Persistent Diarrhea in Developing Countries

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Key Words

Diarrhea, persistent · Micronutrient deficiency · Malnutrition · Immune deficiency · Therapy, inappropriate, acute diarrhea

Abstract

Globally diarrheal diseases account for almost a fifth of all deaths of children under 5 years, with an estimated 2.2 million deaths annually. Of these deaths, a significant proportion are related to episodes of persistent diarrhea (PD; defined as diarrhea of >14 days with growth faltering). PD has been shown to identify children with a substantially increased diarrheal burden. These account for 36–54% of all diarrhea-related deaths. Although the exact pathogenesis of PD remains unclear, most episodes are related to prior acute infectious diarrhea with prolongation of the most recent episode. This may be related to several host factors such as preexisting undernutrition, micronutrient deficiency, immune deficiency and inappropriate therapy of the most recent acute diarrheal episode. The common final event appears to be prolonged intestinal mucosal injury and ineffective repair. In contrast to post-infectious PD, some infants may have severe intractable diarrhea due to a variety of disorders, many of which have a hereditary basis. These now form the dominant type of prolonged diarrhea in developed countries. The management of PD depends upon close attention to nutritional rehabilitation and early recogni-

tion of complications. Although a variety of pathogens have been associated with PD, there is little role for oral antimicrobial therapy in the routine treatment of PD. However, attention to rehydration, appropriate screening and treatment of systemic infections and enteral nutrition rehabilitation with easily digestible diets are critical in managing such children, frequently in ambulatory settings. Administration of zinc and vitamin A may shorten the duration of PD and also help reduce recurrences. However, the most important preventive strategies for PD are exclusive breastfeeding in the first 6 months of life, continued breast-feeding for 2 years with appropriate complementary feeding and optimal management of acute diarrheal episodes.

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Introduction

Despite considerable advances in the understanding and management of diarrheal disorders in childhood, globally these still account for a large proportion (20%) of childhood deaths, with an estimated 2.2 million deaths [1]. In a global estimate of the burden of diarrheal disorders in 1980 the World Health Organization calculated that there were over 700 million episodes of diarrhea annually in children under 5 years of age in developing countries (excluding China), with approximately 4.6 million deaths [2]. More recent reviews of studies published

in the last 10 years indicate that although global mortality may have been reduced, the overall incidence remains unchanged at about 3.2 episodes per child year [2–5]. However, it is important to point out that the amount of information available from good quality epidemiological surveys between these time periods also varied significantly and relatively few studies were conducted recently. The previous survey undertaken in 1993 included 276 studies conducted in 60 countries [3], whereas the 2003 review had data from only 31 studies conducted in 20 countries [5].

It is recognized that most diarrheal disorders form a continuum, with the majority of cases resolving within the first week of illness. However, a smaller proportion of diarrheal illnesses fail to resolve and persist for longer than 2 weeks. Persistent diarrhea (PD) is defined as episodes that began acutely but last for at least 14 days [6]. These criteria identify children with a substantially increased diarrheal burden and an increased rate of diarrhea-related deaths. Such episodes were recognized to account for 3 to 20% of all diarrheal episodes in children under 5 years of age [7]. In several large community-based studies of diarrhea [8, 9] it has been shown that PD is directly responsible for between 36 and 54% of all diarrhea-related deaths. It has, however, been pointed out that such differences in mortality between different regions may be related to environmental characteristics and differences in the utilization of health care and oral rehydration therapy [10]. Although PD accounted for only 5% of all diarrheal episodes in a large prospective study of diarrhea in north India, the case fatality rate for PD was 14% in comparison with 0.7% for episodes of shorter duration [11].

It is important to recognize that most cases of PD in developing countries represent post-infectious diarrhea. The majority of cases of diarrhea in developing countries are of acute onset and are shorter than 1 week in duration. However, a group of children develop episodes of longer duration, some lasting longer than 14 days [12]. Although the aforementioned division of diarrheal episodes into acute and PD may be arbitrary, this operational definition identifies children with significantly increased diarrheal burdens. In a prospective study in northeastern Brazil, Lima et al. [13] demonstrated that all children with a heavy diarrheal burden (defined as >16% of total days spent with diarrhea) had at least one episode of PD during a 1-year study period. Similar observations by Moy et al. [14] in a rural cohort of 204 children in Zimbabwe indicated that although PD accounted for only 6% of all diarrheal episodes, these included 22% of the total days of diarrhea recorded in this study and that these children

also had higher rates of diarrheal relapse at follow-up. Thus, children with PD may not represent a distinct subgroup but form part of a continuum in susceptibility to diarrhea. Many children (especially infants and toddlers) in developing countries may have frequent recurrent episodes of acute diarrhea. While few individual episodes may persist beyond 14 days, frequent recurrences of acute diarrheal episodes do result in nutritional compromise and may predispose these children to develop PD.

In contrast to PD in developing countries, cases of prolonged diarrhea among young children in developed countries may fall under the category of intractable diarrhea of infancy. These cases are defined as diarrhea lasting for at least 2 weeks where at least 50% of the daily fluid requirement may need to be provided intravenously. Many of these disorders have a genetic basis and may also be seen in developing countries, although their prevalence is greatly overshadowed by those of post-infectious PD.

Review Methods

A recent working group on PD reviewed the information and actions needed at the level of pediatricians, training institutions and professional societies [15]. However, the review did not elaborate upon recent epidemiological trends, and interventions needed in public health systems. This current review will present an overview of the current status of epidemiological information and evidence gaps for clinical care as well as public health interventions.

In order to assess recently available information and trends, we reviewed all the available information on diarrhea epidemiology and PD over the last 15 years (1990–2004) in electronic medical (PubMed/Medline, Extra Med, Pop Line) and social science libraries. Other search terms such as ‘chronic diarrhea’, ‘prolonged diarrhea’ and ‘intractable diarrhea’ also were used to search for published relevant reports. In addition a manual search of relevant monographs and WHO/UNICEF materials also was conducted to access recent information on PD and management strategies targeting children. The available studies were then classified into those addressing epidemiology or burden estimates, pathogenesis, management strategies at either facility or community settings and available randomized controlled trials. We also evaluated studies of PD that related to the HIV status of populations and related pathogens such as cryptosporidium, *Giardia lamblia*, etc.

Fig. 1. Incidence of childhood diarrhea in community settings [11, 17–20].

It was evident that the bulk of the epidemiological information on the relationship of acute diarrheal episodes to PD was derived from studies undertaken over a decade ago. There was a remarkable paucity of recent data on this subject, especially from non-HIV endemic areas. However, it was evident from studies in HIV endemic areas that chronic enteropathy and PD was increasingly recognized as common manifestations of advancing HIV infection and AIDS [16].

There is little evidence overall that the true global incidence of PD has decreased. Figure 1 indicates the duration of diarrhea from several community-based studies in developing countries [11, 17–20]. Although recent data from community-based studies on diarrhea are relatively sparse, the overall rates of PD from community settings appeared remarkably constant over the period between 1980 and 1992. A recent community-based study from Bangladesh [20] indicates that PD accounted for less than 0.5% of all cases of diarrhea in an urban community setting, and it is difficult to generalize about trends in the reduction of the burden of PD. There is a clear need to review the previously estimated proportions of acute diarrheal episodes that become prolonged.

The HIV/AIDS epidemic in Africa has resulted in a change in the usual etiological patterns of diarrhea. Prolonged episodes associated with infections due to relatively rare organisms such as cryptosporidium are more common.

Pathogenesis of PD

Prolonged diarrhea in childhood also may arise from a large number of conditions, many of them non-infectious. The most common of these disorders are: cow/soy milk protein intolerance (in infants <6 months old, often with blood-tinged stools); celiac disease (gluten-sensitive enteropathy), and cystic fibrosis (creatorrhea and steatorrhea secondary to pancreatic insufficiency). In other instances, toddler's diarrhea also may be seen in relatively well-nourished infants.

However, globally the most important underlying trigger for PD is an acute diarrheal episode due to an enteric infection and the consequences thereof. There have been several studies on pathogens causing PD in developing countries but few have pinpointed a major causative organism. Although it may appear that PD is a consequence of poor management of acute infectious diarrhea, some pathogens are isolated with greater frequency from children with PD. Table 1 indicates the various organisms that have been associated with PD among children from different parts of the world.

Globally almost a quarter of all diarrhea deaths are associated with dysentery, a large proportion caused by *Shigella* organisms. In a recent study from Bangladesh [21], PD was seen in 23% of children with shigellosis and *Shigella* infections were significantly associated with an increased risk of PD (age-adjusted relative risk 1.83; 95% confidence interval 1.19–2.81). Infection by multiple an-

Table 1. Pathogens associated with prolonged and persistent diarrhea

Bacteria	Enteroaggregative <i>Escherichia coli</i> Enteropathogenic <i>Escherichia coli</i> <i>Campylobacter</i> <i>Salmonella enteritides</i> <i>Shigella</i> species <i>Clostridium difficile</i> <i>Arcobacter butzleri</i> <i>Klebsiella</i> species
Parasites	<i>Giardia lamblia</i> <i>Blastocystis hominis</i> ¹ <i>Cryptosporidium</i> spp. ¹ <i>Entamoeba histolytica</i> <i>Cyclospora cayetanensis</i> ¹
Viruses	Human astrovirus 3 Enterovirus Picobornaviruses

¹ Especially associated with HIV infections/AIDS.

Table 2. Etiology of intractable diarrhea of infancy

1	Congenital chloride diarrhea
2	Microvillus inclusion disease
3	Epithelial dysplasia or Tufting enteropathy
4	Autoimmune enteropathy
5	Food allergy
6	Chronic intestinal pseudo-obstruction/Hirschsprung's disease
7	Intestinal lymphangiectasia
8	Abeta-lipoproteinemia
9	Eosinophilic enteropathy
10	Intestinal neurodysplasia
11	Congenital enzymatic deficiency (congenital glucose-galactose malabsorption, sucrase-isomaltase deficiency, etc.)
12	Trichorrhexis nodosa, facial dysmorphism, immune deficiency and cirrhosis

tibiotic-resistant *Shigella* isolates (age-adjusted relative risk 3.76; 95% confidence interval 1.51–9.36) and occurrence of shigellosis during infancy were observed to be risk factors for initiation of *Shigella* diarrhea persistence. However, 88% of the persistent shigellosis episodes occurred in older children, 50% were associated with non-dysenteric shigellosis and 79% were caused by *Shigella* species other than *Shigella dysenteriae*. Other organisms may similarly affect mucosal inflammation. An additional pathogenic mechanism underlying entero-aggregative

Escherichia coli infections may include the induction of IL-8 and mucosal inflammation.

In contrast to PD, there is much greater understanding of the mucosal absorptive and transport mechanisms underlying intractable diarrhea in developed countries. Table 2 indicates some of the major causes of intractable diarrhea of infancy.

It is now recognized that mutations of the Cl⁻/HCO₃⁻ exchanger of the ileocolonic apical membrane (solute carrier family 26, member 3 gene [SLC26A3, alias CLD or DRA]) result in the net secretion of chloride by the intestine and a clinical syndrome recognized as congenital chloride-losing diarrhea [22]. Similarly it is recognized that congenital glucose/galactose malabsorption is the result of a genetic defect resulting in a reduction or absence of functional sodium-coupled glucose transporter SGLT1 at the enterocyte cell surface [23], and a number of genotype/phenotype relationships have been recognized [24]. Congenital sucrase-isomaltase deficiency (CSID) also presents with osmotic diarrhea following the introduction of sucrose/complex starches into the weaning diet. Molecular and cell biological studies have defined the pathogenesis of CSID extremely well demonstrating that CSID appears to be a result both of defective synthesis and glycoprotein processing [25].

In contrast, detailed studies from developing countries of mucosal abnormalities and factors underlying mucosal abnormalities in PD are woefully rare and none have explored the molecular mechanisms of prolonged intestinal injury. The most striking example of the critical role that the immune system plays in the pathogenesis of PD is the relationship of HIV/AIDS with PD. This is exemplified by a host of studies linking PD with cryptosporidiosis [26] and other parasitic infections in Africa and Asia. Although these observations suggest that immune deficiency may be related to the risk of prolonged diarrhea [27], there also has been much interest in the possibility that a transient immune deficiency also may be a marker of concomitant micronutrient deficiency [28, 29].

An additional factor underlying poor intestinal repair may include key micronutrient deficiencies that can influence this process. From initial studies indicating the potential benefit of zinc supplementation on reducing the risk of prolonged diarrhea [30], recent meta-analyses of zinc supplementation in diarrheal illnesses indicate a significant reduction in the duration and severity of diarrheal illnesses [31]. Thus zinc deficiency may significantly contribute to the prolongation of mucosal injury and delayed intestinal repair mechanisms. The benefits of

Fig. 2. Pathway to prolonged and persistent diarrhea.

zinc in reducing mortality from childhood diarrhea have led to its inclusion in the current recommendations for diarrhea management by WHO/UNICEF [32]. However, very little is known about the mechanisms of action of zinc in reducing diarrhea duration and severity and maintaining intestinal mucosal integrity.

Poor intestinal repair is regarded as a key component of abnormal mucosal morphology. However, the exact factors underlying ineffective repair processes and continuing injury are understood poorly. The end result of mucosal derangement is poor absorption of luminal nutrients and increased permeability of the bowel to dietary or microbial antigens. Although PD is recognized widely as a nutritional disorder, there is remarkably poor understanding of the mechanisms underlying PD and the mucosal immunopathology in children who develop this syndrome. However, several factors that contribute to diarrheal persistence have been recognized, including general undernutrition, and micronutrient and immune deficiencies, suggesting that delayed intestinal repair following initial injury may be an important contributory factor. Figure 2 indicates the mechanisms associated with delayed intestinal repair and prolonged enteropathy that may underlie post-infectious PD.

A clear understanding of the alterations in intestinal morphology and physiology is crucial to the development of interventional strategies. However, a wide variety of post-PD pathological changes have been described by fairly small studies [33–35]. These studies indicate important findings suggestive of chronic inflammation and impaired mucosal integrity. In this regard there needs to be much more concerted work on representative populations.

Management of PD

The most important aspect in the management of the child with PD is an immediate assessment and triage for subsequent therapy. The management of PD in undernourished children is based on the principles of management of diarrhea and undernutrition. Although a subgroup may be severely undernourished requiring rapid nutritional rehabilitation, often in hospital, in other cases ambulatory management may be possible. Given the long time it may take to recovery, prolonged hospitalization may be quite problematic in developing countries, and whenever possible ambulatory or home-based therapy must be stressed.

Fig. 3. Suggested algorithm for the management of persistent diarrhea.

The following represent the basic principles of management of PD and a suggested therapeutic approach is summarized in figure 3 [36].

(1) Initial Resuscitation and Stabilization

Most children with PD and associated undernutrition are not severely dehydrated and oral rehydration may be adequate. However, acute exacerbations and associated vomiting may require brief periods of intravenous rehydration with Ringer's lactate. Acute electrolyte imbalances such as hypokalemia and severe acidosis may require correction. More importantly, bacterial translocation [37] and systemic infections have been recognized in severely undernourished children with PD and are a frequent cause of early mortality. These must be screened for on admission. Up to half of all undernourished chil-

dren with PD may have an associated systemic infection requiring resuscitation and antimicrobial therapy [38, 39]. In severely ill undernourished children requiring hospitalization, broad-spectrum antibiotics on initial admission and stabilization may be required while awaiting cultures. Some may also require empirical therapy for cryptosporidiosis, especially in HIV-infected children [40].

(2) Oral Rehydration Therapy

Although in general the standard WHO oral rehydration solution is adequate for replacing on-going losses, recent evidence indicates that low osmolality oral rehydration fluids [41, 42] may be advantageous in undernourished children, with no associated risk of hyponatremia.

(3) Enteral Feeding and Diet Selection

It is exceedingly rare to find PD in exclusively breast-fed infants and, with the context specific possible exceptions of situations where PD accompanies perinatally acquired HIV infection, breastfeeding must be continued.

Despite mucosal abnormalities and diminution in digestive and absorptive mechanisms, most children with PD have adequate absorption capacity and tolerate enteral feedings. Metabolic balance studies in undernourished children with PD indicate that satisfactory carbohydrate, protein and fat absorption can take place on a variety of diets [43, 44]. In general, therefore, withdrawal of milk and replacement with specialized (and expensive) lactose-free formulations is unnecessary.

Most children with PD are not lactose intolerant, although administration of lactose loads exceeding 5 g/kg/day are associated with higher purging rates and treatment failures [45]. Alternative strategies of reducing lactose loads in undernourished children with PD include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt. These dietary interventions have been evaluated extensively in several studies, and found to be efficacious and acceptable in comparison to several expensive formulations [7, 46].

Rarely when dietary intolerance precludes the administration of cow's milk-based formulations or cow's milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blenderized chicken-based diet or an elemental formulation [47]. It must be pointed out that although effective in some settings [48], the latter are unaffordable in most developing countries. However, a guar gum-comminuted chicken combination has been found to be effective in children with PD [49]. In addition to the above, the addition of green banana or pectin to the diet [50] has been shown to be effective in the treatment of PD.

The usual energy density of any diet used for the therapy of PD should be around 1 kcal/g, aiming to provide an energy intake of at least 100 kcal/kg/day, and a protein intake of between 2 and 3 g/kg/day. The commonly used rice-lentil formulations in South Asia such as *khitchri* provide this energy density in combination with an optimal protein intake and amino acid ratio.

(4) Micronutrient Supplementation

It is recognized widely that most undernourished children with PD have associated deficiencies of micronutrients including zinc, iron and vitamin A. This may be a consequence of poor intake and continued enteral losses

and requires replenishment during therapy [51]. Although the evidence supporting zinc administration in children with PD is persuasive, it is likely that these children have multiple micronutrient deficiencies. Concomitant vitamin A administration to children with PD was shown to improve outcomes [52, 53], especially in HIV endemic areas [54]. It is therefore important to ensure that all children with PD and undernutrition receive an initial dose of 100,000 units vitamin A and a daily intake of at least 3–5 mg/kg/day of elemental zinc.

(5) Follow-Up and Nutritional Rehabilitation in Community Settings

Given the high rates of relapse in most children with PD, it is important to address the underlying risk factors and institute preventive measures. These include appropriate feeding (breastfeeding and 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 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 that can be used to manage children with PD. Given that the majority of cases of PD occur in the community and that parents frequently are hesitant to seek institutional help, there is a need to develop and implement inexpensive and practical home-based therapeutic measures. Available evidence indicates that it may be entirely feasible to do so in community settings [55, 56].

Preventive Strategies for PD

Although optimal nutritional rehabilitation of children with PD is regarded as a cornerstone of management [44], prevention is critical. For this purpose large-scale improvements in diarrhea prevention and management strategies in developing countries are critical. As indicated by us in reviewing available child survival interventions, existing interventions can prevent almost 55% of all deaths globally in children under 5 years [57], a fifth of which are related to diarrhea.

These interventions include exclusive breastfeeding and safe complementary feeding strategies to prevent diarrhea and, in the event episodes occur, optimal management with improved oral rehydration, zinc supplementation and continued feeding. As indicated above, this re-

quires that all episodes of diarrhea are recognized promptly and managed optimally with oral rehydration and enteral feeding with inexpensive, home-available and culturally acceptable diets that can be used to manage children with PD in ambulatory settings. The next steps would be to integrate these interventions so that families and community health workers can implement them in a variety of situations [58].

Providing essential preventive and therapeutic interventions to reduce PD in health systems are necessary in order to achieve the millennium development goals of reducing child mortality by two thirds by the year 2015. Early and unhygienic introduction of milks other than breast milk and recurrent acute diarrheal episodes that are managed poorly are important predisposing factors to the development of PD. It is important that these be prevented. These risk factors are generally prevalent in poor communities and both poverty alleviation and social sector support mechanisms are fundamentally im-

portant. Thus promotion of exclusive breastfeeding for at least 6 months, avoidance of unhygienic formula feeding, timely and adequate weaning with hygienic nutritious foods will help to prevent episodes of post-infectious PD. These must be coupled with environmental control measures and provision of safe water and safe foods [59]. In the absence of the latter, interventions to promote hand-washing strategies and domestic measures to purify water are key to reducing the burden of diarrhea [60, 61].

A combination of allocation of appropriate resources for public health and basic needs, staff training and community mobilization are necessary to reduce the global burden of diarrhea and PD. This requires sustained and concerted efforts. In many parts of the developing world these interventions require that, apart from biomedical interventions, we give paramount importance to poverty alleviation and promotion of a human rights and equity agenda.

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