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Persistent Diarrhoea And Associated Malnutrition In Children

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The term persistent diarrhoea is used to define the small proportion of episodes of a presumed infectious aetiology that lasts for 14 or more days[1]. The duration of diarrhoeal episodes is a continuum and delineating a subgroup as persistent is, as such, arbitrary. However, a specific definition for persistent diarrhoea is useful for case management purposes and in National Programmes. The term persistent diarrhoea excludes rare chronic diarrhoeas of specific aetiologies, for example, celiac disease or rare metabolic errors.

Thus defined, about 3 to 20 per cent of acute diarrhoeal episodes become persistent. Although such episodes are relatively small in number, persistent diarrhoea is important because of a several-fold higher case fatality rate than acute watery diarrhoea; this is, to a large extent, because malnutrition is more often associated with the former.

RISK FACTORS

Persistent diarrhoea is often associated with malnutrition. Although some recent studies suggest that malnourished children may not have an increased incidence of enteric infections, it is well established that when they are infected, the illness tends to be of longer duration, increased severity and with a substantially higher risk of death[2]. On the other hand, diarrhoea may itself cause growth faltering, and seriously worsen existing moderate malnutrition. The mechanisms underlying the prolongation of acute diarrhoea in the malnourished child include achlorhydria, local and systemic immuno incompetence, reduced levels of intestinal and pancreatic enzymes and an ineffective intestinal epithelial cell repair process in response to an acute enteric infection. Transient immuno incompetence and ineffective mucosal repair may also be the effect of micronutrient deficiency, particularly of vitamin A and zinc and possibly others[3]. In children with acute diarrhoea who are either severely malnourished or have subclinical zinc deficiency, zinc supplementation shortens the duration of illness and reduces the frequency of watery stools[4].

A transient cutaneous anergy to multiple antigens has been found to be associated with a substantially increased risk of persistent diarrhoea, independent of anthropometric status; the mechanisms underlying this transient cutaneous anergy need to be defined[5]. The observation that a preceding recent diarrhoeal illness increases the risk of persistent diarrhoea may reflect a higher predisposition to illness in these children. Alternatively, an acute diarrhoeal illness may alter either the intestinal epithelium or impair immune responsiveness to subsequent infection; the latter could be the result of substantial losses of zinc in the stools during acute diarrhoea[6]. Measles is followed by a period of impaired cellular immunity and during this period the affected children experience more acute and persistent diarrhoea.

SUPPLEMENTATION

Several clinical trials have examined the efficacy of supplementation with zinc and vitamin A administered during acute diarrhoea on the outcome of the supplemented episode.

Initial studies by Roy *et al* in Bangladesh[7] and Sachdev *et al* in Delhi[8] suggested that in the subgroup of children who are severely malnourished or who have subclinical zinc deficiency indicated by low zinc levels in rectal mucosa, zinc supplementation shortens the duration of illness and reduces the frequency of watery stools.

More recently, Sazawal *et al*[9] in a more definitive field study in Delhi, randomised 931 children with acute diarrhoea $\geq$ 7 days duration to supplementation with either zinc or placebo. In the zinc group, there was a significant reduction of 39 per cent in episodes lasting more than seven days after supplementation when supplementation was started within three days of onset of diarrhoea. In the logistic regression model, the odds

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ratio for reduction in risk of diarrhoea lasting more than seven days with zinc was 0.79 (95 per cent CI 0.64-0.96). The odds ratio was 0.74 (95 per cent CI 0.57-0.95) when the model was restricted to episodes enrolled by three days of onset. The reduction in diarrhoea lasting more than seven days was 65 per cent in the subgroup of stunted children. There was a 39 per cent reduction in the mean number of watery stools per day in zinc supplemented children ($p < 0.02$).

The impact of vitamin A (200,000 IU) during an acute diarrhoeal episode on its outcome was investigated in two studies. In the study by Henning *et al*[10], vitamin A did not reduce stool output or duration of diarrhoea in hospitalised children with acute diarrhoea and dehydration.

The study was too small to detect a reduction in stool output of less than 50 per cent with 80 per cent power. The other study by Bhandari et al was a field trial, in which 900 children with acute diarrhoea lasting less then seven days were randomised to either vitamin A (200,000 IU) or placebo. In the overall analysis, vitamin A children had significantly less persistent diarrhoea ($p < 0.05$) and there was a trend towards lesser mean total watery stools in the episodes ($p = 0.05$).

When data were analysed separately by breast feeding status, administration of vitamin A during acute diarrhoea had no impact in breast-fed infants and the reduced risk of persistent diarrhoea in the overall analysis was entirely contributed by non breast-fed children.

Overall, these recent studies emphasise the importance of nutritional host factors in the outcome of acute diarrhoea. While there is increasing evidence that severely malnourished children with acute diarrhoea need to be supplemented with zinc and vitamin A, the benefit in moderately malnourished children with acute diarrhoea needs to be evaluated.

MILK FEEDING AND RISK OF PERSISTENCE

It is widely believed that low lactose and lactose-free feeding during acute diarrhoea may decrease the severity of the illness including the risk of persistent diarrhoea. This explains the widespread dilution or withholding of milk in the acute phase (one to seven days) or the intermediate phase (seven to 13 days) of diarrhoea.

A recent WHO study conclusively showed that even in infants receiving artificial milk, use of full strength animal milk does not increase stool output, diarrhoeal duration or risk of treatment failure[11]. A study at AIIMS (Table 1) showed that use of yoghurt instead of milk as a part of a mixed diet in malnourished children with acute diarrhoea does not affect the outcome of the episode; indeed, the milk-cereal group gained significantly more weight by virtue of a higher intake (Bhan *et al*, in press).

INTAKE AND ABSORPTION

There is a substantial impairment of fat and protein absorption during persistent diarrhoea; carbohydrate malabsorption is only moderately affected on diets that are predominantly cereal-based. Secondary malabsorption of sugars, particularly of lactose,is common. In a proportion of cases, disaccharides other than lactose are also malabsorbed to a clinically significant degree.

Clinically significant monosaccharide malabsorption is fortunately infrequent. The causes of carbohydrate malabsorption are acute or persistent enteric infection and malnutrition by decreasing brush border enzymes. Unabsorbed sugars are osmotically active and induce water and electrolyte secretion into the intestinal lumen.

The role of dietary protein intolerance in persistent diarrhoea is highly contentious. Based on studies in India and other developing countries, it is unlikely to be of significance in the pathogenesis of persistent diarrhoea[12]. Although increased intestinal uptake of intact proteins has been demonstrated following acute gastroenteritis in early infancy, the clinical significance of this phenomenon is not established.

Faltered growth in persistent diarrhoea is not only the result of nutrient malabsorption — inadequate dietary intake due to anorexia, a continuation of faulty pre-illness feeding practices, or as a response to diarrhoeal illness itself by the family or physicians — are all important.

NUTRITIONAL FACTORS

The common causes of persistent diarrhoea as seen in developing countries are persistent infection with one or more enteric pathogens, sequential enteric infection, disaccharide and rarely monosaccharide malabsorption, as well as dietary protein intolerance. The hallmark of the disorder is persistent mucosal damage which may result from failure to eliminate the causative agent or delayed and ineffective mucosal restoration. Protein energy malnutrition and micronutrient deficiency in humans are known to be associated with abnormalities in intestinal structure and function. Delayed regeneration of the epithelium with reduced crypt cell multiplication and ineffective maturation of cells during their migration up the villi, following an enteric infection, have been demonstrated in experimental malnutrition. Pathogenic bacteria cause mucosal damage and diarrhoea through mu-

TABLE 1
Comparison Of Yoghurt And Milk In Acute Diarrhoea

Outcome variables	Milk (n = 49) Mean±SD	Yoghurt (n = 47) Mean±SD	P value
Total stool (g/kg)	161.3±202.1	164.4±257.0	0.81#
Mean % weight gain at 120h compared to post rehydration weight	0.12±3.1	-1.90±4.8	0.02#
Proportion of patients recovered			
Day - 3	33 (67.3)	30 (63.8)	0.92*
Day - 5	40 (81.6)	39 (83.0)	0.56*
Day - 7	44 (89.7)	43 (91.5)	0.4*

Unpublished data from Bhan et al, *AIIMS, New Delhi.*
 # Non parametric test.
** Chi-square.*

cosal effacement or invasion, and action of enterotoxins or cytotoxins; malnutrition in the host prolongs the healing of the injured mucosa, the state of malabsorption and diarrhoea. In a proportion of cases, an immunological response to luminal, bacterial or dietary antigens has also been proposed as the basis for gut mucosal damage in persistent diarrhoea but the data are still inconclusive.

FLUID THERAPY

Intravenous therapy may be required initially when dehydration is severe, to correct major electrolyte abnormalities or acidosis, and in extremely cachexic or systemically infected infants who accept oral fluids poorly.

Children with some but not severe dehydration can be effectively treated with oral fluids. The Oral Rehydration Salt (ORS) solutions, recommended by WHO/UNICEF containing 20 g glucose, 3.5 g sodium chloride, 1.5 g potassium chloride, 2.9 g sodium citrate or 2.5 g sodium bicarbonate (total osmolarity 311 mOsmol/l), has been adopted by the National Diarrhoeal Disease Control Programme. Recent studies show that the rate of stool output is significantly decreased in dehydrated children with acute as well as persistent diarrhoea when the osmolarity of the WHO-ORS is reduced from 311 to between 224 and 250 mOsmol/l by decreasing its sodium and glucose content. It has been suggested that the sodium content of the WHO-ORS (90 mmol/l) is sufficiently high to induce fluid overload in severely malnourished children. A change in the composition of the standard ORS is under active consideration by the WHO. In the interim, a feasible option in severely malnourished children with acute and persistent diarrhoea is to administer the estimated fluid deficit in eight to 12 hours instead of the usual four to six hours, offering plain water in between or to dilute a packet of WHO-ORS in 1.5 rather than the recommended 1 litre of water. As the latter option would further decrease the potassium concentration of the WHO-ORS (20 mmol/l) which may be already too low for severely malnourished children, it is important to provide additional potassium supplements. It must be emphasised that the current WHO-ORS is safe and effective in dehydrated children who are well nourished or only marginally malnourished.

When clinical dehydration is not associated, fluids available at home are appropriate for replacement of ongoing stool losses. These include rice water or *kanji, dal* water, *lassi* or butter milk, *sharbat*, coconut water, lemon water and plain water. While recommending cereal-based fluids, it is important to ensure that mothers do not consider these as substitutes for nutritionally adequate foods.

RECENT STUDIES

Several general principles have been established through recent studies in persistent diarrhoea.

In developing countries, the need to use total intravenous nutrition arises very rarely. Optimal oral feeding, based on an appropriately constituted diet is well tolerated and achieves recovery and catch up growth in the vast majority of these patients. Although there is some malabsorption of nutrients in persistent diarrhoea, about 80-90 per cent of carbohydrates and 70-75 per cent of fats and proteins are actually absorbed from mixed diets, based on locally available ingredients.

Breast feeding is safe and well tolerated during diarrhoea. Although a few predominantly breast-fed infants with acute diarrhoea may continue to pass stools with more than the usual frequency or stools of somewhat liquid consistency for more than two weeks, physical growth is well maintained.

In the non breast-fed babies, an important issue is whether milk should be totally eliminated or simply reduced in amount during persistent diarrhoea.

Brown and colleagues[13] reported increased stool weights on diets predominantly based on whole milk as compared to lactose hydrolysed milk. The milk intakes were equivalent to about 6 g/kg/day or more of lactose; few children in Indian communities take such large quantities of milk. The issue of whether lower intakes equivalent to 2.5 g/kg lactose load per day would also be poorly tolerated has been recently examined in a clinical trial; preliminary analysis showed greater weight gain in the group receiving a mixture of cereals with milk in which the latter provided 35 per cent of the total calories than in the other group consuming an isocaloric cereal-based diet without milk. There was only a modest 15 per cent increase in the stool output in the milk group but the treatment failure rates were similar. (Bhatnagar *et al*, in press — Table 2.)

Similarly, Bhutta *et al*[14] reported lower stool output and greater weight gain in persistent diarrhoea with curds cereal mixtures than with lactose-free soy-based diets. Together, these studies make a case for reduction rather than total elimination of milk as the initial step. A modest amount of milk in cereal diets improves their protein quality, trace elements and mineral content. Further, the consistency and palatability ensures higher intakes of these diets than with purely cereal -based diets. The possibility of occasional milk protein allergy is outweighed by the benefits offered by adding modest amounts of milk to cereal-based diets.

SPECIFIC RECOMMENDATIONS

Once a child is ready for oral feeding after a few hours of stabilisation,

TABLE 2
Comparison Of Milk-based And Milk-free Diet In Persistent Diarrhoea

	Milk-cereal # (n = 58)	Egg-cereal (n = 55)	P value
Stool weight in males (g/kg/h) 0-120h	1.9 (SD 1.4)	1.7 (SD 1.4)	0.419
% weight gain at 120h compared to post rehydration weight	3.1 (SD 3.8)	2.1 (SD 3.7)	0.21
Treatment failures	10 (17.2)	13 (23.6)	0.4
Calories kg/day in 0-120h	101.9 (SD 26.2)	94.5 (SD 28.6)	0.16

Unpublished data from Bhatnagar et al, *AIIMS, New Delhi.*
 # Lactose load 2.8 g/kg/day.

the choice of an initial diet would be milk-rice mixtures with added oil, yielding an energy density of about 85-95 kcal/100 g with 30-35 per cent calories from milk. The diet provides the ideal minimal 10 per cent energy from a protein source. The composition of one such diet is given in Table 3. It is now well established that in persistent diarrhoea, any convenient fat source may be used. Studies at AIIMS (Bhan *et al*, personal communication) showed that neither coconut oil nor medium chain triglycerides improve fat absorption.

In a small proportion of patients with very severe diarrhoea where some clinicians feel reluctant to use milk even in small quantities, diets based on rice, sugar and oil are appropriate. Egg is well tolerated and provides useful animal protein in such diets.

Nearly 25 per cent of hospitalised patients show a poor response to Diet A. The factors related to treatment failure on low lactose (milk), cereal-based diets are systemic infections, severe carbohydrate intolerance involving not only lactose but also other disaccharides and starch. Therefore, dietary modification should be made only after effective treatment of associated systemic infections. Poor oral intake as a result of systemic infection is more often the cause of weight loss than true dietary failure in hospitalised children. In milder cases that are managed at the household level, a common reason for poor weight gain is the offering of only small quantities of thin foods to the child by the family. The second line diet should be milk-free with substitution of part of the starch by sucrose or glucose (Diet B). This mixture of sugars achieves the right balance between dietary osmolarity, digestibility and energy density. In such a diet, egg or chicken is a suitable protein source. An example of such a diet is given in Table 3 (Diet B and Diet C). Monosaccharides as the only carbohydrates in the diet should be used for the few patients who are treatment failures on Diet B, as it is difficult to provide sufficient energy density with the permissible 2-3 per cent glucose concentration; at higher concentrations osmotic diarrhoea may develop (Table 3, Diet D).

Until their role in the management of persistent diarrhoea is well established, generous but safe amounts of micronutrients equivalent to two times the RDA should be provided. These may include vitamin A, zinc, iron, folate and, when feasible, others.

TABLE 3
Examples Of Diets

Ingredients	Diet A	Diet B	Diet C	Diet D
Puffed rice (g)	12.5	7.0	13.50	–
Egg (g)	–	–	11.00	–
Chicken (g)	–	7.0	–	12.0
Milk (g)	40.0	–	–	–
Sugar (g)	2.25	–	–	–
Glucose or sucrose (g)	–	3.0	3.5	3.0
Oil (g)	2.0	4.0	3.5	4.0
Water to make	100.00	100.00	100.00	100.00
Energy density (cal/100 g)	96.0	78.4	95.22	60.48
Per cent protein	10.0	11.75	9.51	20.56
Per cent carbohydrate	55.87	41.6	56.9	19.84
Per cent lactose	.73	–	–	–
Per cent fat	33.9	46.41	33.29	60.60
Amino acid score	1.0	1.00	1.00	1.00

Diet A: Example of initial diet.
Diet B: Example of diet for failures on initial diet.
Diet C: Second example of Diet B.
Diet D: Compostion of third line diet.

Severely malnourished children should receive magnesium 1-1.5 ml/kg body weight of a 50 per cent solution, given IM for two to three days. Patients on a milk-free diet should also receive calcium supplementation.

COMMERCIAL DIETS

Several commercial diets are also available. For reasons that are not fully explained, home-based low lactose or lactose-free diets perform much better than commercial soy-based formulations. Semi-elemental diets like Nutramigen or Progestimil are useful but expensive. They usually contain protein hydrolysate or calcium caseinate, a mixture of disaccharides and oligosaccharides and part or all of the fats as medium chain triglycerides. Micronutrients and vitamins are already added. Diet B is based on similar principles and is at least as effective. Its advantage is that the concentration of the individual sugars can be tailored to each child individually, it is cheap and can be easily prepared by mothers at home and in small hospitals. The disadvantage is that vitamins and minerals need to be supplemented.

COMMUNITY SETTING

As diarrhoea is common in children from poor communities where family feeding habits contribute to malnutrition, an interaction with health care providers during the illness offers a good opportunity to improve nutrient intake through purposeful nutritional counselling. Mixtures of milk and cereals or of cereals and legumes fortified with oil are well tolerated during acute and persistent diarrhoea. They have the required energy density and palatability. About 30-40 per cent of calories are derived from fat sources without any deleterious effect. Mothers must receive nutritional counselling from health care providers that is practical and takes into account family views and realities and also includes clear instructions on the frequency of meals, the amount to be fed at each meal and the solutions to problems of the individual child and family. This is currently the weakest link in the sick child and health care provider interaction.

The vast majority of patients with persistent diarrhoea are unable to avail hospital care due to the physical and situational constraints of the family. Therefore, it is the outpatient nutritional care of persistent diarrhoea patients that needs strengthening in-