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Persistent diarrhea in children of developing countries

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Diarrheal diseases continue to be an important public health problem in developing countries.[1, 2] Acute, short lived illnesses with dehydration can result in death unless prompt and appropriate fluid replacement is provided. Most efforts in national diarrheal disease control programs are currently directed at improving management of acute diarrhea. However, more prolonged illnesses, although fewer in number in comparison with acute episodes and not often associated with dehydration, may deserve more attention: (1) it is now appreciated that a substantial proportion of diarrhea-associated deaths in young children are with persistent, not acute, diarrhea.[3] Furthermore as oral rehydration therapy programs achieve greater success in controlling deaths from acute dehydrating diarrheas, deaths from persistent diarrhea become proportionally more important, (2) persistent diarrheas in developing countries have a striking association with growth faltering and malnutrition, suggesting that even more attention to nutritional management must be given to the long duration illnesses[4], and (3) the persistent episodes are frustrating management problems for family members as well as health professionals, resulting in a substantial cost in time and purchase of numerous drugs and other remedies in an attempt to terminate the illness.

The epidemiology, pathophysiology and clinical management of persistent diarrhea have until recently been ill-defined.[5] This paper constitutes a stock taking of our understanding, providing information of relevance for current diarrheal disease control program efforts and recommending selected research topics.

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DEFINITION OF PERSISTENT DIARRHEA

Although most diarrheal episodes resolve within the first week, a small proportion continue for 2 weeks or longer. Studies in a number of developing countries indicate that the distribution of episode durations is continuous but skewed toward the longer durations (Fig. 1). Thus establishing a specific definition of persistent diarrhea as an illness of more than a given number of days is arbitrary. Nevertheless doing so is desirable for gaining better comparability in research studies and for implementing program strategies for case management. For these reasons a World Health Organization meeting in December, 1987, recommended that persistent diarrhea be operationally defined as an episode that begins acutely and lasts for at least 14 days.[5] Recent studies have largely adopted this definition.

Previous studies used a variety of definitions of persistent diarrhea which may have affected the rates found.[6, 7] The term "persistent diarrhea" is not intended to encompass chronic diarrheal disorders, such as hereditary syndromes, gluten-sensitive enteropathy or blind loop syndrome, although these may be difficult to distinguish on initial presentation.[8]

MORTALITY ASSOCIATED WITH PERSISTENT DIARRHEA

Recent information from four countries (India, Bangladesh, Brazil and Senegal) indicates that acute watery diarrhea may account for only 35% (range, 25 to 46%) of all diarrhea-associated deaths.[3, 9-12] The remainder of the diarrhea-associated deaths in these studies was associated with either dysentery (20%; range, 8 to 24%) or persistent nondysenteric diarrhea (45%; range, 23 to 62%). Because these studies largely combined dysenteric illnesses of any duration, one

pathogens were found in duodenal fluid, but many were less frequently identified from this source than from stool.[84] For example EAEC-AA were found in 16% of stool samples but in only 1% of duodenal fluid samples. Studies in Brazil also identified all three types of EAEC in duodenal fluid, but their relative importance and role in pathogenesis could not be ascertained.[34] In Peru specific enteric pathogens were isolated from duodenal fluid in only a few children.[83] Although these studies are still inconclusive, they would not support an argument that continued colonization of the small bowel with specific enteric pathogens is a frequent or necessary event in the pathogenesis of persistent diarrhea.

MANAGEMENT OF PERSISTENT DIARRHEA

Antibiotics. The observation that specific enteropathogens such as EAEC or other forms of pathogenic coli may be associated with persistent diarrhea and the possible role of bacterial colonization of the small bowel in the pathogenesis of persistent diarrhea led some to speculate that antibiotics might be useful for treatment of this illness. Investigators in South Africa reported the use of oral gentamicin, metronidazole and cholestyramine for persistent diarrhea.[85] In a small controlled trial with a factorial design, children with persistent diarrhea treated with oral gentamicin appeared to have a greater decrease in stool output than those not receiving the drug. Metronidazole had no effect on stool output.

Because preliminary findings in a study of persistent diarrhea in the United States also suggested a possible effect of oral gentamicin,[86] two randomized, double blind, placebo-controlled trials of oral gentamicin in the treatment of persistent diarrhea were initiated.[87,88] In Guatemala among 92 cases entered in the clinical trial, there was no efficacy of gentamicin; 42% of the 45 gentamicin-treated children and 43% of the 47 placebo-treated children stopped having diarrhea, in both cases similar to the rate of spontaneous cessation of diarrhea between Days 15 and 21 previously observed in this population.[87] Although EAEC were identified in 46% of children in this trial, there was no significant treatment effect in children with this enteric pathogen. Furthermore children with a high count of aerobic organisms in their small bowel did not have an effect from the oral gentamicin. In India results were similar in finding no efficacy with oral gentamicin treatment of children with persistent diarrhea.[88]

Because shigellosis is known to respond to appropriate antibiotic therapy and *Shigella* infection can be associated with persistent diarrhea, specific therapy of shigellosis or perhaps empirical therapy of dysentery for *Shigella* infection would be justified. The need for treatment of *G. lamblia* is unknown and needs further study. Amebiasis is an unusual cause of persistent diarrhea in children in developing countries and would justify treatment only after documentation of erythrophagocytic trophozoites in diarrheal stool.

Other drugs. A number of other drugs have been tried in the management of persistent diarrhea. Cholestyramine has been used because it has been hypothesized that bacteria in the small bowel may result in unconjugated bile acids which then result in mucosal injury or a cathartic effect on the colonic mucosa.[89,90] In South Africa children with persistent diarrhea treated with cholestyramine had a significantly greater decrease in stool output during the first day of treatment, but not thereafter.[85] Unfortunately little other information is available from controlled trials in developing countries. Thus the possible role of cholestyramine in therapy of persistent diarrhea cannot be assessed, but any such therapy should carefully monitor adverse effects, such as the development of acidosis or the malabsorption of fat and fat-soluble vitamins, possibly leading to nutritional deficits. Even if there is an effect of cholestyramine, this is not a practical means for management of persistent diarrhea in developing country children because of high costs and difficulties of administration.

Bismuth subsalicylate has been used for the treatment of both acute and persistent diarrhea, but few controlled trials for the latter have been published. In a double blind trial in children with persistent diarrhea in the United States, those treated with bismuth subsalicylate had significantly fewer and firmer stools with less water content and gained more weight than the placebo-treated children.[91] The applicability of this study in relatively mild episodes of persistent diarrhea in nonmalnourished children to the more severe persistent diarrhea seen in malnourished children in developing countries is unknown.

Antimotility drugs, including codeine, paregoric, tincture of opium, diphenoxylate and loperamide, should not be given because they are unlikely to be efficacious and are associated with serious side effects, such as paralytic ileus, drowsiness and prolongation of excretion of enteric pathogens.[73] The so-called adsorbants such as kaolin or charcoal are unlikely to have any significant clinical effect in persistent diarrhea.

Vitamins and minerals. Specific deficiencies in vitamins and minerals in the pathogenesis of persistent diarrhea may lead to possible therapeutic strategies utilizing micronutrient supplements. Controlled studies of supplementation with vitamins and other micronutrients, such as zinc, in persistent diarrhea are needed.[52,92]

Fluid and dietary management. The principles of fluid and electrolyte replacement have been well-established for acute diarrhea and do not differ in

persistent diarrhea. The aim of treatment is to restore initial fluid deficits and to replace ongoing stool losses until diarrhea stops. In nearly all cases this should be possible with the use of oral rehydration solutions. Although dietary management also plays an important role in acute diarrhea, it may deserve special emphasis in persistent diarrhea because of the strong association of this illness with malnutrition in developing country children. Approaches to dietary management need to contend with the problem of anorexia in children with diarrhea, which may be compounded in prolonged illness by fatigue in the caretaker's attempts to provide an adequate diet.

Studies have indicated that the enteral route may result in faster recovery from the illness compared with the parenteral route, as well as having the advantages of decreased expense, increased availability and lower risk of complications.[93] In the management of persistent diarrhea a reduced lactose diet should be used. In a controlled trial in Peru one-third of children consuming a low lactose diet ceased diarrhea within 30 hours compared with only 3% on a full lactose diet.[94]

In the community, where most cases of persistent diarrhea must be managed, foods used must be culturally acceptable, available at a low cost and easy to prepare in the home.[59,60] Recent successes with staple food-based diets in management of acute diarrhea give optimism that similar approaches can be used for persistent diarrhea.[95] Other enteral diets, such as formulas that are free of cow's milk and lactose, are commonly recommended but are too expensive for wide use in most developing countries. In Pakistan children with persistent diarrhea were randomized to be managed with a diet consisting of a local weaning food of rice and lentils along with yogurt (Khitchri-yogurt) or with soy formula.[96] The children fed with the Khitchri-yogurt diet had significantly lower stool volumes and decreased stool frequency than children fed with the soy formula diet. In addition the children in the Khitchri-yogurt group had greater weight gains than children in the other group during the first week of therapy, and addition of this diet to the soy formula group in the second week resulted in increased weight gain in this group as well. In this setting a traditional weaning diet could be successfully used for the dietary management of persistent diarrhea.

It is important to identify characteristics of the children with persistent diarrhea or of the illness itself that could be used to predict delayed recovery or treatment failure. In Pakistan a younger mean age at admission to the hospital and presence of vomiting in the first 8 hours were correlated with treatment failures; and young age, malnutrition (low weight for length) and more severe watery diarrhea were associated with delayed recovery.[97] Likewise in the study in Bangladesh, patients with more severe initial diarrhea and more malabsorption of nutrients had delayed recovery.[98]

RESEARCH QUESTIONS

A partial list of pressing research questions is provided to stimulate further work.

1. A methodology is needed to enable a country or specific setting to determine whether persistent diarrhea is an important public health problem. Aspects of this methodology might determine the types of diarrhea associated with death. Additional work involving community-based surveys is needed to determine the extent to which the magnitude of persistent diarrheal morbidity can be determined by survey. The needed methodologies would also determine the groups, e.g. age, nutritional status, at highest risk of morbidity or mortality from persistent diarrhea.

2. Further analyses are needed of existing or new epidemiologic data to determine the extent to which a high prevalence of diarrhea and episodes of persiste diarrhea are found in a subset of developing country children and if so, what the associated child and family unit characteristics are.

3. The role in persistent diarrhea of the immune system and of transient impairment of cell-mediated immune responsiveness must be better understood. Such studies could include the determinants of immunocompetence in young children and the role of cell-mediated immune factors and the immune system in the recovery from diarrhea and the persistence of some episodes.

4. Additional information is needed on care-seeking behaviors related to diarrheal episodes, especially those of long duration. Much of the work on care-seeking to date has focused on seeking ORS during the initial days of acute watery diarrhea. In relation to persistent diarrhea, attention must also be paid to the second week of illness and beyond. Information is needed on the cost in time and money of this care seeking, as well as the relationship of the care-seeking and treatments used to the episode outcome.

5. The association of enteroadherent *E. coli* with persistent diarrhea needs to be studied in a variety of settings and the relationships between these enteric pathogens and important risk factors and the response to therapeutic approaches must be ascertained.

6. The need for antimicrobial treatment of specific agents, e.g. *G. lamblia* or *Entamoeba histolytica* should be determined. Even with shigellosis, in which individual cases are known to respond to treatment, it is important to describe the costs and benefits of treatment of dysentery at a population level.

7. Information is needed on how the usual weaning diets can be improved and utilized for the management of diarrhea, for convalescent feeding, and for nutri-

tional rehabilitation. There are still cross-cutting questions concerning specific diet components, density, viscosity and type of preparation, as well as about the best process to apply the findings at a country level.

8. Studies on children less than 6 months of age, especially those who are not breast-feeding, are necessary to determine their appropriate dietary management and the special physiologic characteristics of this age group that determine the success of therapy.

9. A dietary management algorithm for persistent diarrhea, using cereal-based diets mixed with milk or other foods as additional sources of calories and protein, needs to be evaluated in health facilities and communities in a variety of settings. Diets using locally available foods are needed for initial management of persistent diarrhea and for use in children who do not respond to the first diet. These studies could also attempt to determine the characteristics of children or their illnesses that would predict delayed recovery or treatment failure. Once appropriate algorithms are demonstrated to be useful, additional work will be needed to learn how to implement these in a national diarrheal disease control program.

10. Because anorexia is likely to be an important determinant of dietary intake, additional information is needed on the physiologic and pathologic determinants of anorexia, and the approaches to overcome it.

11. Studies are needed to determine the importance of specific micronutrients in the pathophysiology of persistent diarrhea and their therapeutic effect to shorten the episode and improve growth. Of particular interest may be vitamin A, zinc and folate. Emphasis should be given to double blind, placebo-controlled trials in either health facility or community settings to provide definitive answers about the role of specific micronutrients. However, additional studies could be included to gain a better understanding of the possible mechanisms by which micronutrients affect diarrhea and their relationship with other factors contributing to persistent diarrhea.

12. Information is needed on the specific indications for hospitalization in the management of persistent diarrhea and on the risks and benefits of hospital-based *vs.* community-based care.

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