although it too can cause trauma to the intestinal lining. Diarrhea associated with *G. lamblia* leads to poor absorption and steatorrhea because the protozoa can attach themselves to the intestinal epithelial and, in sufficiently large numbers, they decrease the area available for digestion and absorption. Electron micrographs showed that *G. lamblia* can also change the microflora of the gastrointestinal track and create an environment that is favorable for more pathologic organisms *(5,6)*. Other diarrheal

causing protozoa, such as cryptosporidium and microsporidium, are usually only present in children who have a reduced immune status.

Intestinal helminthes, such as hookworm and trichuriasis, can damage the epithelial wall without causing acute diarrhea. However, the ensuing blood loss lowers the body's immune response to infection as a result of the loss of iron and other nutrients and may be one of the reasons that helminthes may increase the risk for diarrhea *(7,8)*. Similarly, infections with *Ascaris lumbricoides* (roundworm) may affect nutritional status notably vitamin A by shortening transit time and decreasing the absorption of fat and fat-soluble vitamins possibly as a result of damage to the gut wall *(9,10)*. Intestinal helminthes are important comorbid infections along with other diarrheal causing agents.

The parasitic disease–diarrhea–nutritional status triad is a good example of the different ways that infections can alter nutritional status. Parasitic infections can decrease nutritional status, and thus the cellular immune response, through at least four distinct mechanisms *(11)*: They can cause anorexia thereby reducing the availability of nutrients; increase the utilization and excretion of nutrients; several can effectively compete and sequester essential nutrients from their host; and, in adults, the infections can affect an individual's work capacity or productivity which, in turn, can limit their purchasing power thereby lowering the availability of nutrients for consumption by both the individual and their families.

Immune Response to Persistent Diarrhea

A cell-mediated immune response involving T-helper (Th) cells is responsible for providing the primary resistance against viral, bacterial, and protozoan and intracellular parasites. However, cell-mediated antibody-dependent immunity through a second type of Th cell is the primary immune response to extracellular parasites such as helminthes *(12)*. In helminth infections, the Th2 cells secrete a series of interleukins (IL) that promote the production of IgE and IgG1. However, the cell-mediated Th cells produce interferon (IFN)-γ and IL-2 to promote macrophage activity and the production of IgG2a, IgG2b, and IgG3. Both systems can be affected by nutritional status and it is important to recognize that the gastrointestinal tract is the body's first level of defense against invasive organisms. Therefore, studying the response of the intestinal immunity against infectious agents with changes in nutritional status provide a model for understanding nutrition-immunity interactions.

Studies on helminth infections have indicated that undernutrition is associated with a decrease in Th2 cell responses including IgE, and parasite-specific IgG *(12)*. Furthermore, a deficit in zinc and energy intakes may suppress specific cellular responses *(13,14)*. More importantly, studies on nematodes have

shown that in laboratory animals each nutrient may have its own role in modifying immune responses and is dependent on the nutrient, the infectious agent, and the location of the infection *(12)*.

Early exposure to infections may play an important role in decreasing a healthy child's risk of future diarrheal episodes. Lymphocyte subsets in children with greater exposure to gastroenteritis have peripheral blood lymphocyte profiles that are more similar to adults than children who have fewer episodes of gastroenteritis. In particular, several studies have indicated that early exposure increase the proportion of CD4 cells that display a memory phenotype *(15)*. The increased number of memory T-cells was similar to adult levels in these children who ranged from 6 mo to 3 yr of age. Furthermore, the increased number of memory $CD4^+$ T-cells occurred in children with acute diarrhea and not in children with upper respiratory infections, but this difference disappeared as children become older (closer to 3 yr of age). It may be possible that children who are undernourished early in life are not able to rapidly develop the memory cells and this places them at risk for future infections. Thus, early and controlled exposure to potential infectious agents is important when a very young child has a good nutritional status and responsive immune system. Early undernutrition in the first year of life may increase the risk for diarrheal mortality over a period of time.

Persistent diarrhea is associated with severe morphological changes in the microvilli as well as the permeability of the small intestine. Several studies in the Gambia showed that children with persistent diarrhea had chronic cell-mediated enteropathy, a high number of intraepithelial lymphocytes and an increased number of activated T cells, and a decreased number of B-cells *(16)*. Studies in Bangladesh have looked at the immune response of children who developed persistent diarrhea following acute diarrhea caused by rotavirus infection *(17)*. Among all the observed parameters for the cellular immune response, only an elevated IFN-γ level was associated with the development of persistent diarrhea compared with acute diarrhea. However, only 29 of the 149 children with an initial diarrhea were diagnosed with rotavirus and only 10 of these children developed persistent diarrhea. More studies are needed to determine which immune reactions play the major roles in the development of persistent diarrhea.

Expanding the Undernutrition-Diarrhea Interaction Paradigm

The association between undernutrition and diarrhea can be a vicious cycle. Simply stated, poor nutritional status increases a child's susceptibility to infection and infection decreases a child's nutritional status. This cycle continues until there is a successful intervention. The use of appropriate nutrition interventions can be an important adjuvant to conventional therapies during diar-

Table 2
Nutrition Interventions As an Adjuvant to Diarrhea Prevention and Treatment

Nutrition Intervention	Results
Zinc	Decrease duration and severity of acute and persistent diarrhea with doses of 20 mg/d
Iron	Parenteral administration is life-threatening. Iron supplement in nonmalarial areas may be beneficial for lowering the risk of diarrhea in nonbreastfed infants. However, nondiscretionary iron supplementation may slightly increase the risk of diarrhea. Breastmilk has greater advantages compared with iron-fortified formula for preventing diarrhea
Vitamin A	Supplements decrease the severity of diarrheal episodes and diarrhea case-fatality rates. However, equivocal results exist regarding vitamin A supplementation on the incidence of diarrhea
Protein and Energy	Decreased wasting and stunting associated with lower incidence, severity, and duration of diarrhea primarily through improved cellular immunity
Probiotics	Consumption of specific lactic acid producing organisms reduces the incidence of diarrheal infections by as much as 50%

rheal episodes. Thus, nutrition interventions need to be included in the current undernutrition-diarrhea paradigm (*see* Fig. 1). A variety of interventions have now been studied (*see* Table 2) including the use of micronutrients and probiotics.

Poor nutritional status is not only related to the onset of an initial diarrheal episode, but also to the severity of the episodes and the duration of the diarrheal episode including the development of persistent diarrhea *(18–20)*. This suggests the existence of a specific undernutrition-diarrhea cycle that is mediated by the lack of a proper immune response. Infectious diarrheas induce undernutrition by inducing catabolic cytokines such as tumor necrosis factor (TNF) and IL-1, IL-6, and IL-8 *(17,21,22)*. Undernutrition, usually defined as wasting or underweight, inhibits the repair of intestinal tissue because of a slower production of mature epithelial cells resulting in immature crypts. Trauma to the gastrointestinal epithelium causes a flattening of the microvilli

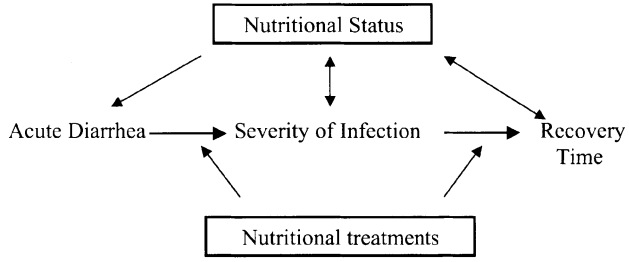

Fig. 1. Expansion of the two-way interaction between nutritional status and infection.

Table 3
The Nine Pillars of Good Treatment of Acute Gastroenteritis

1. Use of oral rehydration therapy
2. Hypotonic solution (Na 60mmol/L, glucose 74–11 mmol/L (industrialized countries only)
3. Fast oral rehydration, over 3–4 h
4. Rapid realimentation with normal feeding (including solids) thereafter.
5. Use of special formula is unjustified
6. Use of diluted formula is unjustified
7. Continuation of breast feeding at all times
8. Supplementation with oral rehydration solution for ongoing losses
9. No unnecessary medication

Source: Ref. *23*.

and significantly decreases the absorptive surface of the small intestines. This leads to malabsorption and poor electrolyte balance and thus changes the intestinal environment, which makes it possible for opportunistic pathogens to colonize and continue the cycle of diarrhea.

The nine pillars of good treatment of acute gastroenteritis developed by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPHGHN) are based on the oral rehydration therapy, feeding the sick child, continuous breastfeeding, and limiting unnecessary interventions (*see* Table 3) *(23)*. These pillars are appropriate for children in developing countries with one exception. The World Health Organization (WHO) recommends a greater sodium content for oral rehydration solution compared with the hypotonic solution recommended by the ESPHGHN *(24)*. Other treatment strategies for diarrhea still need to be scrutinized including the use of smectite (unabsorbable clay) that is popular in some areas because it increases the appearance of formed stools, but it may be masking the loss of liquid *(25)*.

Although a child's initial nutritional status has been the focus of increased risk for diarrheal morbidity and mortality, nutrition interventions during acute infections are being tested as an adjuvant to traditional interventions. Zinc supplementation during an acute diarrheal episode reduces both the duration and severity of acute and persistent diarrhea within a certain set of define parameters *(26)*. About 20 mg/d of zinc, or twice the recommended daily allowance (RDA), is needed. Zinc supplementation resulted in a 15% lower probability that acute diarrhea would continue on any given day and it decreased the probability of having an acute diarrheal episode for at least 7 d by 27%. The results for acute diarrhea did not vary by child age, gender, or nutritional status as measured by weight-for-age. Zinc supplementation also reduced the risk of continuing diarrhea by 24% in children who entered treatment with persistent diarrhea. However, in contrast to the results for acute diarrhea, the effect of zinc supplementation on persistent diarrhea was only significant for male children below 12 mo of age who were wasted at the start of treatment.

Vitamin A supplementation decreases the risk of mortality in infants and young children. Much of the decrease in case mortality is associated with lower case-fatality rates from diarrhea *(27,28)*. A meta-analysis on the affect of vitamin A supplementation on the incidence of diarrheal episodes provided equivocal results. The same analysis indicated that vitamin A supplementation reduces the severity and duration of diarrheal diseases *(29)*. This suggests that vitamin A is able to prevent the death of children who may have the pathology, but it has little affect in children whose diarrhea is not severe and who would not die without the supplement. The mechanism for the lower case-fatality rates in children with severe diarrhea may be by upregulating the cellular immune systems of the weakest children during diarrheal episodes *(29)*.

Although zinc and vitamin A supplementation are beneficial for managing diarrheal disease, the situation with iron is different—particularly in malaria endemic areas. Treating iron deficiency reverses impaired immune responses, but no studies have looked at its effect as an adjuvant to diarrheal treatments. A meta-analysis of the effect of iron supplementation on infectious disease found children supplemented with iron are at 11% greater risk of developing diarrhea, but this translated to only 0.05 episodes per child year *(30)*. In a comprehensive review on the association between iron and immunity and infection, Oppenheimer *(31)* concluded "that breast milk confers greater advantages than powdered milk, iron fortified or otherwise" for reducing the risk of diarrhea.

Probiotics, the use of live microorganisms of human origin to improve health, have been shown to be a successful strategy to prevent diarrheal infections *(32)*. The major probiotics studied in conjunction with diarrhea are *Lactobacillus GG*, *Bifidobacterium*, *Streptococcus thermophilous*, and

Saccharomyces boulardii (nonhuman origin). Studies with *Lactobacillus GG* reduced the incidence in diarrheal episodes in formula-fed infants. *Lactobacillus GG* also reduced non-*Clostridium difficile* antibiotic induced diarrhea by 66% when children weighing less than 12 kg were given two capsules containing $\geq 10^{10}$ organism. *Lactobacillus GG* also reduced the risk of traveler's diarrhea by 25–50%. The mechanism for these outcomes may be a direct competition to the colonization of the gastrointestinal tract. However, it is also known that these lactic acid bacteria may be improving immune function by enhancing phagocytosis, cellular immune response, and the humoral immune response.

Infant Feeding Patterns

The most important nutritional prevention of infant diarrheas is breastfeeding along with the introduction of liquids and solids at the appropriate age. Thus, infant feeding practices have a strong effect on the likelihood of a child developing diarrhea, as well as being an antecedent for undernutrition.

Studies on the pattern of infant feeding in Lima, Peru, described an environment that led to a high incident of diarrhea *(33)*. In this community, formula milk was introduced at an early age along with other liquid foods and, by 4 mo of age, more than 80% of infants were consuming a liquid other than breast milk. Close monitoring of infant feeding and diarrheal episodes, through home visits every third day, showed that the relative risk for both the number and the duration of diarrheas was significantly greater in children not exclusively breastfed. Infants fully weaned before 6 mo of age who were receiving formula milk were three times more likely to get diarrhea than those who were exclusively breastfed: The incidence rate for diarrhea increased from 7.6 to 26.1 per 100 d of observation. The trend continued for infants who were both breastfed and receiving complementary food. Furthermore, formula-fed infants were at five times-greater risk of being ill for more days. This study illustrates both the clear benefit of exclusively breastfeeding to limit diarrheal morbidity to a minimum and also the detrimental affect of introducing complementary food too early.

Exclusive breastfeeding can also prevent acute diarrhea from becoming persistent diarrhea *(34)*. The continuation of breastfeeding during diarrheal episodes provides children with a number of substances that protect against infections. Both specific and nonspecific immune substances such as lymphocytes, macrophages, and secretary IgA assist infected hosts with combating infectious agents. At the same time, breast milk promotes the repair of damaged epithelial tissues *(35,36)*. The naturally low pH in the intestinal tract, along with exclusive breastfeeding, promotes the growth of probiotics, especially bifidobacterium. An effective treatment for persistent diarrhea in the

Table 4
WHO Recommendations for Treating Persistent Diarrhea

Continue breastfeeding
Provide a nutritious age-appropriate diet
Limit the content of lactose from animal milk
Provide at least 110 kcal/kg/d of energy
Include supplementary vitamins and minerals
Feed small amounts of food at one time, at least six times/d

Source: Ref. *25*.

young child includes breast milk along with age-appropriate feeding practices (*see* Table 4).

Most children can be treated at home for persistent diarrhea if proper nutrition can be provided and action is taken to prevent dehydration. However, some children may need to be hospitalized. The criteria for hospitalization include cases with moderate or severe dehydration in children who are not candidates for enteral feeds or with stool outputs that can exceed 30 g/kg/d. Nonetheless, any partial parental nutrition is only feasible in specialized hospitals in developing countries *(7)*. Children with serious systemic infectious such as pneumonia or sepsis also need to be admitted and observed. Special care must also be given to younger infants. Infants less than 4-mo-old should be cared for in a clinic or hospital setting.

Diarrheal Vaccines

The development of vaccines to prevent and treat diarrheas is underway. Vaccines to provide both active and passive immunity are being developed (*see* Table 5). The most promising progress has been made for rotavirus and cholera *(4,37)*, but studies are ongoing for *Shigella* and *E. coli* vaccines *(38)*. Vaccines for larger parasites such as *Entomoeba histolytica*, *Giardia lamblia*, and helminthes have required different approaches. For helminthes, the goal of an effective vaccine is to reduce the worm burden to a nonpathologic level rather than to provide sterilizing immunity or to focus on reducing the pathologic properties of the helminthes *(39)*. The approach being followed in the development of nematode vaccines is also to target parasite molecules that are required for nutrition or survival *(40)*. Hyperimmune milk has been investigated for cryptosporidium and other small protozoa and may provide some protection for at-risk individuals *(17)*. A hyperimmune bovine colostrum product is also available for rotavirus and is licensed in Australia *(41)*.

Data on the efficacy of diarrhea preventing vaccines are limited. At most, only data on basic protection are available for the viral and bacterial vaccines. Few trials have determined how much protection the vaccines provide when

Table 5
Immunological Approaches to Preventing Selected Diarrheal Diseases

Active Immunity (Vaccinations)	Passive Immunity (Hyperimmune Colostrum)	Targeted Immunity (Harm Reduction)
	Rotavirus	Hookworm
Rotavirus	Cryptosporidium	
Cholera	Enterotoxic *E. coli*	
Shigella	*Clostridium difficile*	
Campylobacter	Campylobactor	
Enterotoxic *E. coli*		
Salomenella typhi		

Source: Refs. *1, 39, 40.*

given to children with different nutritional status or concomitant infections. This is an important consideration because there is some evidence that polio vaccine is not completely protective when given to infants who have diarrhea *(42)*. This is clearly an important concern and may be specific to an oral vaccine compared with intramuscular injections.

Three oral cholera vaccines are currently available and licensed in some countries *(4)*. The development of these vaccines took different routes. One vaccine comprises killed whole-cell *V. cholerae* O1 with a purified subunit of the cholera toxin (WC/rBS). The vaccine provides 85–95% protection for at least 6 mo after two administrations 1 wk apart. Booster doses can be given every 6 mo. Protection remains high at about 60% 6 mo later, but may decline rapidly after this. A similar vaccine has been developed with the purified subunit and field trials suggest it has 66% protection at 8 mo. The third vaccine is an attenuated live oral genetically modified *V. cholerae* 01 strain that provides 95% protection after one dose for *V. cholerae* and 65% protection against *V. cholerae* El Tor for at least 3 mo. Given these results, the WHO has recommended giving the WC/rBS to populations that are at risk for a cholera outbreak within 6 mo *(4)*.

A tetravalent rhesus rotavirus vaccine has been developed and tested in several field trials. Vaccine effectiveness varied between developed and developing countries. Under more ideal conditions, the vaccine is able to prevent 50–70% of all rotavirus cases and 70–90% of severe rotavirus cases. However, reports from in Brazil and Peru suggested that the effectiveness of the vaccine was 35–66% *(37)*. The vaccine schedule indicates it is to be given in three doses at ages 2, 3, and 6 mo. Adverse effects have been reported, including fever after the first dose and the risk of adverse effects increase with age. The most serious adverse effect reported was intussusception (bowel obstruction)

among infants during the first 1–2 wk following vaccination. Fifteen cases were reported from September 1998 to July 1999. Based on these findings, the Advisory Committee on Immunization Practices for the US Centers for Disease Control and Prevention recommended the suspension of the rotavirus vaccine until further studies could be conducted *(43,44)*.

Conclusion

Undernutrition is a major causal factor for persistent diarrhea because it depresses the cell-mediated response and delays repair of the intestinal epithelium. Acute diarrheal episodes elicit an immune response that exacerbates undernutrition by inducing anorexia and increased catabolism. The mechanisms underlying the interaction between diarrhea and undernutrition continue to be elucidated in order to develop appropriate prevention and treatment protocols. The issues that have to be identified when examining this association include the specific pathogenic agents involved, the energy/nutrients (macronutrients and/or micronutrients) required for prevention and treatment, and the temporal sequence between nutritional status and infection. Prevention and treatment protocols for diarrheas, in most cases, will be similar and include preventing dehydration, breastfeeding, and providing an age-appropriate diet. Other nutrition interventions, such as zinc supplementation, are being recognized as additional adjuvant to the treatment of diarrhea. In measuring the outcome of interventions, public health professionals and clinicians must focus not only on the incidence of diseases, but also the severity and duration of diarrheal episodes including the development of persistent diarrhea.

Nutritional interventions must also be accompanied by other preventive behaviors to decrease a child's exposure to infectious agents. Good access to safe water and sanitation facilities is critical for decreasing exposure to pathogens. Improved hygiene from hand washing at home and in child- or day-care centers will also prevent infections and epidemics of infectious diarrheas. Personal hygiene and public health interventions need to work hand in hand to decrease the incidence of diarrhea and the devastating outcomes associated with it. The morbidity and mortality associated with diarrhea is a priority for improving the health of children worldwide. Millions of childhood deaths can only be averted by improved nutrition and hygiene. Public health and clinical approaches to preventing and treating diarrhea need to incorporate proven nutritional strategies. These strategies include micronutrient supplementation, food-based programs, and community education programs. The general public and health care professionals need to be aware of the effect that nutrition interventions can have on decreasing diarrheal morbidity and mortality. Thus, the new knowledge that is rapidly being accumulated on how nutrition and infant

feeding practices improve the lives of children need to be incorporated into daily practice.

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