Persistent Diarrhea in Children

in Developing Countries

Seyed Mohsen Dehghani, MD MPH

Professor of Pediatrics,

Pediatric Gastroenterologist and Hepatologist,

Shiraz University of Medical Sciences

February 2023

Introduction

- In the year 2018, 5.3 million children under the age of 5 years died; around 29% of these deaths were due to diarrhea, pneumonia, and malaria.
- After respiratory diseases, **diarrhea** constitutes a serious public health challenge, and a leading cause of death among children under the age of 5 years and is the second leading cause of infant mortality.

Introduction

The **common risk factors** for diarrhea include:

- Young Age
- Low Socioeconomic Status
- Suboptimal Breastfeeding
- Early Weaning
- Malnutrition
- Low Maternal Education
- Lack of Handwashing
- Poor Hygiene and Sanitation Practices
- Untreated Water Supply at Home

Introduction

- Interventions such as **handwashing with soap** can reduce the risk of diarrhea by 31%, **improved sanitation** can reduce the risk by 36%, **improved water quality** can decrease the risk by 17%, **ORS** reduces the risk by 69%, **zinc** by 23%, and **vitamin A** by 23%.
- There is a **10.5 times** greater risk of mortality among children **not breastfed** during 0–6 months, with **28%** risk of mortality due to diarrhea.

Case Presentation

- 8 months old male formula-fed infant presented with watery diarrhea since 27 days ago.
- Four weeks ago he developed fever and vomiting and severe watery diarrhea the day after.
- He took cefixime for 5 day without significant improvement.
- His diarrhea continue till now and he loss one Kg of his weight.
- On P/E his weight is 6.3 Kg and had no sign of dehydration.

Introduction

- **Persistent diarrhea** refers to episodes of diarrhea that last 14 days or longer.
  - Although less common than acute diarrhea, constitute a **significant portion of the global burden of diarrhea** and these lengthy episodes are increasingly implicated in childhood undernutrition, micronutrient deficiencies (such as folate, vitamin A, and zinc), immune deficiency, adverse neurodevelopment outcomes, and higher morbidity and mortality from other diseases.

Etiology

- The cause of persistent diarrhea in developing countries is associated with **serial enteric infection** (without enough recovery time), which **follows an acute episode** of diarrhea.
- In developing countries, persistent diarrhea may increase the risk of **malnutrition** and **intercurrent illnesses** such as respiratory diseases.
- Persistent diarrhea is usually caused by infections which includes **bacteria** (Campylobacter, C. difficile, E. coli, Salmonella, Shigella), **parasites** (Cryptosporidium, E. histolytica, Giardia), and **viruses** (rotavirus, norovirus).

Etiology

- A few pathogens have been particularly associated with persistent diarrhea include **enteroaggregative E. coli** (EAEC), and **enteropathogenic E. coli** (EPEC), **Cryptosporidium**, **Shigella**, **Campylobacter**, **Yersinia**, and **Giardia lamblia**.
- These pathogens cause **continuous damage to mucosal lining** of the intestine.
- These agents cause **destruction of villus tips** which leads to intestinal damage and reduced intestinal absorptive surface area, which in turn interferes with the absorption of nutrients.

Etiology

- Disrupted intestinal flora and delayed healing cause prolonged diarrhea and exposure to enteropathogens which cause a **new infection before the recovery of the previous infection** leading to persistent diarrhea.
- In epidemic situations, **E. coli**, **C. difficile**, and **V. cholerae** have been reported as the causative agents of diarrhea in China, **Iran**, Nigeria, and Yemen.

Risk Factors

- Medications (antibiotics)
- Malnutrition
- Altered immune system
- Lack of access to clean water
- Poor sanitation
- Intolerance to food products (lactose, gluten)
- Thyroid, Metabolic and Intestinal disorders, Reduced intestinal blood flow

Risk Factors

- Persistent diarrhea is commonly seen in **association with significant malnutrition** and the relationship between persistent diarrhea and malnutrition is bidirectional.
- The evidence of micronutrient deficiencies, especially of **zinc** and **vitamin A** in malnourished children with persistent diarrhea, indicates **impaired immunological mechanism** that is associated with an increase in inflammatory mediators, leading to tissue damage caused by enteric infection.

Risk Factors

- **Lactose intolerance** is prevalent in many children with persistent diarrhea, but the role of specific dietary allergies in inducing and perpetuating enteropathy of malnutrition is unclear.
- High risk of prolonged diarrhea with **lactation failure** and **early introduction of artificial feeds** in developing countries, in particular, the administration of unmodified cow milk is associated with prolongation of diarrhea, suggesting the potential underlying role of **cow's milk protein allergy** (CMPA) and **milk protein enteropathy**.
- **Inappropriate management of acute diarrhea** is also an important risk factor.

Risk Factors

- **High stool frequency**, **not being breastfed**, **young age**, and **acquiring diarrhea in the rainy season** have also been identified as risk factors for prolonged diarrhea.
- **HIV** has also shown association with persistent diarrhea.
- In an **immune-suppressed setting**, infection with opportunistic agents such as Blastocystis hominis, Candida albicans, and Cryptosporidium leads to mucosal injury and diarrhea.

Risk Factors

- **Starvation** and **inappropriately prolonged administration of parenteral fluids**
- Continued breastfeeding is important, and **unnecessary food withdrawal** and **replacement of luminal nutrients**, especially breast milk, with non-nutritive agents is a major factor in prolonging the mucosal injury after diarrhea.
- Routine administration of **antibiotics, antimotility** agents, and **semistarvation diets** should be avoided in cases of prolonged diarrhea.

Consequences of Persistent Diarrhea

- As diarrhea becomes “persistent,” **malnutrition** becomes increasingly manifest secondary to anorexia and impaired nutrient balance resulting from mucosal injury, malabsorption, and nutrient losses.
- Mucosal injury also explains why by day 14 the manifestations of persistent diarrhea are primarily those of a **malabsorption and malnutrition syndrome** that requires careful dietary and nutritional management until the mucosal damage is reversed and new normally functioning epithelial cells are regenerated

Consequences of Persistent Diarrhea

- **Causes:** Achlorhydria with increased risk of small bowel contamination, systemic immune deficiency, intestinal and pancreatic enzyme deficiency, and altered intestinal mucosal repair mechanisms following an infectious insult.
- **Poor intestinal repair** is regarded as a key component of the abnormal mucosal morphology.

Management

- It is imperative to consider the **child's age** and **clinical manifestations** to determine proper treatment in cases of persistent diarrhea.
- **Paucity of diagnostic facilities** limits the microbiologic evaluation of diarrhea.
- Lack of awareness regarding **cow's milk protein allergy** and **immunodeficiency-associated diarrhea** is of particular concern.

Management

- **Optimal prevention and management of acute diarrheal illnesses** are the ideal strategies to prevent persistent diarrhea.
- Treatment is focused on **reversing dehydration** (if present), **nutritional interventions** including balanced protein energy, **pancreatic enzyme replacement therapy** (PERT), **micronutrient supplements**, and **judicious use of antibiotics** for certain types of inflammatory diarrhea.
- Oral rehydration solutions, micronutrient supplementation, algorithm-based diet regimens, and good supportive care are sufficient in most children above 6 months of age with persistent diarrhea.

Rapid Resuscitation, Antibiotic, Stabilization

- Most children with persistent diarrhea and associated malnutrition are not severely dehydrated and **oral rehydration** may be adequate.
- Routine use of **IV fluids** in severe acute malnutrition should be avoided; acute severe dehydration and associated vomiting may require brief periods of IV rehydration with **Ringer's lactate**.
- Acute electrolyte imbalance such as **hypokalemia** and **severe acidosis** may require correction.

Rapid Resuscitation, Antibiotic, Stabilization

- Associated **systemic infections** (bacteremia, pneumonia, and UTI) are well-recognized complications of severe acute malnutrition in children with persistent diarrhea and a frequent cause of early mortality.
- Almost 30–50% of malnourished children with persistent diarrhea may have an **associated systemic infection** requiring resuscitation and antimicrobial therapy.
- Children with **bloody diarrhea** require antibiotic therapy for enteric pathogens.
- Treatment against strain of Shigella is recommended to be changed if no improvement is observed **within two days** of treatment.

Rapid Resuscitation, Antibiotic, Stabilization

- There is **little role for oral antibiotics** in persistent diarrhea as in most cases the original bacterial infection triggering the prolonged diarrhea has disappeared by the time the child presents.
- Possible exceptions are appropriate treatment for **dysentery** and adjunctive therapy for **cryptosporidiosis in children with HIV** and persistent diarrhea.

Oral Rehydration Therapy

- Death by persistent diarrhea is usually caused by **malnutrition** or by **hypovolemia** (dehydration).
- **ORT** is the preferred mode of rehydration and replacement of on-going losses.
- WHO has recommended a new low osmolarity solution for the management of diarrhea, which contains **75 mmol/L glucose**, **75 mEq/L sodium**, and **20 mEq/L potassium**, at an **osmolarity of 245 mOsm/L**.
- **Potassium chloride** can also be added in ORS solution (to provide 40 mEq/L of potassium) for severely malnourished children with depleted potassium levels.

Oral Rehydration Therapy

- A number of modifications have been proposed, for example, **cereal (rice)-based ORT**, addition of certain **amino acids** (glycine, alanine, or glutamine) to further increase sodium absorption and/or hasten intestinal repair, or **supplementation with zinc**, but none have been shown to be consistently superior to low osmolality ORS.

Enteral Feeding

- **Nutritional rehabilitation** can break the vicious cycle of chronic diarrhea and malnutrition and is considered the ***cornerstone of treatment***.
- With the exception of situations where persistent diarrhea accompanies perinatally acquired HIV infection, **breastfeeding must be continued**.
- Although children with persistent diarrhea may not be lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure.

Enteral Feeding

- Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include **addition of milk to cereals such as rice and noodles** and **replacement of milk with fermented milk products such as yogurt**.
- **Lactose-free diet** and **low-sucrose and -carbohydrate diet** has also been effective in minority of the cases.
- **Yogurt-based diet** is recommended as the **first choice** for the nutritional management of a mild to moderate persistent diarrhea.

Enteral Feeding

- Elimination diet is considered when **allergic enteropathy** is induced by a **cow's milk protein** or **soy protein**.
- It may be necessary to administer **specialized milk-free diets** such as a comminuted or blended **chicken-based diet** or an **elemental formulation**.
- In addition to **rice-lentil formulations**, the addition of **green banana** or **pectin** to the diet has also been shown to be effective in the treatment of persistent diarrhea.

Enteral Feeding

- Among children in low- and middle-income countries, the use of **locally available age-appropriate foods** should be promoted for the majority of diarrhea cases.
- Nutritionally complete diets comprising locally available ingredients can be used at least as effectively as commercial preparations or specialized ingredients.

Enteral Feeding

- The usual **energy** density of any diet used for the therapy of persistent diarrhea should be around **1 kcal/g**, aiming to provide an energy intake of a minimum **100 kcal/kg/day**, and a **protein** intake of between **2-3 g/kg/day**.
- **Potassium** should also be included in the diet providing approximately **5 mEq/kg/day**.

Enteral Feeding

- Recent WHO guidelines recommend that children with severe acute malnutrition who present with either acute or persistent diarrhea can be given **ready-to-use therapeutic food (RUTF)**.
- These children with severe acute malnutrition are typically managed by a **course of broad-spectrum antibiotics** with a **gradual increase in full caloric intake**.
- **Hypophosphatemia** is common during the refeeding syndrome which is mitigated by providing phosphorus-rich food such as milk-based feed to the children.

Micronutrient Supplementation

- It is now widely recognized that most malnourished children with persistent diarrhea have associated deficiencies of micronutrients including **copper**, **folic acid**, **zinc**, **iron**, **vitamin A**, and **minerals**.
- This may be a consequence of poor intake and continued enteral losses and requires nutritional rehabilitation.
- While the evidence supporting **zinc administration** in children with persistent diarrhea is persuasive, it is likely that these children have multiple micronutrient deficiencies.

Micronutrient Supplementation

- Concomitant **vitamin A administration** to children with persistent diarrhea has been shown to improve outcome.
- WHO recommended **10 mg/day of zinc for 10–14 days for children <6 months** and **20 mg/day for children >6 months**.
- Zinc has shown a significant effect among children >6 months with **shortened duration** of persistent diarrhea by approximately **16 hours**.
- Zinc decreases the absorption of copper and causes **copper depletion** in the body.

Micronutrient Supplementation

- While the association of **significant anemia** with persistent diarrhea is well recognized, **iron replacement therapy** is best initiated only **after recovery from diarrhea** has started and the diet is well tolerated.
- In July 2019, WHO has recommended to administer **folate, iron, vitamin A, copper, and magnesium twice a day for two weeks**.

Antidiarrheal Drugs

- Antidiarrheal drugs are **not recommended** due to their inefficiency, side effects, and possibly also as causing prolonged release of enteric pathogens.
- **Antiemetic drugs** are also **not encouraged** because of the sedation caused by them which may interfere with ORT.

Pancreatic Enzyme Replacement Therapy

- Persistent diarrhea causes **pancreatic exocrine insufficiency** due to decreased stimulation to pancreas caused by prolonged mucosal injury.
- **PERT prescribed in conjunction to regular treatment** has proved to be beneficial in replacing pancreatic enzyme deficiency.
  - In children (6–60 months) with pancreatic enzyme deficiency PERT (8000 units of lipase) three times a day for a month showed decrease in duration of diarrhea by 3–7 days.

Prevention

- Improved management of acute diarrhea is a **key factor** in reducing the burden of prolonged episodes and persistent diarrhea.
- The WHO/UNICEF recommendations to use **low-osmolality ORS** and **zinc** supplementation for the management of acute diarrhea, coupled with **selective and appropriate use of antibiotics**, have the potential to reduce the number of diarrheal deaths among children.

Prevention

- Water sanitation
- Exclusive breastfeeding for 6 months
- Adequate complementary feeding among children 6–23 months, with adequate micronutrient intake
- Preventive zinc supplementation
- Preventive vitamin A supplementation
- Vaccines for rotavirus
- ORS

Other Potential Modalities

- The factors associated with persistent diarrhea are **small intestinal mucosa injury**, **persisting infective colonization**, and **bacterial particles and toxins that are translocated into the host cell** and **downregulated host immune system**.
- These circumstances alter **interrelation between the normal flora and the host**, which can worsen prolonged inflammation.
- The rationale for using **probiotics** in the treatment of persistent diarrhea lies in their ability to survive and reproduce in the host's gut and in their proven role in the treatment of acute diarrhea.

Other Potential Modalities

- Recent evidence suggests modest effect of probiotics with reduced duration of persistent diarrhea and stool frequency.
- Because of **probiotics known immunomodulatory effect** and very significant mortality and morbidity rate from persistent diarrhea in developing countries, it is imperative to highlight the necessity for well-designed studies to define the role of probiotics in persistent diarrhea.

Follow-Up and Nutritional Rehabilitation

- Given the **high rates of relapse** in most children with persistent diarrhea, it is important to address the **underlying risk factors** and institute preventive measures.
- These include **appropriate feeding** (breastfeeding, complementary feeding) and close attention to **environmental hygiene and sanitation**.

Follow-Up and Nutritional Rehabilitation

- The challenge in most settings is to **develop and sustain a form of dietary therapy** using inexpensive, home-available, and culturally acceptable ingredients which can be used to manage children with persistent diarrhea.

Conclusions

- Persistent diarrhea in children contributes to childhood malnutrition and mortality.
- Given the emerging evidence of the long-term impact of childhood diarrhea on developmental outcomes, it is imperative that due emphasis is placed on **prompt recognition and appropriate management** of persistent diarrhea besides the focus on **improving child nutrition and hygiene**.

Thanks