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Cryptosporidium and *Cyclospora* Diarrheal Infection in Malnourished Children: a Nutritional Approach

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Abstract
Purpose of Review Over two million children under 5 years of age die each year in developing countries because of acute diarrhea. *Cyclospora* and *Cryptosporidium* are parasites recognized as a major cause of diarrhea in children and immunocompromised patients. The clinical expression of the parasites, however, is mainly determined by host defenses, and when they are weakened, parasitic diarrhea is frequent and severe. Protein-energy malnutrition is by far the most important cause of immune deficiency in developing countries. The purpose of this review is to consolidate the main nutritional interventions in malnourished children in developing countries with diarrheal infection by *Cyclospora* and *Cryptosporidium*.
Recent Findings Higher isolation rate of *Cryptosporidium* and *Cyclospora* is seen among malnourished children. *Cryptosporidium* is a second leading cause of moderate-to-severe diarrhea in infants according to GEMS study.
Summary We review the etiology and characteristics of *Cryptosporidium* and *Cyclospora* and the consequences of diarrhea in children under five, especially those with malnutrition and other risk factors. The main interventions to treat these pathogen diarrheal infections include antibiotics and antiparasitic agents, oral rehydration, zinc supplementation, and dietary modifications. Prevention strategies include safe water, sanitation, hygiene, and breastfeeding.

Keywords *Cryptosporidium* · *Cyclospora* · Diarrhea · Malnourished children

Introduction

Tropical diseases occur mainly in the tropics because of the hot and humid climate, including countries in Central America, Caribbean, and South America.

Cyclospora cayetanesis is an obligate, intracellular, coccidian protozoan parasite. Humans are the only natural hosts of *C. cayetanesis*. The role of animals as natural reservoirs is uncertain, and it is unclear whether zoonotic transmission occurs. It has a broad geographic distribution, most frequently reported in Latin America (especially Guatemala, Peru, and Mexico), the Indian sub-continent, and Southeast Asia. It is transmitted by the fecal-oral route. Person-to-person transmission is virtually impossible because the oocysts must sporulate outside the host to become infectious [1, 2••].

Cryptosporidium is also an obligate, intracellular, coccidian protozoan parasite with a complex life cycle including sexual an asexual replication. The genus *Cryptosporidium* has about eight species, of which *Cryptosporidium parvum* is responsible for most human infections, although other species can also cause illness like *Cryptosporidium hominis*. Cryptosporidiosis generally causes a self-limiting diarrhea lasting for about 1–2 weeks, sometimes extending up to 2.5 months among immunocompetent and becoming a more severe life-threatening illness among immunocompromised individuals [2••, 3, 4••, 5]. It is transmitted by the fecal-oral route, and the major route of infection is person-to-person contact. Other routes of infection include the consumption of

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contaminated food and water, and direct contact with infected farm animals and possibly domestic pets [2••, 5, 6]. Transmission through food is mostly with contaminated raspberries, lettuce, peas, and other fresh food items [7, 8••].

Cryptosporidium hominis, *Cryptosporodium parvum*, and *Cyclospora cayetanensis* are among the most frequent causes of human infection, commonly affecting the immunocompetent (particularly children under the age of 5 years and adults with immune disorders such as HIV infection, primary B cell defects with global antibody deficiency, and severe acute malnutrition (SAM) [6, 9].

Clinical manifestations of an infection related to *Cyclospora* and *Cryptosporidium* include watery diarrhea as a result of local inflammation in the intestinal epithelium and villous atrophy due to the attachment of the parasites, accompanied with gastrointestinal symptoms such as abdominal pain and distention, fever, nausea, vomiting, malaise, and loss of appetite [7, 8••, 10, 11].

A continuing lack of safe water and adequate sanitation in many parts of the world means that diarrhea remains a leading cause of death globally among children under 5 years of age, especially in low- and middle-income countries [6, 12, 13].

Diarrhea contributes to reduced resistance to infections, nutritional deficiencies, and impaired growth and development. Severe diarrhea leads to fluid loss and may be life threatening, particularly in young children and people who are already malnourished or have impaired immunity [14, 15].

Diarrheal diseases account for one in nine child deaths worldwide, making diarrhea the second-leading cause of death among children under the age of 5. Few studies suggest that child deaths under 5 years due to diarrhea are among 2.1 and 2.5 million [16–18], killing more young children than AIDS, malaria, and measles combined [14, 18].

Relationship Between Malnutrition and Diarrhea

Optimal nutrition status results when children have access to affordable, diverse, nutrient-rich food; adequate health services; appropriate maternal and child-care practices; and healthy environment including safe water, sanitation, and good hygiene practices. The interaction between undernutrition and infection creates a potentially lethal cycle of worsening illness and deteriorating nutritional status [9, 19••].

SAM and diarrhea are major causes of morbidity and mortality among children in the developing world. The relationship between malnutrition and diarrhea is bidirectional; diarrhea impairs the absorption carbohydrates, protein, fat, potassium, zinc, and other nutrients as well as fluids, which can worsen the state of malnutrition. Malnutrition predisposes children for a greater incidence and duration of diarrhea [6, 9, 19••].

Significant water losses from diarrhea can lead to dehydration, electrolyte imbalance, shock, and ultimately, death. The etiology and management of the diarrhea is particularly important in SAM patient treatment to ensure an adequate recovery, decrease mortality, improve growth outcomes, and enhance the success of the communities [6, 15, 20]. The approach treatment for patients with diarrhea due to *Cryptosporidium* and *Cyclospora* will depend upon the immune status of the host as well as the severity of the symptoms.

One third of under-five mortality are attributable to malnutrition since malnutrition predisposes to various infections through infancy like pneumonia, diarrhea, malaria, HIV, measles, etc. A child who is severely underweight is 9.5 times more likely to die of diarrhea than a child who is not, and for a stunted child, the risk of death is 4.6 times higher [19••].

In 2015, 50 million children under 5 years old were detected with wasting and 156 million with stunting globally [21].

There are at least 21 countries in the world who have a stunting prevalence of at least 40%, Guatemala being the sixth among them [19••].

Guatemala has the highest prevalence of undernutrition and stunting of the Latin America and Caribbean region with 12.6 and 46.5%, respectively [21].

Interventions

The standard treatments of acute diarrhea in children are oral rehydration salts (ORS) and zinc supplementation as recommended in the World Health Organization (WHO) guidelines [14].

Antibiotics and Antiparasitic Agents

Cryptosporidium parvum and *Cyclospora* have been commonly found in children with SAM and diarrhea. Metronidazole has been first-line therapy for the treatment for many years, but more recently, nitazoxanide has been shown to be effective against these pathogens in children with diarrhea. Malnourished children are more likely to present with gastrointestinal infections and have an increased diarrheal disease severity [6, 13, 22]; therefore, nutritional recovery is important for the eradication of the pathogen so the immune function can be restored.

Oral Rehydration

Dehydration and fluid loss is the principal cause of death in children with diarrhea. Malnourished children with dehydration often have different electrolyte imbalances than those without malnutrition. WHO guidelines currently recommend rehydration solution for malnutrition (ReSoMal) to correct

such imbalances in malnourished, and standard ORS among the children without malnutrition [6].

Zinc

Zinc plays an important role in many biological human mechanisms, and it is necessary for structure and catalytic functions of many pathways in the human body [23, 24]. It is important for cellular growth, cellular differentiation, and metabolism, skin, and mucosal resistance to infection, growth, and the development of the nervous system, as well as an important antioxidant. In the gastrointestinal tract, zinc restores the mucosal barrier's integrity and enterocyte brush-border enzyme activity [24, 25••, 26].

According to recent estimates, 17.3% of the world's population is currently at risk of inadequate zinc intake. Zinc deficiency is mainly due to inadequate dietary intake and is estimated to be common in many countries, especially in children [25••].

The foods rich in zinc are "expensive foods" such as meat and fish. Although zinc is also present in seeds, nuts, legumes, and whole-grained cereals, the high phytate content of these foods reduces its absorption [25••, 26].

In addition, zinc requirements are highest in children due to their rapid rates of growth [25••, 27]. Considering this information, children in developing countries are at special risk as they have a lower intake of bioavailable zinc, higher requirements, and those with diarrhea, higher losses (50% of zinc excretion takes place through the gastrointestinal tract and is increased during episodes of diarrhea).

Zinc deficiency can cause an impairment of the immune system and loss of the skin and mucosal resistance to infection, therefore, exposing the person to different infections [23, 25••].

Zinc supplementation has been shown to reduce the duration and severity of diarrhea and to prevent subsequent episodes, although the mechanisms by which this metal exerts antidiarrheal effect are not fully understood [14, 25••, 26, 28]. It is believed that since some of the symptoms are caused by the release of inflammatory mediators (cytokines and chemokines), the zinc could act as a modulator of the inflammatory response to the infection [26, 29].

Zinc is usually given as zinc sulfate, zinc acetate, or zinc gluconate, which are all water-soluble compounds [25••].

As mentioned above, two standard treatments for acute diarrhea according to the WHO guidelines are ORS and zinc supplementation [28, 30] at a dosage of 20 mg per day for children older than 6 months or 10 mg per day in those younger than 6 months for 10–14 days [14, 25••, 30]. These are used to treat and prevent diarrhea in the next 2–3 months [30, 31].

Modified Feeding Strategies

Current WHO guidelines on the management and treatment of diarrhea in children strongly recommend continued feeding alongside the administration of oral rehydration solution and zinc therapy, but there remains some debate regarding the optimal diet or dietary ingredients for feeding children with diarrhea [32•].

High Soluble-Fiber Diet?

Dietary fiber is generally classified into short-chain and long-chain carbohydrates grounded on their solubility and fermentation properties. Among the long-chain carbohydrates are two commonly known fibers: soluble and insoluble fiber. Soluble fiber's main characteristic are: highly fermentable and viscous with a water-holding/gel-forming capacity [33, 34].

Soluble fiber has been popularly recommended among the health care professionals for the management of diarrhea and loose stools. It is believed soluble fiber solidifies the stool and reduces the duration of diarrheal episodes and its severity.

Nonetheless, there is no general recommendation for its use.

Low Lactose

Young children with acute diarrhea, typically due to infectious gastroenteritis or parasitic disease, in which epithelial cell damage causing atrophy of intestinal villi consequently causes a lactose malabsorption. New epithelial cells can replace the older ones, but the new ones do not have an adequate lactase activity; in consequence, these children may not digest lactose, the main sugar in milk which may worsen or prolong the diarrheal illness [32•, 35•, 36].

Compared to lactose-containing milk, milk products, or foodstuffs, lactose-free products may reduce the duration of diarrhea, especially in children who are not predominantly breastfed, by an average of about 18 h and reduce treatment failure (defined variously as continued or worsening diarrhea or vomiting, the need for additional rehydration therapy, or continuing weight loss) by around half.

Diluted lactose-containing milk or fermenting lactose-containing liquid feeds do not affect the outcome of acute or persistent diarrhea [32•, 35•].

Continuing feeding is important to limit the nutritional consequences of decreased intake, digestion, and absorption of essential nutrients during diarrheal episodes. Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to specialized lactose-free formulas and ingredients is limited, continued breastfeeding should be encouraged as well as the use of locally or home-available age-appropriate foods to

children from 6 to 59 months, especially grains and cereals. Lactose intolerance can be managed with nutritionally complete diets comprised of locally available ingredients which can be used effectively as well as commercial preparations of lactose-free formula or specialized ingredients [32•]. An abrupt re-introduction of lactose should be avoided to prevent gastrointestinal symptoms.

Prevention

Recognizing People at Risk

Several studies identify different risk factors related to the infection of these two pathogens: low socioeconomic status, rural environment, children under 2 years, presence of animals inside the house, lack of safe water, rainy humid environment, low birth weight, stunting, wasting, vitamin A deficiency, and lack of breastfeeding [9, 11, 37].

Those who are at increased risk are the immunocompromised, including HIV/AIDS patients, patients using immunosuppressive drugs, and children with malnutrition [38].

Exclusive Breastfeeding

Breastfeeding is the ideal way to feed infants. It is important in every child's health for the formation of the human microbiome. Exclusive breastfeeding is recommended until 6 months of age, and then breastfeeding accompanied by proper introduction of complementary foods [39•].

Multiple studies have demonstrated that early initiation of breastfeeding and exclusive breastfeeding are significantly correlated with lower risk of diarrhea; this protective effect is mainly because of the IgA content in breast milk [9, 11, 37, 39•, 40–42]. Infants not breastfed are 11 times more likely to die from diarrhea than children who are exclusively breastfed [19••].

Water, Sanitation, and Hygiene

Improvements in access to safe water and adequate sanitation, along with the promotion of good hygiene practices (particularly handwashing with soap), can help prevent childhood diarrhea [9, 14, 18]. It is estimated that 88% of diarrheal deaths worldwide can be attributed to the use of unsafe water, insufficient hygiene, and inadequate sanitation [14, 18].

The World Health Organization's guideline for drinking-water classifies *Cryptosporidium* and *Cyclospora* as waterborne pathogens of significant public health importance, aided in part by the organism's low infective dose and resistance to conventional water treatment. The oocysts are extremely resistant to oxidizing disinfectants and are not activated by chlorination practices generally applied in the production of drinking-water. Because of their relatively small size, the oocysts represent a challenge for removal by conventional granular media-based filtration processes [2••,43].

Some control measures that can be applied to manage potential risk from *Cyclospora* and *Cryptosporidium* include mainly the prevention of source water contamination by human and livestock waste, then an adequate treatment and protection of water before consumption [2••].

In developing countries, one viable alternative to treat water against these pathogens is through thermal treatment, boiling water for consumption for at least a minute.

Conclusions

Immunocompromised patients are at high risk of diarrheal infections, especially malnourished children who are vulnerable to infectious pathogens such as *Cyclospora* and *Cryptosporidium*.

The relationship between malnutrition and diarrhea is bidirectional since diarrhea causes malabsorption leading to malnutrition, and malnutrition predisposes children for a greater incidence and duration of diarrhea.

Diarrhea caused by *Cyclospora* and *Cryptosporidium* should be treated with antiparasitic agents and antibiotics, as well as oral rehydration and zinc supplementation.

There are no guidelines regarding lactose removal from the diet, but there is significant evidence about less failure to treatment and weight gain.

Breastfeeding remains the best feeding alternative due to its multiple benefits including immune protection. Continued breastfeeding should be encouraged in patients with diarrhea as well as the use of locally or home-available age-appropriate foods to children from 6 to 59 months.

The use of soluble fiber, while commonly used for the clinical management of diarrhea, still needs clinical trials to validate its use.

Authors' Recommendations

We recommend more trials regarding soluble fiber in the management of diarrhea.

Lactose removal in diarrheal infection should not be a standard intervention. We recommend individualized assessment and thoughtful consideration before the removal of lactose and when feasible, maintain breastfeeding.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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