Editorial

PERSISTENT DIARRHEA IN INFANTS AND YOUNG CHILDREN

Persistent diarrhea was arbitrarily defined as diarrhea of a presumed infectious cause that begins acutely and lasts for 14 days or more(1). The 14 day cut-off is consistent with significant increase in mortality for episodes longer than 14 days than for those that lasted between 7-14 days in an Indian cohort study(2). Thus defined, 3-20% of acute diarrheal episodes in children in developing countries are persistent.

Persistent diarrhea is associated with a deterioration in nutritional status and there is a substantial risk of death. In rural north India, nearly half of all diarrheal deaths in children up to 5 years of age are related to persistent diarrhea(2). In 25% of the episodes that end fatally, respiratory infections develop in the terminal stages(2). Similar high contribution of persistent diarrhea to childhood diarrhea related mortality was observed in Bangladesh and northern Brazil(3).

Several risk factors for persistent diarrhea have been identified. These include antecedent malnutrition(4), an age of less than 1 year, impaired immunological status, introduction of animal milk in the diet(1) and occurence of a recent diarrheal episode(5). In early infancy this last cause may be associated with one or more of several mechanisms: (*a*) reduced intake of breast milk; (*b*) contamination of animal milk with pathogenic bacteria; (*c*) intestinal mucosal damage by animal protein, and (*d*) osmotic diarrhea due to secondary lactose intolerance during acute diarrheal episodes. The type of animal milk used may be important. Sazawal *et al.*(6) reported a much higher risk of persistence of acute diarrhea with liquid animal milk than with spray dried infant formula when compared to breast feeding as the reference risk. The study does not explain whether the results are related to reduced antigenicity of milk by exposure to high temperatures during spray drying, or the lower osmolarity and solute load due to the lower lactose content of infant formula.

The introduction of safe weaning practices in Indian children is likely to reduce the incidence of persistent diarrhea. These include exclusive breast feeding during the first six months of life, avoidance of unmodified cow's milk particularly during early infancy and the feeding of hygienically prepared semisolid foods in optimal quantities after the age of 6 months to avoid malnutrition.

The role of antimicrobial agents is still unsettled. Several studies show pathogen excretion to be common in patients with persistent diarrhea, isolation rates varying between 55-70%. The common excretion of these pathogens by asymptomatic children in developing countries makes their interpretations difficult(7). The prominent stool pathogens identified in persistent diarrhea are Shigella, nontyphoidal Salmonella, enterotoxigenic *Escherichia coli,* enteroadherent *Escherichia coli* particularly those of aggregative phenotype, enteropathogenic *Escherichia coli, Giardia lamblia* and *Entameba*

histolytica(8). The single largest isolation was of enteroaggregative *E. coli* in a third of cases of persistent diarrhea in rural north India(8) and nearly half the cases in Mexico(9). Two recent studies(7,10) found no differences in duodenal aerobic or anaerobic counts between infants and young children with persistent diarrhea and malnutrition and non diarrheal age category matched malnourished controls. However, colonization with Enterobacteriaceae was more common in persistent diarrhea than control children: The purge rates were significantly greater in the presence of duodenal Enterobacteriaceae.

Controlled clinical experience with antibiotic therapy is limited. Hill *et al.*(11) reported beneficial effect with oral gentamicin therapy in persistent diarrhea; their strategy allowed selection mainly of cases of severe high purging diarrhea of more than 5-7 days. A recent Indian study(12) found no improvement in purge rates, weight gain or overall illness among children with persistent diarrhea treated with oral gentamicin than with a placebo. Interestingly, this lack of clinical benefit was despite clearance of stool pathogens at the end of a week of hospitalization suggesting that elimination of offending pathogens like adherent *Escherichia coli* at this late stage does not lead to prompt recovery as the mucosa is already severely damaged; therefore nutritional support is the key to repair. A possibility remains that systematically absorbed antibiotics may perform better: the results of several ongoing trials must be awaited to confirm or refute the possibility.

Currently, antimicrobial agents may be used in the presence of bloody stools associated with Shigellosis. The nature of antibiotic therapy should be guided by the current sensitivity of isolated pathogens in the local settings. Giardiasis and amebiasis should be treated only when a specific diagnosis of trophozoites is made on stool microscopy. Antimotility or antisecretory agents are not useful and are contraindicated. The use of cholestyramine, which binds unconjugated bile salts or bacterial toxins, is also not recommended. Cholestyramine may aggravate steatorrhea. Lactobacillus or fecal streptococci to replace intestinal microflora and adsorbents like kaolin and pectin do not offer therapeutic benefit(1).

Fluid and food are the important components of therapy. Fortunately few patients have dehydration and when present, a complete ORS of the composition recommended by the WHO is usually appropriate. Additional potassium supplementation is desirable in these poorly nourished children. Intravenous fluids (IV) for the initial day or two and occasionally longer are needed in the presence of recurring dehydration, extreme lethargy, abdominal distension or poor oral intake due to associated systemic infection or extreme inanition.

Several general principles were established through recent experience in dietary management. In developing countries there is very rarely the need to use intravenous nutrition. Secondly, there can be no single diet for all cases because severity and disruption of absorption of lactose, starch and oligosaccharides varies considerably(13). A practical algorithm needs to be developed with appropriate guidelines for when to change one diet to another so as to remove the unjustified mystery around the treatment of this disorder.

The initial step is to identify patients for intravenous or antibiotic therapy and those in whom oral feeding may not be tolerated because of vomiting, abdominal

distension or risk of aspiration. This is a small number of 4-5% hospitalized cases.

What should be the initial diet in those who accept oral feeding? Breast feeding is safe and well tolerated during persistent diarrhea. The important issue is whether the other milks should be withheld in the initial diet. Brown and colleagues(14) 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 of lactose; few children in Indian communities take such large quantities of milk. Bhan and Bhatnagar recently addressed the issue of whether lower intakes equivalent to 2.5 g/kg lactose load per day would also increase stool rates; preliminary analysis showed significantly greater weight gain in the group receiving cereals with milk providing 35% of the total calories than in the other group consuming cereals without milk (unpublished data). Two other lessons were learnt. Caloric density of 85-95 per 100 g of low milk rice based feeds were well tolerated at all ages. Secondly, these very high energy intakes were not correlated with increase in purge rates and also considerably shortened hospital stay (unpublished data). Similarly, Bhutta *et al.*(15) reported better clinical results in persistent diarrhea with curds cereal mixtures than with lactose free soy based diets. Together, these studies make the case for reduction rather than total elimination of milk in non breast fed, not critically ill infants and young children with persistent diarrhea. Thus, the choice of an initial diet would be milk rice mixtures with added oil, yielding an energy density of about 85-95 with 30-35% calories of milk origin. The diet provides an ideal 10% energy from protein source. 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 out weiged by the benefits offered by adding modest amounts of milk to cereal based diets. In a small proportion of very severe patients where some clinicians feel reluctant to use milk even in small quantities, rice sugar oil based diets need to be fortified with protien like egg white or calcium caseinate.

About 10-15% children gain weight poorly or experience ongoing diarrhea on these initial diets; this is more often due to infection and less frequently as dietary failure. The determinants of poor outcome are: (*a*) systemic infection including in the urinary tract and less frequently gastrointestinal tract; and (*b*) more severe carbohydrate intolerance involving not only lactose but also starch and sucrose. Therefore, the second line diet should avoid milk and reduce the starch load by using sucrose or glucose. However, glucose when used alone in large quantities to provide increased energy density is hyperosmolar, hence a mixture of glucose or sucrose with rice is preferable. In such a diet egg or chicken is a good protein source. One recent study has shown egg protein to be well tolerated orally (unpublished data). Fortunately, acquired monosaccharide intolerance is rare. The diagnosis is suspected when diarrhea increases in pateints consuming significant amounts of ORS without other fluids or foods, decreases considerably on nil orally IV regimen and recurs on reintroduction of monosaccharide based fluids. This disorder is transient; a practical approach is to use total intravenous nutrition and wherever not feasible intravenous glucose with egg

or chicken as the protein source and oil by mouth(16).

In all these diets it needs to be ensured that safe, generous amounts of vitamins, trace elements and electrolytes are supplemented.

Overall, about 5% of the hospital referred patients require intravenous support for few days before full oral feeding is possible. In the remaining, about 85-90% recover on the initial diet and 10% require change to milk free diet providing carbohydrates as mixtures of rice starch and glucose or glucose alone. Although, the role of antibiotics in achieving recovery from persistent diarrhea has not been substantiated, systemic antibiotics may be required in nearly one third of the hospitalized persistent diarrhea cases for associated pneumonia, urinary tract infection or bacteremia as is true for any group of severely malnourished hospitalized cases. This may not be true of milder cases in outpatient practice.

The multi step dietary treatment, good supportive management especially for those critically ill initially, identification of systemic infection particularly in the urinary tract, avoidance of unnecessary medication, prevention of hospital acquired infection and a clear understanding of when to change the initial diet should keep mortality down to 2-3% in these cases. It would also help in achieving larger and more rapid weight gain within 5-7 days of hospital care. Weight loss or poor weight gain despite 5-7 days of consuming at least 110 cal/kg/day of the respective diet and significant continuing diarrhea of 7 or more diarrheal stools per day may be a reasonable criterion for changing the initial diet. However, poor weight gain is often the result of low dietary intake due to associated systemic infection; in such situations dietary change is unwarranted. Persistent diarrhea is a disorder that can be treated with modest inputs in any large or small hospital in India, once the issues are well documented.

M.K. Bhan,
Shinjini Bhatnagar,
Division of Gastroenterology and Enteric Infections, All India Institute of Medical Sciences, New Delhi 110 029.

REFERENCES

1. Anonymous. Persistent diarrhea in children in developing countries. Memorandum from a WHO meeting. Bull WHO 1989, 66: 709-717.
2. Bhan MK, Arora NK, Ghai OP, Ramchandran R, Khoshoo V, Bhandari N. Major factors in diarrhea related mortality among rural children. Indian J Med Res 1986, 83: 9-12.
3. Victora CG, Huttly SRA. International differences in clinical patterns of diarrheal deaths: A comparison of children from Brazil, Senegal, Bangladesh and India. International study group on mortality due to diarrhea. Report WHO September, 1991.
4. Bhandari N, Bhan MK, Sazawal S, Clemens JD, Bhatnagar S, Khoshoo V. Association of antecedent malnutrition with persistent diarrhea: A case control study. BMJ 1989, 298: 1281-1287.
5. Sazawal S, Bhan MK, Bhandari N, Clemens J, Bhatnagar S. Evidence for recent diarrheal morbidity as a risk factor for persistent diarrhea: A case control study. Int J Epid 1991, 20: 540-545.
6. Sazawal S, Bhan MK, Bhandari N. Type of milk feeding during acute diarrhea and the risk of persistent diarrhea: A case control study. Acta Pediatr Scand 1992, (Suppl) 381: (in press).

7. Bhatnagar S, Bhan MK, George C, Gupta U, Kumar R, Bright D, Saini S. Is small bowel bacterial overgrowth of pathogenic significance in persistent diarrhea? Acta Pediatr Scand 1992, 381 (Suppl): (in press).

8. Bhan MK, Raj P, Levine MM, Kaper JB, Bhandari N, Shrivastava R, Kumar R. Enteroaggregative *Escherichia coli* associated with persistent diarrhoea in a cohort of rural children in India. J Infect Dis 1989, 159: 1061-1064.

9. Cravioto A, Tello A, Navarro A, Ruiz J, Villafan H, Uribe F, Eslava C. Association of *Escherichia coli* HEp-2 adherence patterns with type and duration of diarrhea. Lancet 1991, 337: 262-264.

10. Penny ME, Paredes P, Brown KH, Laughan B, Smith H. Lack of a role of the duodenal microflora in pathogenesis of persistent diarrhea related malabsorption in Peruvian children. Pediatr Infect Dis K 1990, 9: 479-487.

11. Hill ID, Mann MD, Housheham KC, Bowiei MD. Use of oral gentamicin, metronidazole and cholestyramine in the treatment of severe persistent diarrhea in infants. Pediatrics 1986, 77: 477-481.

12. Bhatnagar S, Bhan MK, Sazawal S, Gupta U, George C, Arora NK, Kashyap D. Efficacy of massive dose oral gentamicin therapy in non-bloody persistent diarrhea with associated malnutrition. J Pediatr Gastroenterol Nutr 1992, 12: 117-124.

13. Khoshoo V, Bhan MK, Jain R, Jayshree S, Sazawal S, Mathur M. Intestinal glucoamylase and other disaccharidases in children with protracted diarrhea.Indian J Med Res 1990, 92: 1-4.

14. Penny ME, Paredes P, Brown KH. Clinical and nutritional consequences of lactose feeding during persistent postenteritis diarrhea. Pediatrics 1989, 84: 835-844.

15. Bhutta ZA, Molla AM, Issani Z, Badruddin S, Hendricks K, Snyder JD. Dietary management of persistent diarrhea: Comparison of a traditional rice-lentil based diet with soy formula. Pediatrics (Indian edition) 1992, 4: 44-51.

16. Khoshoo V, Bhatnagar S, Bhan MK. Monosaccharide intolerance complicating protracted diarrhoea in infancy. J Pediatr Gastroenterol Nutr 1989, 9: 131-134.