Persistent Diarrhea in Children in Developing Countries

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Introduction

In the year 2018, 5.3 million children under the age of 5 years died [1]; around 29% of these deaths were due to diarrhea, pneumonia, and malaria [2]. After respiratory diseases, diarrhea constitutes a serious public health challenge, especially as it constitutes 63% of the global burden and a leading cause of death among children under the age of 5 years and is the second leading cause of infant mortality [3]. The diarrhea burden is specifically concentrated in Asia, Africa, and South America and is the cause of every one in eight child mortality annually of children under the age of 5 years [4, 5].

Diarrhea is defined as "the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)" [6]. The common risk factors for diarrhea include young age, low socioeconomic status, suboptimal breastfeeding, early weaning, malnutrition, low maternal education, seasonal variations, lack of handwashing, poor hygiene and sanitation practices, and untreated water supply at home [3, 7–9].

Diarrhea has been classified into three types by common clinical criteria. *Acute watery diarrhea* is brief and lasts several hours or days (1–3 days) and is often due to gastrointestinal pathogens including viruses (rotaviruses and caliciviruses) and bacteria (including *Escherichia coli* and *Vibrio cholerae*). *Acute bloody diarrhea*, also called dysentery, is marked by stools containing blood and/or mucous; common pathogens include *Entamoeba histolytica* (amoebic dysentery) or *Shigella* species (bacillary dysentery). *Persistent diarrhea* refers to episodes of diarrhea (either watery or dysentery) that last 14 days or longer. It is majorly caused by *E. coli*, *Shigella* or *Cryptosporidium*. Although less common than acute diarrhea, prolonged and persistent episodes of diarrhea in childhood constitute a significant portion of the global burden of diarrhea and these lengthy episodes are increasingly implicated in childhood undernutrition [10], micronutrient deficiencies (such as folate, vitamin A, and zinc), immune deficiency, adverse neurodevelopment outcomes, and higher morbidity and mortality from other diseases [11]. As mortality from acute watery diarrhea is decreasing, the proportion of deaths due to persistent diarrhea has increased and recent studies estimate that between 5% and 18% of all episodes are persistent diarrhea, and though a small portion of episodes, they are responsible for significant diarrheal morbidity and up to 50% of all diarrhea-related deaths since persistent diarrhea has a high case fatality rate [12, 13]. It is estimated that diarrheal incidence and mortality among children under the age of 5 years are associated with 40.25 million disability adjusted life years (DALYs) lost in 2016 [14]. After accounting the long-term sequel of malnutrition and diarrhea, the DALYs double by 40% to 55.78 million years [14]. These findings indicate the continuing need to focus on prevention and management of childhood diarrhea, especially in developing countries where most of the burden lies. But there is scarcity of data on persistent diarrhea, and it is likely that the diminished publication output also reflects reduced research interest in the subject [15]. Although effective interventions exist, which can not only halt the progression from acute diarrhea to persistent diarrhea and its sequelae, but also have a substantial impact on total diarrhea burden and mortality, these interventions do not have universal access. The integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) by the

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United Nations Children's Fund (UNICEF) reported that interventions such as handwashing with soap can reduce the risk of diarrhea by 31%, similarly other interventions like improved sanitation can reduce the risk by 36%, improved water quality can decrease the risk by 17%, oral rehydration solution (ORS) reduces the risk by 69%, zinc by 23%, and vitamin A by 23% [16]. There is a 10.5 times greater risk of mortality among children not breastfed during 0–6 months, with 28% (RR 2.28–10.52) risk of mortality due to diarrhea [16]. An analysis using the Lives Saved Tool (LiST), a methodology to estimate the effect of increasing the use of a package of interventions, has shown that if water, sanitation, and hygiene (WASH), breastfeeding, ORS, rotavirus vaccine, vitamin A supplementation, zinc for the treatment of diarrhea, and antibiotics for dysentery are scaled up to at least 80% and that for immunizations to at least 90%, then 95% of diarrheal deaths in children younger than 5 years could be eliminated [17].

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 [4]. In developed countries, children are not likely to be exposed to malnutrition and enteric infections, however, it is most likely to be caused due to celiac disease, food allergies, and inflammatory bowel disease (IBD). In developing countries, persistent diarrhea may increase the risk of malnutrition and intercurrent illnesses such as respiratory diseases [18].

Persistent diarrhea is usually caused by infections which includes bacteria (*Aeromonas*, *Campylobacter*, *C. difficile*, *E. coli*, *Plesiomonas*, *Salmonella*, *Shigella*), parasites (*Cryptosporidium, Cyclospora*, *E. histolytica*, *Giardia*, *Microsporidia*), and viruses (rotavirus, norovirus) [3]. A few pathogens have been particularly associated with persistent diarrhea or are preferentially identified when an episode becomes persistent, such pathogens include enteroaggregative *E. coli* (EAEC), and enteropathogenic *E. coli* (EPEC), *Cryptosporidium*, *Shigella*, *Campylobacter*, *Yersinia*, and *Giardia lamblia* [18–20]. These pathogens cause continuous damage to mucosal lining of the intestine.

The exact cause of persistent diarrhea within population is still poorly understood and individual mechanism of action is still unknown [19]. The original infectious agents are particularly virulent and difficult to clear (e.g., *Shigella* species) [18]. 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. 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 [18].

Based on the pathogenic processes and clinical features, diarrheagenic *E. coli* (DEC) has been clustered into six pathotypes. The six pathotypes are EPEC, EAEC, enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), diffusely adherent *E. coli* (DAEC), and enteroinvasive *E. coli* (EIEC) [21–23]. In epidemic situations, *E. coli*, *Clostridium difficile*, and *Vibrio cholerae* have been reported as the causative agents of diarrhea in China [24, 25], Iran [26], Nigeria [27], and Yemen [28, 29]. In Bangladesh, *Cryptosporidium* (an intestinal parasite) was reported in chronic diarrheal cases, whereas *Giardia lamblia* was reported in acute and chronic cases of diarrhea in Peru [18, 30].

Risk Factors

The risk factors of persistent diarrhea includes 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, and reduced intestinal blood flow [3, 31, 32].

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. Malnutrition also increases the chances of death due to persistent diarrhea [3]. It impairs tissue repair mechanisms, and the infection tends to be more severe for longer duration. 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. Several studies have highlighted the high risk of prolonged diarrhea with lactation failure and early introduction of artificial feeds in developing countries. In particular, the administration of unmodified cow or buffalo milk is associated with prolongation of diarrhea, suggesting the potential underlying role of cow's milk protein allergy (CMPA) and milk protein enteropathy [33]. Inappropriate management of acute diarrhea is also an important risk factor. The association of prolongation of diarrhea with starvation and inappropriately prolonged administration of parenteral fluids has been recognized for over half a century [34]. 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. In particular, routine administration of antibiotics, antimotility agents, and semistarvation diets should be

avoided in cases of prolonged diarrhea [35]. There is now clear evidence supporting the enteral route for nutritional rehabilitation of malnourished children with persistent diarrhea [36] as starvation has been shown to have deleterious effects on the intestinal mucosa [37] with a reduction in gastrointestinal structure and function. It is therefore imperative that malnourished children with persistent diarrhea should receive enteral nutrition during their period of rehabilitation. 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 [38].

HIV has also shown association with persistent diarrhea. It affects several cellular mechanisms, for example, it causes the release of transactivating factor protein (Tat) by the virus which impacts enterocytes, both as an enterotoxin and a viral cytotoxin. This impairs cell growth, proliferation, and inhibition of ion transport [39]. In an immune-suppressed setting, infection with opportunistic agents such as *Blastocystis hominis*, *Candida albicans*, and *Cryptosporidium* leads to mucosal injury and diarrhea. HIV directly and indirectly causes malnutrition, immune impairment, and intestinal dysfunction. Antiretroviral therapy may also cause persistent diarrhea [10].

The aforementioned risk factors highlight the importance of recognizing that optimal management of diarrheal episodes is essential to progression to persistent diarrhea. It is natural that given the close relationship between diarrheal disorders, malnutrition, and HIV, persistent diarrhea is widely recognized as a nutritional disorder and that optimal nutritional rehabilitation is considered a cornerstone of its management.

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 [40]. This sequence is supported by the observation that *Shigella* infection – characterized by intense tissue catabolism and nutrient losses – almost doubles the risk of persistent diarrhea [41], dehydration [3], and why bloody diarrhea (caused by *Shigella* spp. in 45–67% cases and *Campylobacter* in 35–37% cases) so often reported to be a risk factor for persistent episodes [3, 42]. Children with bloody diarrhea are at high risk of morbidity and mortality [3]. The importance of *Shigella* is reflected in the report from at a large hospital center in Bangladesh that the frequency of persistent diarrhea diminished as the isolation rate of *Shigella* decreased between 1991 and 2010. 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.

There are several reasons why malnutrition should both predispose to and follow persistent diarrhea. These range from 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. An independent relationship has also been demonstrated between cutaneous anergy and the subsequent risk of development of persistent diarrhea [43]. There has been much interest in the possibility that such transient immune deficiency may also be a marker of concomitant micronutrient deficiency [44]. The most striking example of the critical role that the immune system plays in the pathogenesis of persistent diarrhea is the relationship of HIV/AIDS. This is exemplified by the host of studies linking persistent diarrhea with cryptosporidiosis [45] and other parasitic infections [46] in Africa and Asia.

A clear understanding of alterations in intestinal morphology and physiology is crucial toward the development of interventional strategies, but there has been little progress in our understanding of this problem in developing countries. This has been largely due to a paucity of studies formally evaluating intestinal biopsy findings in representative populations. A wide variety of pathological changes has been described after persistent diarrhea, however, ranging from near-normal appearance to mucosal flattening, crypt hypertrophy, and lymphocytic infiltration of the mucosa [47]. Recent elaborate electron microscopic studies of intestinal mucosa in persistent diarrhea reveal patchy villous atrophy and intraepithelial lymphocytic infiltration as well as severe mucosal damage and villous atrophy [48, 49]. Poor intestinal repair is regarded as a key component of the abnormal mucosal morphology. However, the exact factors underlying this ineffective repair process and continuing injury are poorly understood. The end result of this mucosal derangement is reduced absorption of luminal nutrients, as well as increased permeability of the bowel to abnormal dietary or microbial antigens [50]. Alterations of intestinal permeability in early childhood may reflect changes in intestinal mucosal maturation [51] and may be affected by concomitant enteric infections [52].

Management

It is imperative to consider the child's age and clinical manifestations to determine proper treatment in cases of persistent diarrhea. A paucity of diagnostic facilities limits the microbiologic evaluation of diarrhea in many parts of the world. Lack of awareness regarding cow's milk protein allergy and immunodeficiency-associated diarrhea is of par-

Table 17.1 Impact of interventions to prevent and control diarrhea

Intervention	Effect estimates
Water sanitation and hygiene	31–48% risk reduction for diarrhea by handwashing with soap and 31–52% risk reduction for diarrhea with improved water quality
Exclusive breastfeeding for 6 months	165% (10.5 times greater risk of death) increase in diarrhea among 0- to 6-month-old infants if not breastfed Not breastfeeding exclusively results in excessive risk of diarrhea prevalence (RR 2.15–4.90), incidence (RR 1.26–2.65), mortality (RR 2.28–10.52) and all-cause mortality (RR 1.48–14.40) in infants 0–5 months
Adequate complementary feeding among children 6–23 months, including adequate micronutrient intake	6% reduction in all child mortality
Preventive zinc supplementation	23% reduction in diarrhea-related mortality
Preventive vitamin A supplementation	23% reduction in all-cause mortality
Vaccines for rotavirus	74% reduction in very severe rotavirus infection 47% reduction in rotavirus hospitalization
Vaccines for cholera	52% effective against cholera infection
ORS	69% reduction in diarrhea-specific mortality
Prevention of HIV in children	2% reduction in all child mortality
Dietary management of diarrhea	Lactose-free diets reduce the duration of diarrhea treatment failure significantly by 47%
Therapeutic zinc supplementation	66% reduction in diarrhea-specific mortality 23% reduction in diarrhea hospitalization 19% reduction in diarrhea prevalence
Antibiotics for cholera	63% reduction in clinical failure rates 75% reduction in bacteriological failure rates
Antibiotics for *Shigella*	82% reduction in clinical failure 96% reduction in bacteriological failure rates
Antibiotics for cryptosporidiosis	52% reduction in clinical failure rates 38% reduction in parasitological failure rates
Community-based intervention platforms for prevention	160% increase in the use of ORS 80% increase in the use of zinc in diarrhea 76% decline in the use of antibiotics for diarrhea
Community case management (CCM)	CCM of diarrhea with zinc and ORS reduced diarrheal deaths among children under the age of 5 years by 93%
Financial support schemes	Conditional transfer programs: 14% increase in preventive healthcare use, 22% increase in the percentage of newborns receiving colostrum, and 16% increase in the coverage of vitamin A supplementation

ticular concern. 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 (Table 17.1).

Rapid Resuscitation, Antibiotic Therapy, and Stabilization

Most children with persistent diarrhea and associated malnutrition are not severely dehydrated and oral rehydration may be adequate. Indeed, routine use of intravenous fluids in severe acute malnutrition should be avoided; acute severe dehydration and associated vomiting may require brief periods of intravenous rehydration with Ringer's lactate. Acute electrolyte imbalance such as hypokalemia and severe acidosis may require correction. More importantly, associated systemic infections (bacteremia, pneumonia, and urinary tract infection) 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 [53, 54]. Children with bloody diarrhea (caused by *Campylobacter*, *Shigella*, or some parasites) require antibiotic therapy for enteric pathogens. Ceftriaxone, ciprofloxacin, and pivmecillinam have shown to be effective against local strains of *Shigella* [55], whereas azithromycin and fluoroquinolones are highly effective against *Campylobacter* gastroenteritis. Treatment against strain of *Shigella* is recommended to be changed if no improvement is observed within two days of treatment.

Emergence of antibiotic resistance strains of enteric pathogens are a great threat worldwide. For example, multidrug resistance has been reported against *Shigella* sp. in Ethiopia [56], Nigeria [57], and Mozambique [58]. In such instances, fortified food therapy (such as zinc and iron), immunotherapy [59–61], lactose-free diet [62], fecal microdata transplantation (used in *Clostridium difficile*-associated diarrhea) [63], and probiotics [64–66] are the alternative treatment options against the enteric pathogens. It should be emphasized that 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 [67] and adjunctive therapy for cryptosporidiosis in children with HIV and persistent diarrhea [68].

Oral Rehydration Therapy

Death by persistent diarrhea is usually caused by malnutrition or by hypovolemia (dehydration). It is over 40 years since the efficacy of oral rehydration therapy (ORT) was clearly demonstrated, following discovery of glucose-stimulated sodium uptake by intestinal villus cells [62, 69, 70]. This is the preferred mode of rehydration and replacement of on-going losses. The net effect is expansion of the intravascular compartment and rehydration, usually sufficient for all but the most severely dehydrated patients require initial intravenous fluids [71]. World Health Organization (WHO) has recommended a new low osmolarity solution for the management of diarrhea [72], 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. In general, the standard WHO oral rehydration solution is adequate, while recent evidence indicates that hypo-osmolar rehydration fluids [73] as well as cereal-based oral rehydration fluids may be advantageous in malnourished children. 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 [74, 75]. However, in Nigeria, homemade fluids and cereal-based oral therapies have proven to be effective in the management of diarrhea [76].

Enteral Feeding

Nutritional rehabilitation can break the vicious cycle of chronic diarrhea and malnutrition and is considered the cornerstone of treatment. It is exceedingly rare to find persistent diarrhea in exclusively breastfed infants, and 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. 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. Mattos et al. [77] claimed that yogurt-based diet is recommended as the first choice for the nutritional management of a mild to moderate persistent diarrhea. A cheap and an easily available yogurt-based diet can be used in mild chronic diarrhea illness of uncomplicated and without enteropathy. Bhutta et al. [36] suggested algorithm for the diagnosis and management of persistent diarrhea (Fig. 17.1). Elimination diet is considered when allergic enteropathy is induced by a cow's milk protein or soy protein [78]. Rarely, when dietary intolerance precludes the administration of cow's milk-based formulations or milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blended chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. 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 [79, 80]. Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, 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. 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 and 3 g/kg/day. Additionally, potassium should also be included in the diet providing approximately 5 mEq/kg per day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques may also be helpful. 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) in the same way as children without diarrhea, whether they are being managed as inpatients or outpatients. And these chil-

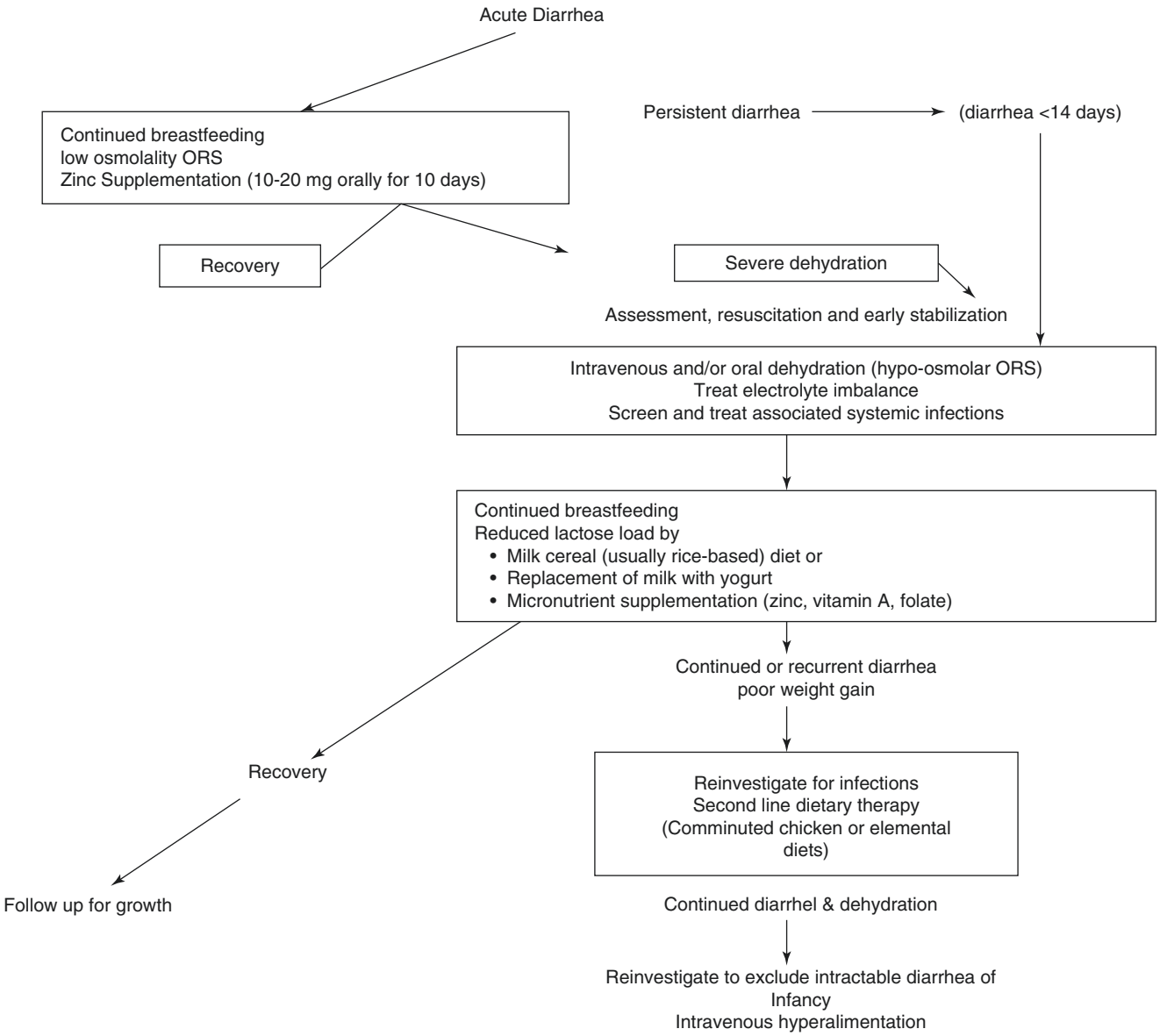

Fig. 17.1 Algorithm of diagnosis and management of persistent diarrhea

dren with severe acute malnutrition (SAM) 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 [3].

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 [81]. This may be a consequence of poor intake and continued enteral losses and requires nutritional rehabilitation [82]. While the evidence supporting zinc administration in children with persistent diarrhea is persuasive, it is likely that these children have multiple micronutrient deficiencies. Concomitant vitamin A administration to children with persistent diarrhea has been shown to improve outcome [83, 84], especially in HIV endemic areas [85]. In Bangladesh, a combination of vitamin A, zinc, and ORS has proven to be effective at reducing child mortality caused by diarrhea [86]. WHO recommended 10 mg/day of zinc for 10–14 days for children <6 months and 20 mg/day for children >6 months [87]. Zinc has shown a significant effect among children >6 months with shortened duration of persistent diarrhea by approximately 16 hours [88, 89]. However,

zinc decreases the absorption of copper and causes copper depletion in the body [89]. 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. Thus, in July 2019, WHO has recommended to administer folate, iron, vitamin A, copper, and magnesium twice a day for two weeks [90].

Antidiarrheal Drugs

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

Pancreatic Enzyme Replacement Therapy (PERT)

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. Studies from Indonesia identified children (6–60 months) with pancreatic enzyme deficiency through fecal elastase-1 test [91, 92]. These children were provided with PERT (8371 United States Pharmacopeia [USP] units of lipase) three times a day for a month. This therapy showed decrease in duration of diarrhea by 3–7 days in the intervention group when compared to the placebo group.

Improved Case Management of Diarrhea

Improved management of diarrhea through prompt identification and appropriate therapy significantly reduces diarrhea duration, its nutritional penalty, and risk of death in childhood. 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 diarrhea, coupled with selective and appropriate use of antibiotics, have the potential to reduce the number of diarrheal deaths among children through Community Case Management (CCM) and Integrated Management of Childhood Illness (IMCI). Community-based interventions to diagnose and treat childhood diarrhea through community health workers leads to a significant rise in care-seeking behaviors for diarrhea and are associated with significantly increased use of ORS and zinc at household level as well as reduction in the unnecessary use of antibiotics for diarrhea by 75% [93].

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. Recent evidence suggests modest effect of probiotics with reduced duration of persistent diarrhea and stool frequency [94]. 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 in Community Settings

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. This poses a considerable challenge in communities deprived of basic necessities such as clean water and sewage disposal.

In addition to the preventive aspects, 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. Given that the majority of cases of persistent diarrhea occur in the community and that parents are frequently hesitant to seek institutional help, there is a need to develop and implement inexpensive and practical home-based therapeutic measures [95] and evidence indicates that it may be entirely feasible to do so in community settings [96, 97].

Conclusions

Persistent diarrhea remains an existential threat, especially among children under 5 years of age in resource-limited countries where quality of life and access to health care are low.

Persistent diarrhea in children contributes to childhood malnutrition and mortality. Most of the knowledge and tools (bioinformatics, metagenomics) needed to prevent diarrhea-associated mortality in developing countries, and especially persistent diarrhea, are available. These require concerted and sustained implementation in public health programs. Given the emerging evidence of the long-term impact of childhood diarrhea on developmental outcomes [98], 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.

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