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Persistent diarrhea: still an important challenge for the pediatrician

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Abstract

Objective: To provide recent guidelines to reduce the incidence of diarrheal diseases. We discuss the definition, clinical aspects, pathophysiology, diagnosis, management, and prevention of persistent diarrhea.

Sources: Electronic search of the MEDLINE database, Google search.

Summary of the findings: Acute diarrhea may be caused by a variety of agents, including bacterial, viral, and protozoan pathogens. The top priority in treatment of diarrhea is replacement of fluid and electrolytes losses, particularly at the acute stage, and, under certain circumstances, eradication of the enteropathogenic agent. On the other hand, treatment of persistent diarrhea should focus on prevention and management of food intolerance and malnutrition.

Conclusions: Promotion of breastfeeding, adequate interventions in the treatment of acute diarrheal episodes, introduction of safe dietary strategies for prevention of malnutrition, and improvements in sanitation and hygiene conditions, including sewage and clean water, are essential measures for the reduction of diarrheal morbidity and mortality rates in children under 5 years of age.

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Introduction

Diarrheal disease still accounts for a substantial proportion of deaths (16%) among children under 5 years of age, second only to pneumonia (17%).[1] This rate remains high despite considerable advances in the management of diarrhea and in our understanding of the various pathophysiological mechanisms whereby enteropathogenic agents cause diarrheal illness. Mortality rates have declined since the early 1980s, when diarrhea led to the deaths of 4.5 million children annually,[2] but it remains the second leading cause of death in under-fives and still accounts for 1.5 million annual deaths worldwide.[1] In a comprehensive review of the literature, Boschi-Pinto et al.[3] reported that the estimated annual under-five mortality rate for diarrheal disease was 1.87 million, which would account for roughly 19% of the 10 million under-five deaths occurring in 2004.[4] According to the authors, a mere 15 developing countries in Africa and Asia accounted for 78% of these deaths.[3]

Until recently, the rate of progression of acute diarrheal episode to persistent diarrhea (PD) in under-fives was estimated to range between 3 and 28%, depending on myriad reasons including the enteropathogenic agent isolated in stool samples, seasonal aspects, geographic considerations, socioeconomic and educational conditions and availability of sanitation. In a previous study of 200 infants under 12 months of age with diarrhea, we found that isolation of enteropathogenic *Escherichia coli* in stool samples was associated with a 28.4% rate of conversion to persistent diarrhea, vs. 6.9% when the acute episode was caused by another enteric pathogen.[5] On the other hand, in direct contrast to the aforementioned statistics, a recent

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study conducted in Salvador, state of Bahia, by Strina et al.[6] found that only 1.4% of acute diarrheal episodes progressed to persistent diarrhea.

PD has a high impact on pediatric morbidity and mortality rates in developing countries; over 50% of diarrhea-related deaths in these countries are associated with persistent diarrheal disease.[7] Most deaths occur in young children living in the rural areas of developing nations, where adequate sanitation is unavailable.[8] Recurring episodes of diarrheal disease in the first years of life usually lead to malabsorption and subsequent malnutrition. As the onset of PD is most often at a critical stage of physical and mental development, it can have a serious adverse impact on growth curves, intellectual and cognitive function, and future educational performance, and can also increase morbidity and mortality due to other diseases.[9-11]

In poorer countries, diarrhea is among the three leading causes of death in under-fives, alongside neonatal disease and pneumonia.[12,13] On the other hand, several universal measures (including frequent, successful campaigns promoting oral rehydration therapy from the 1980s onward), major improvements in sanitation and water quality, and the establishment of the Brazilian Universal Health System and, particularly, its Family Health Program, in 1994, have led to substantial reductions in pediatric diarrheal mortality rates in Brazil.[14] In several regions across the country, these rates have declined approximately 90%, which also reflects a reduction in geographic disparities and socioeconomic inequalities.[14] These results are an example to be followed, as they clearly show that implementation of vertical programs and long-term horizontal approaches can make the fourth Millennium Development Goal – to reduce by two-thirds, between 1990 and 2015, the under-five mortality rate – achievable.[12]

PD continues to pose a challenge to pediatricians in terms of its pathophysiology and clinical management. In an attempt to minimize the morbidity and mortality impact of this condition, the present article provides a comprehensive review of the etiological and pathophysiological aspects of PD, its diagnosis, its most common dietary complications, the currently available therapeutic armamentarium, and methods for prophylaxis.

Definition

PD was defined by the World Health Organization (WHO) in 1987 as "diarrheal episodes of presumed infectious etiology that begin acutely, but have an unusually long duration… [lasting] at least 14 days," leading to a deterioration in nutritional status and a substantial risk of death. The term does not include chronic or recurrent diarrheal disorders such as tropical sprue, celiac disease, cystic fibrosis, or other hereditary diarrheal disorders.[15]

The establishment of a 14-day cutoff value to distinguish acute from persistent diarrhea was justified by the fact that mortality rates were found to be roughly 0.8% when the diarrheal episode lasted 14 days or fewer, only to climb to 14% when duration of the episode exceeded 14 days, which led to the characterization of PD as a potentially lethal condition.[16]

Etiological and pathophysiological aspects

At birth, the bowel is usually sterile; colonization by the maternal (vaginal and fecal) microbial flora begins in the first days of life. This first colonization is one of the most important immune exposures of neonatal life.[17]

Humans are constantly challenged by pathogenic organisms (viruses, bacteria, and protozoa). Although some pathogens are ubiquitous in nature (such as rotavirus, which infects 95% of the under-five population worldwide[18]), enteric infectious diseases depend on environmental factors and vary according to level of hygiene, sanitation, and access to safe drinking water.[8] A wide range of enteropathogenic agents can cause childhood diarrhea. The frequency with which a given enteropathogen is isolated from stool samples can differ between developed and developing nations; within geographic regions; according to age, immunocompetence, and presence or absence of breastfeeding; and depending on the season.[19,20] Knowledge of the etiology of diarrheal disease is of the utmost importance, particularly in developing countries, where morbidity and mortality rates are higher and the vicious cycle of diarrhea and malnutrition is much more easily established.

The enteropathogenic agents isolated during PD are not always the same found in the acute stage of the diarrheal episode, which suggests that secondary infection may play a major role in the um persistence of diarrhea.[21] Infection with several pathogens has also been described.[22] When an infectious agent cannot be isolated, other clinical entities should be considered; the most common culprits include dietary intolerance in its various forms and allergic reactions to foreign proteins.

The following list provides an overview of the main enteropathogenic microorganisms isolated from stool cultures of children with PD, as reported by various centers worldwide.[23]

Bacterial:

- Enteroaggregative *Escherichia coli* (EAEC);
- Enteropathogenic *Escherichia coli* (EPEC);
- *Campylobacter* spp;
- *Salmonella Enteritidis*;
- *Shigella* spp;
- *Clostridium difficile;*
- *Arcobacter butzleri*;
- *Klebsiella* spp.

Protozoan:

- *Giardia lamblia*;
- *Blastocystis hominis**;
- *Cryptosporidium* spp*;
- *Entamoeba histolytica*;
- *Cyclospora cayetanensis**;
- *Enterocytozoon bieneusi* (*Microsporidium* spp)*.

Viral:

- Human astrovirus;
- Enteroviruses;
- Picornaviruses.

* Particularly associated with HIV infection.

The epidemiological features of PD patients do not differ significantly depending on causative agent. In most cases, children with PD were not breastfed or were weaned at an excessively early age. Diarrhea is similar to that of acute episodes, but is associated with a malabsorption syndrome. Unless treated with appropriate dietary management interventions, this will lead to malnutrition and its host of untoward consequences – including increased immune vulnerability, which predisposes children to opportunistic infections that may spread systemically and carry a high mortality rate. Recurrent and/or persistent diarrheal episodes lead to more severe nutritional disturbances. This phenomenon is made even more serious when nutritional support remains inadequate during the convalescent stage, which is usually the case due to anorexia and improper refeeding practices.

PD is the end result of a variety of insults sustained by children who are exposed to frequent, severe diarrheal episodes due to a combination of host-dependent factors and highly prevalent environmental contaminants. These episodes generally occur in children under the age of 3.[24] Protein-energy malnutrition is believed to be the main risk factor for persistent diarrhea, but other determinants should also be taken into account, such as recent history of acute diarrheal episode, zinc deficiency, absence of breastfeeding, male gender, infection with enteropathogenic or enteroaggregative *E. coli* strains, cryptosporidiosis,[25] and history of intrauterine growth restriction.[26]

Bhutta et al.[27] note that the factors associated with increased risk of PD are environment-related, such as poor hygiene, contact with animals, and fecal-oral spread of enteric pathogens. Furthermore, there are other host-related indicators, including young age, worsening nutritional status, and immune deficiency.[27] The authors stress that lack of breastfeeding and a prior history of gastrointestinal and respiratory infection play a decisive role in progression to PD. They also note that errors in nutritional and pharmacological management of acute diarrheal episodes can also lead to persistence of the disease process. Recurring intestinal infection causes mucosal injury of the small bowel, and, as such, may lead to villous atrophy. This reduces the absorptive surface area of the small intestine, increases inflammatory infiltration of the lamina propria, and encourages breakdown of the epithelial permeability barrier, facilitating penetration of potentially allergenic foreign proteins and thus increasing the likelihood of persistent diarrheal disease due to development of intolerance to multiple foodstuffs.[27]

Pathophysiology

Progression from acute to persistent diarrhea is due to an interaction between several complex pathophysiological mechanisms that affect the patient's nutritional status. Among the countless factors that may play a role in perpetuating diarrheal illness, small bowel bacterial overgrowth caused by colonization of the small intestine by colonic flora most certainly has a major impact. This pathophysiological phenomenon, which is particularly associated with anaerobic bacteria such as *Veillonella* and *Bacteroides* species, predisposes to intestinal mucosal injury.[22] Pathologic changes occur as a result of the ability of anaerobic bacteria to induce deconjugation and 7α-dehydroxylation of the primary bile acids cholic and chenodeoxycholic acid, converting them into their respective secondary bile acids (deoxycholic and lithocholic acid), which are highly damaging to the jejunal mucosa. When present in the bowel lumen, these secondary, unconjugated bile acids induce water and sodium secretion and glucose malabsorption, and can also lead to breakdown of the intestinal permeability barrier, facilitating entry of intact – and potentially allergenic – macromolecules. Furthermore, the presence of secondary and unconjugated bile salts in the small bowel prevents formation of mixed micelles, which play an essential role in ensuring solubilization of dietary fats. This pathological mechanism thus contributes to poor digestion and malabsorption of lipids, leading to steatorrhea. The end result of this disturbance is malabsorption of macro- and micronutrients and increased intestinal permeability to bacterial antigens and/or foreign proteins. Patients may therefore develop other clinical complications, such as allergy to dietary proteins or multiple food intolerance, particularly to lactose and even to monosaccharides; this further perpetuates bowel injury and the vicious circle of diarrhea, malabsorption, and protein-energy malnutrition, which is the single greatest determinant of jejunal mucosal recovery failure, as well as specific micronutrient deficiencies.

Characterization of the damage caused by PD, with identification of the changes in digestion, absorption, secretion, and resorption of minerals, carbohydrates, proteins, and lipids induced by chronic enteropathy, is extremely important for gaining a better understanding of this condition.[28] The bowel injuries described in children with PD appear to be caused by a variety of factors that act separately or in concert to prolong the intestinal mucosal injury of diarrhea and delay clinical and nutritional recovery.

Secondary infections can also play an important role in prolonging diarrheal illness.[20] A study of 16 patients with PD used jejunal secretion cultures and ultrastructural analysis of the small bowel mucosa to confirm the presence of bacterial overgrowth. Examination of the mucosa showed villus stunting, effacement of intercellular spaces (which hampered individual visualization of enterocytes), and presence of lymphocytes and fat droplets in the small bowel lumen. In most patients, vast amounts of mucus covered the epithelial surface of the jejunum, and in some cases, a mucus-fibrinoid pseudomembrane was found in direct contact with enterocytes. This most probably led to severe impairment of nutrient absorption due to enterocytes obstruction, thus perpetuating a malabsorption syndrome, which was present in nearly all patients in the study.[29] Patients presented with allergy to foreign proteins, including cow's milk and soy proteins, lactose intolerance, monosaccharide intolerance, and colitis (confirmed by rectal biopsy).[29]

It is important to distinguish the enteropathy caused by persistent bacterial colonization from the post-infections enteropathy that occurs secondary to failed or delayed regeneration of the bowel mucosa.[30]

Diagnosis

Malabsorption and malnutrition are common factors in PD. The former is defined as the presence of nutrients in stool with concomitant weight loss or failure to thrive, despite an age-appropriate diet. As PD has a presumably infectious etiology and is perpetuated in the form of multifactorial complications, precise diagnosis and determination of the causative agent and potential secondary complications will require detailed information on the following topics: a comprehensive clinical history extending as far back as the onset of the diarrheal illness; prior dietary history; breastfeeding history; socioeconomic status and living conditions; prior medical history, including prior infectious diseases; and family history. History and physical examination can outline a profile of the patient's nutritional status and other consequences of the diarrheal illness.

The laboratory workup of a patient with PD should include stool cultures (for detection of common bacterial, viral, and protozoan enteropathogens) and an ova and parasites (O&P) test, performed on a fresh specimen. Some authors, who believe no single enteric pathogen is associated with PD in developing countries and that pathogens are isolated as often in children with diarrhea as in healthy controls, which would indicate that enteropathogenic agents are not the cause of PD, suggest that stool cultures are only warranted in conditions amenable to routine investigation.[20] On the other hand, as PD has been known to occur in patients with acquired immunodeficiency syndrome (AIDS), tests should also focus on isolating the pathogens most often found in people with HIV. A study carried out in Africa concluded that *Microsporidium* infection is often associated with HIV/AIDS, and both induces and perpetuates more extensive bowel injury than that found in other opportunistic infections.[31] It is therefore recommended that these pathogens be considered, and therapeutic alternatives for their management studied, in younger pediatric populations.

Stool samples should also be tested for pH, reducing substances, white blood cells, occult blood, alpha 1-antitrypsin, and steatocrit. In light of the high prevalence of dietary carbohydrate intolerance as a factor perpetuating diarrhea in patients with PD, the laboratory workup should include challenge tests with the various carbohydrates consumed as part of a regular diet, including lactose, glucose, and fructose. A lactulose challenge test should also be performed to detect potential small bowel bacterial overgrowth. All challenges should preferably be performed through the hydrogen breath test technique, as it is a noninvasive and highly sensitive and specific method.[32]

If possible, fecal electrolyte testing should also be performed, as it can distinguish osmotic from secretory diarrhea.[33] Small bowel biopsy is indicated in many cases as an adjunct to laboratory testing, as it enables assessment of the villous architecture and analysis of the inflammatory infiltrate of the lamina propria, to rule out specific causes and determine the extent of intestinal damage.[34]

Once the intensity and extent of morphological injury have been established, dietary and therapeutic management can be planned more reliably. When rectal bleeding is present in addition to diarrhea, rectal biopsy is required for assessment of the degree and type of inflammatory process at hand.[35]

Management

In 2003, Lins et al.[36] showed the importance of proper rehydration and dietary management in acute diarrheal episodes as a means of preventing progression to PD. Regarding antimicrobial therapy in patients with established PD, the current evidence suggests that, in certain circumstances, antibiotics can shorten the duration of symptoms and, in some cases, reduce the likelihood of transmission.[37] However, as enteropathogens are isolated from the stool samples of children prone to diarrheal disease no more often than from stool specimens of healthy controls and the relationship between the isolated pathogen and the current disease process is questionable at best, routine antimicrobial therapy is not recommended.[20,38] Antibiotics are indicated in prolonged *Salmonella, Giardia, Cyclospora, Strongyloides*, and enteroaggregative *E. coli* infection (in the latter case, particularly when the patient is younger than 3 months, malnourished, immunosuppressed, or presents with evidence of invasive disease).[37] Antibiotic therapy for *Shigella* infection may be indicated when there is blood in the stool and the pathogen can be isolated from

fecal cultures.[39] The decision to prescribe antibiotics is restricted by laboratory confirmation of an enteropathogenic agent in stool samples and by the presence and extent of antimicrobial resistance.[40,41]

Some pharmaceuticals have been employed in an attempt to prevent prolongation of acute diarrheal episodes. A 3-day course of *Saccharomycis boulardii* has been found to reduce duration of diarrhea, increase stool consistency and decrease the frequency of bowel movements.[42] Other agents, such as racecadotril and bismuth subsalicylate, have proved effective in reducing stool output in children with acute diarrhea.[43] More recently, oral diosmectite was found to significantly reduce stool output and disease duration in children with acute diarrhea.[44]

Oliva & Palma[45] list the following as risk factors for adverse progression of diarrheal illness: age younger than 6 months or, in the presence of severe malnutrition, younger than 1 year; dehydration and/or metabolic derangements; and prolonged diarrhea with major nutritional status derangement or frequent recurrence of dehydration and/or acidosis. The management strategy of choice for this clinical picture is refeeding with formulas based on extensively hydrolyzed protein or, if necessary, an amino acid mixture. In the event of persistent anorexia, the patient should be fed through a nasogastric or, if possible, a nasoenteral tube, preferably on a continuous drip, and always with the objective of transitioning back to oral feeding as soon as possible. If attempts at nasogastric or enteral feeding are unsuccessful, parenteral nutrition is indicated (preferably through a peripheral line, to minimize the risk of systemic catheter-associated infection), again with the objective of transitioning back to oral feeding as soon as possible.[45]

In light of the severity of diarrhea, which still poses a public health issue and cannot be overcome if patients' immune systems are compromised, Rocha et al.,[46] in a meta-analysis, confirmed the major positive impact of zinc and vitamin A supplementation on cellular immunity as an adjunct to treatment of acute and persistent diarrhea. The authors conclude that zinc is not only an essential curative element in diarrheal episodes, but also an important prophylactic against diarrheal disease. As a preventive measure, zinc should be administered daily at a dose of 10 mg/day for at least 2 to 3 months after resolution of the diarrheal episode; furthermore, permanent access to adequate nutritional sources must be ensured so that Reference Daily Intakes of this important micronutrient are achieved. Lukacik et al.[47] proved the efficacy of this strategy for management of PD, and suggested its effect is due to increased water and electrolyte resorption in the bowel and improvement of the regenerative capacity of the bowel epithelium. Increased levels of brush border disaccharidases are indicative of a transporter effect for this electrolyte and of a potent immune response assisting intestinal defenses. This finding has also been described with adequate serum levels of zinc.[47]

Prophylaxis

In 2009, the United Nations Children's Fund (UNICEF) and the WHO published a report proposing six measures for worldwide implementation as a strategy for control of diarrheal disease, namely: 1) fluid replacement to prevent dehydration; 2) zinc treatment; 3) rotavirus and measles vaccinations; 4) promotion of breastfeeding and vitamin A supplementation; 5) promotion of handwashing with soap; 6) improvement of water supply quantity and quality, including treatment and safe storage of household water; 7) community-wide sanitation promotion.[1] Interventions indicated for reducing the incidence of PD include promotion of exclusive and prolonged breastfeeding and safe feeding strategies to ensure adequate growth, as protein-energy malnutrition is a risk factor for PD.[23] Malnutrition is one of the main factors contributing to pediatric morbidity and mortality. Achieving an adequate nutritional status is much more difficult in the setting of recurrent gastrointestinal infections ultimately leading to malabsorption. Infections are even more devastating in malnourished patients. Intestinal infection leads to malnutrition and malnutrition increases the risk of new intestinal infection. Breaking the vicious cycle of diarrhea and malnutrition should be the priority objective of all pediatricians if children are to develop to their fullest potential.[48]

Measures required during an acute diarrheal episode include ensuring adequate hydration, zinc supplementation, and uninterrupted feeding. When an acute episode stretched over more than 7 days, it is termed prolonged diarrhea (Pro-D, duration 7-13 days). The epidemiology of Pro-D has yet to be studied in depth. A recent study conducted in Northeast Brazil (Fortaleza, state of Ceará) by Moore et al.[49] showed that children affected by prolonged diarrheal episodes are 2.2 times more likely to develop PD in late childhood. This increased risk is due to the effects of prolonged diarrhea on nutritional status and immune function, and due to induction of changes in the intestinal barrier or gut flora.[49]

In conclusion, improvements in sanitation and hygiene are of the utmost importance if the incidence of diarrhea and, in particular, progression to PD is to be reduced. Achievement of the fourth Millennium Development Goal – to reduce by two-thirds, between 1990 and 2015, the under-five mortality rate – will require efforts toward ensuring access to oral rehydration therapy, vitamin A and zinc supplementation, and measles vaccination.[50] This vertical approach should be followed by an expansion of care made available through public health systems.[14]

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