Memoranda
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Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.

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Persistent diarrhoea in children in developing countries: Memorandum from a WHO Meeting*

This Memorandum summarizes current knowledge of the epidemiology, etiology, and pathophysiology of persistent diarrhoea and describes current approaches to its management. A number of research topics are presented which focus especially on improving understanding of the causes of persistent diarrhoea and on developing more effective methods for treatment and prevention.

Children under 3 years of age in the developing countries may have as many as 10 diarrhoea episodes per year, although a rate of 3–4 per year is reported more often. The majority of attacks are of relatively short duration (less than 7 days) and can be treated easily and effectively by oral rehydration therapy and continued feeding with an appropriate diet; antibiotics are necessary only when dysentery is recognized or cholera is likely. Childhood mortality due to diarrhoea has been reduced worldwide by this simple treatment regimen.

Sometimes the diarrhoea lasts longer than usual; these "persistent" cases are often associated with a deterioration in nutritional status and present a substantial risk of death. Relatively few studies have been directed towards the description, treatment and prevention of persistent diarrhoea. This Memorandum summarizes current knowledge about various aspects of persistent diarrhoea and proposes a number of research topics to improve understanding of the causes and to develop more effective methods for control.

EPIDEMIOLOGY

The epidemiology of persistent diarrhoea is only partly understood; several aspects concerned with children in the developing countries are presented in this section. The discussion is based mostly on data obtained from prospective, community-based studies carried out in Bangladesh, Brazil, Guatemala, India, Indonesia and Peru; some of these studies have not yet been completed or fully analysed and the results summarized here must be considered as preliminary.

Definition of persistent diarrhoea

When defining "persistent diarrhoea", it is necessary first to consider the terms "diarrhoea" and "diarrhoeal episode". Diarrhoea is usually defined as the passage of three or more liquid motions (i.e., liquid enough to take the shape of the receiving container) during a 24-hour period. However, for exclusively breast-fed infants the definition is usually based upon what the mother considers to be diarrhoea. A diarrhoeal episode is conventionally defined

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as beginning with the first 24-hour period that meets the definition of diarrhoea and ending with the last diarrhoeal day that is followed by at least two consecutive days which do not meet the definition of diarrhoea. The first subsequent diarrhoeal day is considered to be the start of a new episode. These definitions are used for both acute and persistent diarrhoea, but may be less satisfactory for the latter because of day-to-day variations in the frequency and characteristics of stool output.

"Persistent diarrhoea" refers to diarrhoeal episodes of presumed infectious etiology that begin acutely, but have an unusually long duration. The term does not include chronic or recurrent diarrhoeal disorders such as tropical sprue, gluten-sensitive enteropathy, other hereditary diarrhoeal disorders or blind-loop syndrome. Studies in Brazil have shown that the duration of acute diarrhoeal episodes forms a continuum, most episodes terminating within 7 days, and progressively smaller proportions persisting for 14, 21 or 28 days. Viewed from this perspective, persistent diarrhoea does not represent a statistically determined subgroup of acute episodes, and its definition is arbitrary. In most studies it is operationally defined as an episode that lasts *at least 14 days*, and that definition is used in the remainder of this report. Using this definition, studies in several developing countries have shown that 3–20% of acute diarrhoeal episodes in children under 5 years of age become persistent. They also show that the occurrence of persistent diarrhoea is directly related to the total burden of diarrhoeal illness in individual children: in a 30-month prospective study of children under 5 years of age in rural Brazil, all children who had diarrhoea on more than 13% of all observation days experienced at least one episode of persistent diarrhoea; in this study, episodes of persistent diarrhoea accounted for nearly half of all recorded diarrhoeal days.

Incidence and impact of persistent diarrhoea

Incidence. The reported incidence of persistent diarrhoea varies widely in different regions. Rates as high as 210 (children aged 6–23 months in urban, northeastern Brazil), 83 (Gambian infants), and 31 (Indian infants) episodes per 100 child-years have been reported; these contrast with a very low, declining incidence in developed countries. Since persistent diarrhoeal episodes are more frequent in children who have already suffered such episodes, this problem may be concentrated in a relatively small proportion of children. Nevertheless, in northeastern Brazil, 63% of children under 5 years in an urban slum experienced at least one episode of persistent diarrhoea during a 28-month observation period; similarly, in rural Guatemala, 21% of children aged 0–30 months experienced persistent diarrhoea during an observation period of only 7 months, and in northern India 15% of children aged 0–35 months experienced persistent diarrhoea during one year of surveillance.

In India and Peru, the peak incidence of persistent diarrhoea occurred in infants less than 1 year of age; in Brazil, it was in children aged 6–24 months. Late age peaks have been observed in other countries, but in all studies most episodes occur during the first 3 years of life. No appreciable differences in incidence have been noted between the sexes, but higher rates have been described for either males or females in some settings, presumably reflecting sex-related differences in child-care practices. The seasonal incidence of persistent diarrhoea has not been well defined, but it appears to be greatest during periods when acute diarrhoea occurs most frequently.

Mortality. Episodes of persistent diarrhoea, although fewer in number than those of acute diarrhoea, are more likely to have severe consequences. In some areas, a substantial proportion of diarrhoea-related deaths in young children is associated with persistent diarrhoea. For example, in a Lima (Peru) shantytown in 1982, 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, 36–56% of all diarrhoea-related deaths among children were related to episodes of persistent diarrhoea. Viewed another way, the study in northern India showed that although only 5% of all diarrhoeal episodes lasted longer than 14 days, the case-fatality rate for such episodes was 14%, compared with 0.7% for shorter episodes.

Nutritional status. During diarrhoea, growth can slow or stop, especially when food is restricted, and weight loss may occur; unless food intake is increased, there may be little or no catch-up growth after recovery. This effect is especially marked during persistent diarrhoea, when weight loss may be substantial. Certainly, persistent diarrhoea is an important contributor to protein–energy malnutrition; marasmus (and less frequently kwashiorkor) may develop rapidly during such episodes. For surviving children, however, the long-term effect on growth is likely to be stunting rather than wasting.

Risk factors for persistent diarrhoea

Identification of the risk factors for persistent diarrhoea may provide important clues to its pathogenesis and prevention. In this regard, it is important to emphasize the potential value of research on factors

that influence the duration of diarrhoea, even when episodes do not meet the definition of persistent diarrhoea. It is possible that at least some factors responsible for an increase in mean diarrhoeal duration from, for example, 4 to 7 days would also be risk factors for persistent diarrhoea.

A number of studies are examining the risk factors and predictors of persistent diarrhoea but most have not yet been completed. The results which are discussed below and summarized in Table 1 are based on preliminary analyses of several ongoing studies.

Host risk factors. Five risk factors have been described.

(*a*) *Age.* The incidence of persistent diarrhoea is usually greatest during the first year of life and the chance that an acute diarrhoeal episode will become prolonged is also greatest in this age group. In northern India, for example, the incidence of persistent diarrhoea was greater in the age grop 0–11 months (31 episodes per 100 child-years) than at 12–23 months (9 per 100 child-years) or 24–35 months (6 per 100 child-years); in addition, the risk of a diarrhoeal episode becoming persistent was 22% during the first year of life compared with 10% in the second year and 3% in the third. Similar results were obtained in rural Guatemala. In northeastern Brazil, however, the peak incidence included the second year of life and the risk of developing persistent diarrhoea was not age-related for children under 3 years.

(*b*) *Nutritional status.* Many studies have shown that diarrhoea contributes to malnutrition. However, several recent studies have shown that malnutrition is also a risk factor for prolonged diarrhoea; thus, in malnourished children, the mean duration of diarrhoeal episodes is longer and there is a higher incidence of persistent diarrhoea. In Brazil, for example, the incidence of persistent diarrhoea increased twofold during sequential 3-month observation periods in young children whose height-for-age was below 90% or whose weight-for-age was below 75% of NCHS standards at the beginning of the observation period, when compared with the incidence in better-nourished children.

Table 1. Possible risk factors for persistent diarrhoea

1.	*Host factors*
	Young age, especially < 12 months
	Malnutrition
	Impaired cell-mediated immunity
2.	*Previous infections*
	Recent acute diarrhoea
	Previous persistent diarrhoea
3.	*Pre-illness feeding practices*
	Recent introduction of animal milk
4.	*Microbial isolates during acute phase*
	Enteroadherent *E. coli*
	Shigella
	More than one pathogen
5.	*Drugs used during acute phase*
	Antiparasitic drugs

(*c*) *Immunological status.* Studies in both Bangladesh and Peru indicate that the risk of developing persistent diarrhoea can be predicted from the capacity of children to produce normal, delayed-type hypersensitivity reactions to standard skin-test antigens. In both sites, children with impaired skin-test responses were more likely to develop persistent diarrhoea during follow-up than were children with normal responses. This effect persisted after controlling for both age and initial nutritional status. The factors responsible for impaired immunological reactivity were not defined, but in Peru it was not due to known causes such as measles. The relationship between impaired skin-test reactivity and persistent diarrhoea has not been explained, but suggests that intact cell-mediated immunity is required for prompt termination of enteric infections. It is of interest that the impaired skin-test reactivity observed in these studies was often transient, returning to normal during subsequent observation periods. Again, this variation was unrelated to nutritional status.

(*d*) *Previous infections.* Three categories are recognized.

—*Recent acute diarrhoea.* In Guatemala and India the risk of developing persistent diarrhoea increased two- to fourfold during the 2 months following an episode of acute diarrhoea. Whether this association reflects the damage inflicted on the gut mucosa during the earlier episode or other alterations in the host's defences that in some way predispose to persistent diarrhoea is not clear. Nor is it known whether the risk is related to the specific etiology of the preceding acute episode.

—*Previous persistent diarrhoea.* Two studies in Guatemala have shown that children suffering one documented episode of persistent diarrhoea have a three- to sixfold increased risk of developing at least one additional episode during the same year. This observation, combined with the relationship between acute and persistent diarrhoea, accords with the finding in northeastern Brazil that nearly half of all diarrhoeal days documented during 30 months of active surveillance were experienced by children who suffered at least one episode of persistent diarrhoea.

—*Recent non-enteric infections.* A study in Peru showed that children who had recently had measles

experienced diarrhoeal episodes somewhat more frequently during the first month of convalescence (relative risk, 1.6), and that these episodes lasted 30% longer than in measles-free controls; however, the incidence of diarrhoeal episodes lasting more than 14 days did not increase. A study in India showed that a recent history of acute non-diarrhoeal illness (including respiratory infection, otitis media or febrile exanthems) was not a risk factor for developing persistent diarrhoea.

(*e*) *Pre-illness feeding practices.* The possibility that pre-illness feeding practices, especially breast-feeding, may affect the risk of developing persistent diarrhoea has been studied in India and Peru. According to the preliminary results of these studies, there is no evidence that the risk of developing persistent diarrhoea is related to pre-illness feeding patterns, i.e., exclusive breast-feeding, supplemented breast-feeding, and use of breast-milk substitutes. These results are surprising, given the marked protective effect of breast-feeding on the incidence and severity of acute diarrhoea, especially in infants, and further study of this topic is needed. The study in India has shown, however, that the incidence of persistent diarrhoea does increase two- to threefold during the first month following the introduction of animal milk. Whether this increase is due to reduced intake of protective factors in breast milk, contamination of animal milk with enteric pathogens, damage to the gut mucosa due to hypersensitivity to animal milk proteins, intolerance to lactose, or other mechanisms is not known.

Etiological agents. Most of the bacteria and parasites that are known to cause acute diarrhoea have also been isolated from patients with persistent diarrhoea. Whether certain pathogens are especially able to cause persistent diarrhoea has, however, not been exclusively studied. The available data on this topic and on other aspects of the microbiology of persistent diarrhoea are considered below (see p. 713).

Drug and dietary management. Several studies have examined the possible role of drug therapy and dietary management as risk factors for persistent diarrhoea.

(*a*) *Antidiarrhoeal drugs and antibiotics.* It has been postulated that ineffective peristalsis after the administration of antimotility drugs or inappropriate use of antibiotics may favour the overgrowth of pathogenic or commensal bacteria in the proximal small intestine, leading to malabsorption, other disorders of mucosal function and persistent diarrhoea. However, the data available to date have not shown any relationship between the early use of such drugs and the risk that an acute diarrhoeal episode will become persistent. The only exception is a study in Guatemala which suggested that early treatment with antiparasitic drugs, most frequently metronidazole, was associated with a twofold increased risk of development of persistent diarrhoea. On the other hand, it has been postulated that early, appropriate management of diarrhoea with oral rehydration therapy may reduce the risk of progression to persistent diarrhoea.

(*b*) *Dietary management.* The influence of dietary management on the duration of acute diarrhoea has not been adequately studied. The following practices may affect the duration of diarrhoea:

—*Food restriction.* Withholding food during acute diarrhoea directly contributes to a worsening of nutritional status. In most studies, however, fasting had no appreciable effect on the duration of diarrhoea.
—*Breast-feeding.* A study in Burma has shown that the duration of acute diarrhoea is shorter in children who are breast-fed during the episode than in those who are not breast-fed. However, it is not known whether continued breast-feeding protects against the development of persistent diarrhoea.
—*Animal milk.* Continued feeding of cow's milk, especially at full strength, can lead to prolonged diarrhoea in some children who become lactase-deficient during the acute episode. This may not be a frequent problem, however. In recent studies in Ecuador and Egypt, only 1 of 75 children under 24 months of age, given full-strength cow's milk throughout the course of treatment for acute diarrhoea, developed clinically evident lactose malabsorption, with increased and prolonged diarrhoea. These results do not preclude the possibility, however, that lactose malabsorption is an important factor in the subgroup of children whose diarrhoea becomes persistent.

Prognostic factors for persistence of acute diarrhoeal episodes

Certain features of acute diarrhoea have been shown to indicate an increased likelihood that an episode will become persistent, even though they are not themselves risk factors. These include clinical features that reflect the severity or pathogenesis of the episode. For example, in Peruvian children, the risk of developing persistent diarrhoea was nearly fourfold greater when at least six liquid stools were passed per 24 hours during the initial phase of illness than when the disease was less severe. Similarly, studies in Guatemala, India and Peru showed a two- to threefold increased risk of development of persistent diarrhoea when stools during the acute phase contained leukocytes, mucus or visible blood. Although the findings were statistically significant, the predictive value of

these clinical features was too low to help identify individual diarrhoeal episodes with a high risk of becoming persistent.

INTESTINAL PATHOPHYSIOLOGY

Theoretically, diarrhoeal illness may be prolonged by (*a*) factors that continue to injure the intestinal lining, or (*b*) failure of the intestinal mucosa to heal after an acute episode. In either event, impaired absorption or abnormal secretion of solutes and water persists and the diarrhoea is prolonged.

Continuing mucosal injury

Probable causes of continuing mucosal injury include microorganisms that either invade the mucosa or attach to its luminal surface. Clearly, the status of the host's mucosal barrier and the capacity for mirobial clearance, by immunological or other mechanisms, may influence vulnerability to continuing microbial damage.

Dietary constituents, notably disaccharides (especially lactose) and animal proteins, constitute another group of potential causes of continuing intestinal injury. The role of the latter is most contentious, at present, since absorption of antigenically significant amounts of intact protein has been shown to occur in experimental models of acute viral enteritis. Whether this triggers immune mechanisms that contribute to mucosal damage has, however, not been proved.

Altered intraluminal metabolism of bile salts has been suggested as a possible factor in persistent diarrhoea. In theory, malabsorption of bile salts in the terminal small bowel could result in excessive quantities reaching the colon, where they could influence fluid secretion. However, the available evidence does not support this process as a major determinant of persistent diarrhoea. Also, small bowel bacterial overgrowth could lead to intraluminal deconjugation of bile salts, which in turn could cause fat malabsorption, but there are no controlled data on this issue.

Delayed mucosal repair

A major determinant of delayed mucosal repair, demonstrated in animal models of acute viral and bacterial enteritis and suggested by epidemiological data, is chronic protein–energy undernutrition. Whether impairment of the capacity of the gut epithelium to renew and differentiate contributes to the prolongation of diarrhoea has not been established, nor has the possible therapeutic benefit of micronutrients such as zinc, iron, vitamin A, folate and vitamin B_{12} been determined. Nevertheless, clear evidence that malnutrition is a significant risk factor for persistent diarrhoea suggests an important role for delayed mucosal repair and argues strongly for the importance of adequate nutrition in the management of this disorder.

INTESTINAL MICROFLORA

Role of known enteropathogens

As mentioned above, most of the enteropathogens that cause acute diarrhoea have also been associated with persistent diarrhoea, the notable exceptions being vibrios and viruses, including rotavirus. The enteropathogens identified in patients with persistent diarrhoea can be divided into two broad groups: (1) those that are isolated with about equal frequency from episodes of acute and persistent diarrhoea, and (2) those that are isolated with greater frequency from episodes of persistent diarrhoea.

The first group includes *Shigella*, non-typhoid *Salmonella*, enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, *Aeromonas hydrophila* and, less frequently, *Giardia lamblia*, *Yersinia enterocolitica*, *Clostridium difficile* and *Entamoeba histolytica*. The observation that episodes associated with these organisms frequently respond to treatment with appropriate antibacterial or antiparasitic agents strongly suggests that they were the cause of the persistent diarrhoea. However, the fact that they have been isolated with equal frequency from acute and persistent episodes suggests that they are not especially able to induce prolonged illness; rather, their continued presence in episodes of persistent diarrhoea probably reflects an impaired ability of the host to terminate infection by immunological mechanisms.

The second group includes enteroadherent *E. coli* (EAEC), enteropathogenic *E. coli* (EPEC) and cryptosporidium. Several studies have shown that these organisms have an unusual capacity to cause persistent diarrhoea. In the case of cryptosporidium, and possibly *Shigella*, this is especially true for children with pre-existing malnutrition. The mechanisms by which these agents cause persistent diarrhoea probably relate to their capacity to adhere to or invade the bowel mucosa.

The association of EPEC and EAEC with persistent diarrhoea is of particular interest and requires further investigation. The enteroadherent strains, some of which are also of EPEC serotypes, are characterized by their capacity to adhere to the intestinal mucosal brush border and to cells in tissue culture. At least three patterns of adhesion are recognized: localized adhesion (LA), diffuse adhesion (DA), and auto-

aggregative adhesion (AA). *E. coli* exhibiting LA and DA can be diagnosed by specific gene probes. LA *E. coli* are also termed type I EPEC, and DA *E. coli* type II EPEC. LA *E. coli* have been definitely associated with persistent diarrhoea, during which they colonize the entire small bowel and may produce characteristic mucosal changes (brush-border effacement and pedestal formation); the role of DA *E. coli* in persistent diarrhoea is less clear. AA *E. coli* aggregate in clumps and chains, adhering not only to the cell surface but also to each other. These strains, which usually do not belong to EPEC serotypes, may play an especially important role in persistent diarrhoea, although the exact mechanism by which they cause diarrhoea is not yet known. In India, for example, AA *E. coli* were isolated from 2% of healthy controls, 9% of children with acute diarrhoea, and 26% of children under 3 years of age with persistent diarrhoea.

Role of small bowel microbial flora

In most studies, less than half of the children with persistent diarrhoea have recognized enteric pathogens in their faeces or small bowel fluid. However, a few studies have shown that patients with persistent diarrhoea have increased numbers of aerobic and anaerobic faecal bacteria in the small bowel in comparison with findings in healthy controls in developed countries, in whom the upper small bowel contains only very small numbers of respiratory-type commensal bacteria. It is not known whether these faecal bacteria play a role in the perpetuation of diarrhoea.

A study on the jejunal microflora of Peruvian children with persistent diarrhoea has attempted to clarify this issue. It showed that (*a*) 29% harboured enteric Gram-negative bacilli and 43% anaerobes while only 3% had sterile jejunal fluid; (*b*) enterobacteriaceae were present more frequently in younger than in older children; (*c*) when enterobacteriaceae were present, usually only a single species was isolated; (*d*) anaerobes were present more frequently in older children (12–35 months) than in younger ones (0–11 months); (*e*) the duration of diarrhoea in hospital was not related to the presence or absence of anaerobes (although it was somewhat longer in those with enterobacteriaceae); and (*f*) absorption of nutrients was independent of the type of jejunal microflora. However, generally similar results were obtained from children with acute diarrhoea and also from locally recruited healthy controls, raising doubts as to their relation to the pathogenesis of persistent diarrhoea. The only suggestive differences observed in jejunal microflora were: (i) more children with persistent diarrhoea yielded isolates of anaerobic bacteria, and (ii) above the age of 12 months, *E. coli* were found only in children with persistent diarrhoea.

These results differ from those obtained in (*a*) small bowel overgrowth syndromes due to motility disturbances and obstructive lesions of the bowel, and (*b*) tropical sprue. In both of these syndromes, the small bowel contains a complex aerobic and anaerobic faecal-type flora, and the disease is effectively treated with antibiotics directed against this.

CLINICAL MANAGEMENT

Nutritional problems

The negative impact of diarrhoeal disease on children's growth has been established. The adverse nutritional consequences of persistent diarrhoea may be particularly severe and can be attributed to reduced dietary intake, intestinal malabsorption, loss of endogenous nutrients through the injured gut epithelium, and the increased nutrient requirements imposed by fever and other metabolic responses to infection.

Reduced dietary intake. Dietary intake may be reduced because of anorexia, vomiting or a reduction in the amount of nutrient offered. Hospital-based clinical studies have clearly shown that intake of dietary energy is less during the initial treatment of diarrhoea than during the post-recovery period, but it is not known whether this indicates reduced intake during illness, exaggerated intake during convalescence, or both. Children who receive a major proportion of their nutrients from breast milk maintain adequate dietary intake because breast milk consumption generally remains unchanged during illness. Community-based, quantitative observations show a less dramatic impact of diarrhoea on dietary intake; in this setting declines in *ad libitum* intake may be confined to febrile illnesses.

Intestinal malabsorption and loss of endogenous nutrients. Intestinal malabsorption of macro- and micronutrients has been described during persistent diarrhoea, and is probably related to the extent of the mucosal damage. Despite reductions in the efficiency of intestinal absorption, nutrient absorption is sufficient in most cases to maintain positive balances, if adequate amounts of food are provided. Malabsorption of dietary fat, which has been reported in both acute and persistent diarrhoea, may be especially important because of its major contribution to dietary energy. Steatorrhoea may also cause deficiences in fat-soluble vitamins, and may contribute to the severity of diarrhoea because bacterial metabolites of non-absorbed fat may stimulate mucosal secretion.

Although protein absorption may also be impaired

during persistent diarrhoea, a generous intake of protein can easily maintain a positive nitrogen balance. Incomplete absorption of protein does not appear to affect gut function. However, malabsorption of carbohydrate not only affects the net energy absorption but also stool volume. Unabsorbed carbohydrates, especially mono- and disaccharides, exert an intraluminal osmotic force that draws water into the intestine, causing diarrhoea to worsen.

Loss of endogenous nutrients including protein and other blood components occurs during shigellosis and presumably also during other invasive intestinal infections. When such infections are associated with persistent diarrhoea, nutrient losses of this type may contribute considerably to the nutritional impact of the illness.

Nutritional management of persistent diarrhoea

There have been few studies of the dietary management of persistent diarrhoea, but accumulated 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 indicated 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.

Breast-feeding. Whether continued breast-feeding is beneficial for persistent diarrhoea has not been determined, although the tendency of acute diarrhoeal episodes to be shorter in infants that continue to breast-feed has been noted above (see p. 712). Although further studies are required on this topic, it is recommended that breast-feeding be maintained during episodes of persistent diarrhoea.

Non-human milk. Infants with persistent diarrhoea who are given undiluted animal milk as the sole source of nutrients are sometimes more difficult to manage owing to symptoms of intolerance, which may include increasing severity of diarrhoea. When this occurs it is usually due to malabsorption of lactose. Unfortunately, there is no way to predict which patients will be intolerant to milk. Several studies have indicated that decreasing the lactose in non-human milks—either by traditional fermentation processes (e.g., yoghurt) or by adding microbial lactase—can reduce the severity and possibly the duration of persistent diarrhoea, at least in some patients.

There has been little controlled experience with the use of mixtures containing milk and staple food products for the treatment of persistent diarrhoea, but preliminary trials of milk and cereal mixtures in acute diarrhoea suggest that they would be well tolerated. The combination of milk and cereal permits adequate nutrient intake with the nutritional advantages of milk, while reducing the amount of lactose.

Weaning foods. Few studies have focused specifically on the clinical and nutritional effects of the dietary management of persistent diarrhoea using weaning mixtures prepared from locally available foods. The preliminary results of studies during acute diarrhoea and experience gained in the rehabilitation of severely malnourished children indicate that these diets are generally well tolerated. Factors that must be considered in designing the mixtures include local food availability, cost, and cultural acceptability for use in young children, particularly during diarrhoea. In addition, food mixtures should have high nutrient density and low viscosity, and hyperosmolality should be avoided. The ingredients should be readily digested and the bioavailability of the nutrients should be high. Regarding macronutrient profiles, complementary protein sources should be selected to optimize amino acid intake in relation to requirements. Carbohydrates should be selected with a view to avoiding hyperosmolality and reducing the potential for disaccharide malabsorption; fats that are most readily digestible, namely edible vegetable oils, are preferred, especially if they are locally available.

The dietary regimen should be designed to meet the child's usual nutrient requirements based on ideal weight-for-height. Increased frequency of feeding during illness may maximize absorptive efficiency.

Micronutrients. Because selected micronutrients, such as folate, zinc, iron, vitamin B_{12}, vitamin A and possibly others, are involved in intestinal mucosal and/or a variety of immunological responses, supplementary vitamins and trace elements should probably be given during persistent diarrhoea. Additional studies will be required to determine their impact upon the duration of diarrhoea and whether mixed diets can provide sufficient amounts of these substances.

Convalescent feeding. Despite optimal dietary management during persistent diarrhoea, some children may not satisfy their nutrient requirements because of anorexia and/or severe malabsorption. Therefore, attention must also be directed to appropriate nutritional therapy during convalescence to ensure that the children return at least to their pre-illness nutritional status. Studies from nutritional rehabilitation units have shown that desired levels of nutrient consumption can be achieved in children given nutrient-dense (low-bulk), low viscosity diets. These levels of intake can promote rates of growth far in excess of those expected for normal children of

the same age group, achieving rapid nutritional recovery. More experience is required with the use of specific dietary regimens for convalescent feeding in community-based studies.

Management of infants with persistent diarrhoea and marked weight loss. A small subgroup of children with severe persistent diarrhoea and marked weight loss requires specialized treatment in hospital. The principal objectives of therapy are maintenance of the child's hydration and nutritional status and manipulation of the diet to avoid specific dietary components to which there is intolerance. These patients can be managed initially as described in the preceding section. Patients with dysentery will require specific antimicrobial therapy. Those with severe watery diarrhoea should be evaluated for carbohydrate malabsorption. Although rare, sensitivity to dietary proteins should be considered.

Management of carbohydrate intolerance. Severe watery diarrhoea that increases in intensity following the consumption of disaccharide-containing diets may respond to the removal of these sugars from the diet. Clinical indicators of carbohydrate malabsorption include explosive watery diarrhoea with the presence of reducing substances in the stool (before or after acid hydrolysis), a low faecal pH, and perianal inflammation. A subgroup of very severely affected patients may also be intolerant to monosaccharides and require the removal of all dietary carbohydrate.

Management of protein sensitivity. In children who do not improve following the withdrawal of dietary carbohydrates and appropriate antibiotic therapy (as discussed below), sensitivity to dietary protein should be considered. This syndrome is rare, poorly described and difficult to diagnose. A presumptive diagnosis is made when clinical improvement follows removal of the suspected protein and diarrhoea worsens after it is reintroduced. Such patients can be managed by substitution of dietary protein: children who were initially receiving animal milk may be switched to soya- or meat-based diets. Successful results have been described, for example, with finely ground chicken as a protein source.

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 given only when a specific enteropathogen has been isolated or when dysentery is present. An exception, usually not requiring specific therapy, is *Giardia lamblia* which is frequently present in the stools of both healthy and diarrhoeic children, but is rarely a cause of persistent diarrhoea. 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.

Ongoing research may yield information that calls for a modification of these recommendations on antibiotic use. A recent study in the USA, comparing oral gentamicin with placebo, showed gentamicin to be effective in shortening the duration of illness, but only in patients who harboured EPEC or EAEC in the small bowel (about 50% of the patients studied). Additional studies of oral gentamicin therapy for persistent diarrhoea are under way in several developing countries. Until the results of these studies are available, treatment of persistent diarrhoea with oral gentamicin is not recommended.

Oral rehydration therapy

The efficacy of oral rehydration salts (ORS) in treating dehydration due to acute diarrhoea is well established. In both acute and persistent diarrhoea, the aim of treatment is to restore the initial fluid deficits and to replace ongoing stool losses until diarrhoea ceases. Although the efficacy of the standard formulation of ORS in treating dehydration has not been evaluated in a controlled fashion, experience from some developing countries suggests that ORS is effective in the majority of cases. In a small number of infants with severe persistent diarrhoea, jejunal glucose and fructose absorption is severely impaired. In this situation, oral rehydration solutions are less effective and intravenous fluids and electrolytes may be required. Improved oral rehydration solutions, currently under development for acute diarrhoea, might also be more effective than standard ORS in the treatment of persistent diarrhoea.

Other pharmacological agents

The usefulness of antimotility agents, antisecretory agents and/or intestinal adsorbents has not been clearly demonstrated in persistent diarrhoea, and these agents are not recommended as therapy; the possibility that colestyramine may be beneficial, especially if combined with an oral antibiotic, deserves further study. Likewise, there are no data to suggest that attempting to replace intestinal flora with lactobacilli or faecal streptococci is efffective.

RESEARCH PRIORITIES

(1) Some additional community-based studies describing the epidemiology of persistent diarrhoea are

required. These should define age-specific incidence, seasonality, microbial etiology, nutritional impact, and contribution to diarrhoea-associated mortality.

(2) Risk factors that influence the duration of a diarrhoeal episode or determine severe nutritional impact or mortality from persistent diarrhoea should be more precisely defined. Risk factors should be especially sought that can be modified by specific community- or facility-based interventions.

(3) Prognostic factors that reliably identify a child in whom an acute diarrhoeal episode is likely to become persistent should be sought and used as an indicator of the need for early, appropriate treatment.

(4) The microbial pathogenesis of persistent diarrhoea should be studied in detail. Such studies should include (*a*) comparison of the small bowel flora (enteroadherent *E. coli*, other enteric pathogens, aerobic Gram-negative bacteria) in acute diarrhoeal episodes that do or do not become persistent, (*b*) definition of the role of recent acute diarrhoea (e.g., due to rotavirus) in increasing the risk of a subsequent episode of persistent diarrhoea, and (*c*) determining whether pharyngeal or buccal colonization with Gram-negative enteric bacteria correlates with abnormal colonization of the small bowel with such bacteria.

(5) The epidemiology and causes of transient impairment of cell-mediated immune reactivity should be investigated in young children. The relationship between impaired immunoreactivity and the frequency, duration and etiology of diarrhoea should be defined. The natural history of asymptomatic cellular immunodeficiency in young children should be described.

(6) Diets should be identified that are practical and effective for patients with persistent diarrhoea. Attention should be given to determining how animal milks can be safely used, the amount of fat that can be included, and the best tolerated carbohydrates. Diets should be nutrient dense, yet isosmolar and of low viscosity. They should be cheap, readily available, and culturally acceptable for use in children with diarrhoea. Primary outcome measures in these studies should be food intake, duration of diarrhoea, and weight gain. Feeding requirements to optimize catch-up growth during convalescence from persistent diarrhoea should be defined.

(7) It should be determined whether vitamin A deficiency is a risk factor for persistent diarrhoea and whether vitamin A supplementation of children with subclinical deficiency reduces the duration of the diarrhoeal episode and/or the incidence of persistent diarrhoea. The effect of vitamin A supplementation during acute diarrhoea on the duration of the diarrhoeal episode should also be determined.

(8) Deficiency of other micronutrients (vitamin B_{12}, iron, zinc, folic acid) should be studied as a possible risk factor for persistent diarrhoea and the role of micronutrient supplementation in treatment or prevention determined.

(9) The role of antibiotics in the treatment of persistent diarrhoea should be more precisely defined in relation to the small bowel microflora and the presence of specific enteric pathogens. The efficacy of antibiotics other than oral gentamicin should be studied (e.g., trimethoprim–sulfamethoxazole), especially if current studies of gentamicin show it to be effective. Minimum effective antibiotic regimens should be defined. The efficacy of certain antidiarrhoeal drugs, e.g., colestyramine, should be determined, especially in combination with an antibiotic of proven effectiveness.

(10) It should be determined whether early, appropriate treatment of acute diarrhoea (including continued breast-feeding, other dietary management, or the use of glucose- or cereal-based ORS) reduces the risk of development of persistent diarrhoea.

(11) Practical guidelines should be developed for the prevention and management of persistent diarrhoea. These should define (*a*) the point during an unresolved acute illness at which specific treatment measures should be introduced, (*b*) the role of dietary manipulation, and (*c*) the place of antibiotics (and possibly other drugs), if any. These guidelines should be appropriate for use in peripheral health facilities.