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Persistent Diarrhoea

Children under 3 years of age in the developing countries may experience as many as 10 episodes of diarrhoea per year, although a rate of 3-4 is more usual. Most episodes are of relatively short duration (*i.e.*, less than 7 days) and can be treated easily and effectively with oral rehydration therapy and continued feeding with an appropriate diet.

"Persistent" diarrhoea refers to diarrhoeal episodes, presumed to be caused by infectious agents, that begin acutely, but have an unusually long duration. It is defined as an episode that lasts at least 14 days. Studies in several developing countries have shown that 3-20% of acute diarrhoeal episodes in children under 5 years of age become persistent. Episodes of persistent diarrhoea are often associated with a deterioration in nutritional status and there is a substantial risk of death.

Incidence and Impact

The incidence of persistent diarrhoea varies widely in different regions. Most episodes occur during the first 3 years of life and rates as high as 2.1 (northeastern Brazil), 0.8 (Gambia), and 0.3 (India) episodes per child per year have been reported. Since persistent diarrhoea is more frequent in children who have previously suffered an episode, the problem may be concentrated in a relatively small proportion of children.

Episodes of persistent diarrhoea, although fewer in number than attacks of acute diarrhoea, are more likely to have severe consequences. For example, in a shanty-town in Lima, Peru, 44% of deaths among children under 5 years of age were associated with diarrhoea. Of these, half had had diarrhoea for more than 2 weeks before death. In similar studies in Bangladesh, northeastern Brazil, northern India, and Nepal, one third to one half of all diarrhoea-associated deaths among children occurred following episodes of persistent diarrhoea. Viewed in another way, the study in northern India showed that, although only 5% of all diarrhoeal episodes became persistent, 14% of them ended fatally compared with less than 1% for shorter episodes.

The negative impact of diarrhoeal disease on children's growth is now well established. The adverse nutritional effects are particularly severe during persistent diarrhoea, which is an important contributor to protein-energy malnutrition. Marasmus (and less frequently kwashiorkor) may develop rapidly during such episodes and surviving children are likely to show evidence of stunting.

Risk Factors

Identification of the risk factors for persistent diarrhoea may provide important clues to its pathogenesis and prevention. A number of studies to identify risk factors are under way or have recently been completed, and the available results are summarized below.

Age. The incidence of persistent diarrhoea and the chance that an acute diarrhoeal episode will become persistent are both greatest during the first year of life.

Nutritional status. Several recent studies have shown that malnutrition affects the duration of diarrhoea; thus, in malnourished children, the mean duration of diarrhoeal episodes is longer and there is a higher incidence of persistent diarrhoea.

Immunological status. Studies in both Bangladesh and Peru have shown that the risk of developing persistent diarrhoea is increased in children who do not respond normally to standard skin test antigens. While the cause of this impaired immunological status is unclear, it is unrelated to nutritional state and is frequently transient.

Previous infections. In Guatemala and India, the risk of developing persistent diarrhoea was shown to increase two to four-fold during the 2 months following an episode of acute diarrhoea. Two studies in Guatemala have also shown that children experiencing one documented episode of persistent diarrhoea have a three to six-fold increased risk of developing at least on additional episode during the same year.

Animal milk. A study in India has shown that the incidence of persistent diarrhoea increases in the month after animal milk is first given to a child. Whether this is due to reduced intake of the protective factors in breast milk, contamination of animal milk with pathogenic bacteria, damage to the gut by animal milk proteins, lactose intolerance, or other mechanisms is not known. Continued feeding of cows' milk during acute diarrhoea also causes prolonged disease in a small proportion of children because of damage to the digestive enzyme lactase and the inability to digest lactose.

Enteropathogenic bacteria. Less than a half of all children with persistent diarrhoea have a recognized enteric pathogen in their faeces. The enteropathogens identified in these patients include: (i) those that are isolated with about equal frequency from children with acute and persistent diarrhoea (*Shigella*, non-typhoid *Salmonella*, enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, *Aeromonas hydrophila*), and (ii) those that are isolated with greater frequency from episodes of persistent diarrhoea (enteroadherent *E. coil*, enteropathogenic *E. coil*, and cryptosporidium). The manner in which the latter agents cause persistent diarrhoea may be related to the way in which they adhere to or invade the bowel mucosa.

Clinical Management

The main goal of the clinical management of persistent diarrhoea is to maintain the child's hydration, and especially nutritional, status while the intestinal damage is being repaired. In some instances antibiotics are also given.

Oral rehydration therapy (ORT). In persistent diarrhoea, as in acute diarrhoea, the aim of ORT is to restore the initial fluid deficits and to replace ongoing stool losses until diarrhoea ceases. Although the efficacy of oral rehydration salts (ORS) in treating dehydration due to persistent diarrhoea has not been specifically studies, experience from some developing countries suggests that ORS is effective in the majority of cases. In a small number of infants with severe, watery persistent diarrhoea, in which carbohydrate absorption in severely impaired, ORS is less effective and intravenous fluids and electrolytes may be required.

Nutritional management. There have been few studies of the dietary manage-

ment of persistent diarrhoea, but experience in the nutritional therapy of acute diarrhoea, of chronic diarrhoea of infancy in industrialized countries, and of severe protein-energy malnutrition provides valuable guidance. Several clinical studies have shown that continued feeding during acute diarrhoea results in improved nutritional outcome and, in some cases, less severe diarrhoea. Continued feeding is an essential part of therapy for both acute and persistent diarrhoea. Although the benefits of continued breast-feeding in persistent diarrhoea have not been determined, it is recommended that breast-feeding be maintained during such episodes.

Weaning foods. Studies during acute diarrhoea and experience gained in the rehabilitation of severely malnourished children show that weaning mixtures prepared from locally available foods are generally well tolerated. These food mixtures should be energy-rich, have low viscosity, and have low osmolality. In selecting a diet: (i) complementary protein sources should be used; (ii) complex carbohydrates (starches) should be used to avoid hyperosmolality and reduce the problem of lactose maldigestion - *e.g.*, milk-cereal mixtures are preferable to milk given alone (they are well tolerated in acute diarrhoea and could be used in persistent diarrhoea); and (iii) fats that are most readily digestible should be preferred, especially as a means of increasing the energy intake (edible vegetable oils are usually most appropriate, if they are locally available). Giving small feeds more frequently during illness may help to maximize nutrient absorption.

Vitamins and minerals. Folate, zinc, iron, vitamin B12, vitamin A, and possibly others are involved in intestinal mucosal renewal and/or a variety of immunological responses. Supplementary vitamins and trace elements should be given during persistent diarrhoea, if possible.

Animal milk. Animal milk should not be routinely restricted during the treatment of acute diarrhoea. Nevertheless, as mentioned above, in some infants with persistent diarrhoea, milk intolerance plays an important role in causing diarrhoea to be prolonged. This occurs mostly in infants who receive animal milk as the sole food. Reducing the amount of lactose in the diet of these infants by providing mixtures containing milk and staple food products (i.e., cereals), or by decreasing the lactose in animal milks-for example by traditional fermentation processes (*e.g.*, yoghurt)-can reduce the severity and possibly the duration of persistent diarrhoea.

Convalescent feeding. Attention must also be given to appropriate nutritional therapy during convalescence to ensure that children return at least to their pre-illness nutritional state. Studies from nutritional rehabilitation units have shown that the desired level of energy intake(420-670 J/kg/day) can be achieved by children who are given energy-rich (low bulk), low viscosity diets. This level of intake can promote a rate of growth far in excess of that expected for normal children of the same age group, thus achieving rapid nutritional recovery.

Antimicrobials. There is not yet sufficient evidence to support the routine use of antibiotics in patients with persistent diarrhoea. At present, it is recommended that antimicrobials be give in persistent diarrhoea only when a specific enteropathogen warranting treatment has been isolated or dysentery is present. When antibiotics are given, the choice should be based on

the *in vitro* sensitivity of the isolated pathogen; bloody diarrhoea should be treated as shigellosis, using antibiotics to which most *Shigella* strains in the community are sensitive.

Management of infants with severe persistent diarrhoea. A small subgroup of children with severe persistent diarrhoea (purging rate greater than 5 ml/kg/h and marked weight loss) requires specialized treatment in hospital. These patients can be managed initially as described in the preceding sections. However, particular attention must be paid to maintaining both hydration and nutrition. If signs of carbohydrate intolerance (presence of reducing substances in the stool, low faecal pH, perianal inflammation) are present and improvement does not occur following the restriction of dietary lactose, then monosaccharide intolerance should be suspected. In such cases all carbohydrate should be removed from the diet, at least on a trial basis. Sensitivity to dietary protein should be considered in children who do not improve following the withdrawal of dietary carbohydrate and appropriate antibiotic therapy. Such patients can usually be managed by substitution of dietary protein: children who were initially receiving animal milk may be switched to soya or meat-based diets (for example, successful results have been described using finely ground chicken as a protein source).

Most children will respond to specific dietary and/or antimicrobial therapy (as discussed above). However, some with very severe food intolerance will be unable to take food orally and will have to receive intravenous alimentation for several days of weeks before progressive amounts of chemically defined, readily absorbable nutrients can be administered orally.

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Rotavirus Vaccines

The epidemiological features of rotavirus diarrhoea that are of greatest relevance to vaccine development are as follows:

- Rotavirus is the major cause of severe dehydrating diarrhoea in young children in both developed and developing countries.
- This organism is responsible for 40-60% of the diarrhoea cases requiring hospitalization in developed countries.
- It accounts for 20-40% of severe diarrhoeas among children in the developing world.
- Rotavirus diarrhoea is most common in children 6-24 months of age.

There are four serotypes of rotaviruses, designated 1 to 4. While they all cause disease, serotype 1 appears to be the most common cause of epidemic rotavirus