

Child Health Research Project

Synopsis: Persistent Diarrhea Algorithm

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Persistent diarrhea is any diarrheal illness lasting for fourteen days or more and is a major health problem for children in developing countries. It accounts for less than 10 percent of all diarrheal episodes, but is responsible for 30 to 50 percent of diarrheal death, and is closely associated with malnutrition and recurrent diarrheal illnesses^(1,2). A variety of different pathogens have been associated with it, but they are generally the same pathogens that cause acute diarrhea (Table 1). It has been suggested that some persistent diarrheal illness is caused by sequential infections by different organisms rather than by a single pathogen⁽¹⁾. Ineffective therapy for acute diarrhea, especially excessive use of antibiotics, may further contribute to the development of persistent diarrhea, although appropriate feeding during acute

diarrhea reduces the occurrence of persistent illness. Decreased immunocompetence and measles have also been identified as significant risk factors.

Prolonged and recurrent episodes of diarrhea frequently lead to stunting and growth failure in early childhood. The consequent malnutrition further predisposes patients to episodes of persistent diarrhea, and a vicious cycle of diarrhea-malnutrition-diarrhea follows. The negative nutritional effect of the extended illness is compounded by anorexia, ineffective complementary feeding practices and food withdrawal by caretakers. Persistent diarrhea has thus aptly been labeled a nutritional disorder, and optimal nutritional therapy is considered a cornerstone of its management.

Table 1. Percent of enteric pathogens identified in acute or persistent diarrhea During the first week of illness

Pathogen	Acute Episode: Culture Done in Illnesses of Less Than 7 Days				Persistent Episode: Culture Done in First 7 Days of Illness			
	India n=179	Bangladesh n=823	Bangladesh n=184	Peru n=2431	India n=43	Bangladesh n=251	Bangladesh n=184	Peru n=161
<i>Rotavirus</i>	2.2	3.9	4.3	4.2	2.3	2.8	1.6	.7
<i>Aeromonas sp.</i>	2.8	8.8	4.5	13.1	0	4.8	3.3	9.0
<i>Campylobacter sp.</i>	5.6	1.0	15.7	23.6	4.7	7.1	12.0	32.2
EAEC-AA	12.3	17.9	22.3	11.0	34.9	27.4	18.6	12.0
EAEC-DA	6.1	10.7	10.3	12.0	0	9.6	16.4	12.8
EAEC-LA	7.8	0	2.9	3.4	2.3	0	4.5	4.3
ETEC	15.1	8.8	12.2	25.1	9.3	4.8	14.6	24.2
<i>Salmonella sp.</i>	2.8	.4		.1	4.7	.4		0
<i>Shigella sp.</i>	1.7	9.7	5.4	5.7	2.3	5.6	5.4	7.6
<i>Vibrio sp.</i>	0	.1	2.3	3.4	0	.4	1.1	2.1
<i>Cryptosporidium</i>			1.8	3.6			5.6	.8
<i>Entamoeba histolytica</i>	0	.7	1.8	0	2.3	0	0	0
<i>Giardia lamblia</i>	2.2	9.9	.6	29.4	2.3	1.6	1.2	22.9

* from Black, RE 1993⁽¹⁾; EAEC-Enteroadherent *E. coli*; ETEC-Enterotoxigenic *E. coli*

Until recently, no uniform approach to successful therapy has been developed. Episodes have been treated with a wide variety of expensive, ineffective, and sometimes dangerous methods, including total parenteral nutrition, semi-elemental formulae, and withdrawal of feeding. In this issue, we present the results of a study that evaluated guidelines for the management of persistent diarrhea, developed by the International Working Group on Persistent Diarrhea⁽²⁾. These guidelines, which use feeding with local diets, micronutrient supplementation and appropriate antimicrobial treatment for specific infections, are useful in treating children in the developing world, and have been incorporated into healthcare interventions and policy.

Sponsored by WHO and Harvard University's Applied Research on Child Health (ARCH) Project (through its predecessor, the Applied Diarrheal Disease Research project), the International Working Group developed a method for treating persistent diarrhea which incorporated both dietary and antibiotic interventions (Figure 1). Six medical institutions participated in the evaluation of the guidelines; the ICDDR,B: Centre for Health and Population Research (ICDDR,B), Dhaka, Bangladesh; the All India Institute for Medical Sciences (AIIMS), New Delhi, India; the Hospital Infantil de Mexico Frederico Gomez, Mexico City, Mexico; the Aga Khan University and National Institute for Child Health, Karachi, Pakistan; the Instituto de Investigacion Nutricional (IIN), Lima, Peru; and the Children's Hospital No. 1, Ho Chi Minh City, Vietnam. Persistent diarrhea was defined as a history of >3 liquid stools/day for ≥ 14 days with no more than 2 consecutive days without diarrhea. Children between the ages of 4 and 35 months were included in the study if they met one of the following criteria:

- weight for height < 80 % of the National Center for Health Statistics (NCHS) median, or weight for age < 75% of the NCHS median;
- associated systemic infection severe enough to require hospitalization, or
- signs of severe dehydration.

Figure 1.
Guideline for the management of persistent diarrhea

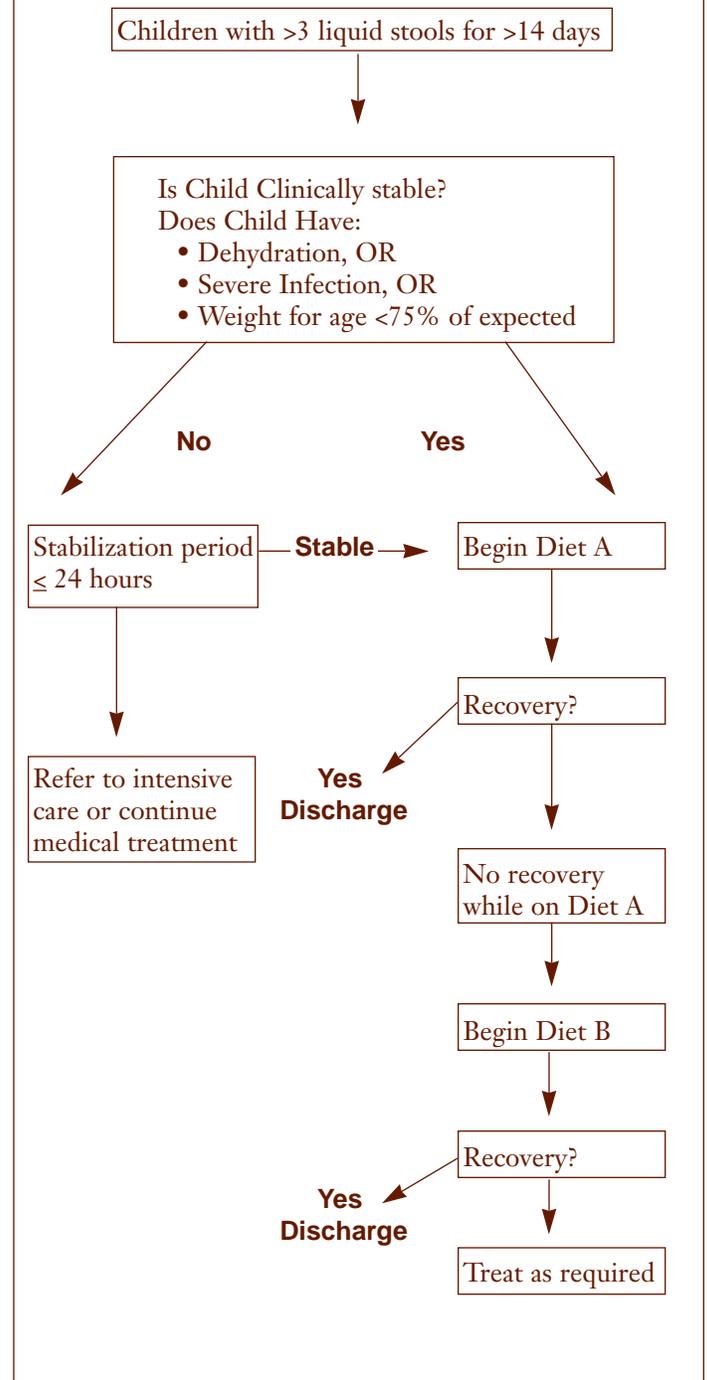


Table 2. Composition of Study Diets

Country	Ingredients	Energy Density (kcal/100g)	Protein (%)	Lactose (g/150 kcal)
Diet A				
Bangladesh	Rice, milk, sucrose, oil	87	9.8	3.70
India	Rice, milk, sucrose, oil	87, 96*	10.0	3.04
Mexico	Maize, milk, sucrose, oil	77	9.6	2.65
Pakistan	Rice, yogurt, lentils (dhal), oil	100	13.1	<1.80
Peru	Rice, milk, sucrose, oil	75	9.6	3.67
Vietnam	Rice, milk, sucrose, oil	85	11.7	2.54
Diet B				
Bangladesh	Rice, egg white, glucose, oil	92	9.7	0
India	Rice, chicken, glucose, oil	78	11.7	0
Mexico	Rice, chicken, glucose, oil	70	13.0	0
Pakistan	Rice, chicken, glucose, oil	120	14.5	0
Peru	Rice, egg white, glucose, oil	75	12.7	0
Vietnam	Rice, chicken, glucose, oil	65	14.1	0

* Energy density varied by age group

The guidelines initially separated children into “unstable” and “stable” categories, based on level of dehydration. Unstable children were given oral rehydration therapy in order to make them stable enough to receive dietary therapy. Stable children were started on “Diet A”, which included local, inexpensive and culturally acceptable foods, consisting mainly of cereals, legumes, vegetable oil and a small amount of milk products (<3.7g lactose /150 kcal). Children who showed an increase in stool weight, volume or number of watery stools at the end of seven days, or who failed to gain weight, were put on “Diet B.” This diet substituted chicken or eggs for milk products, was lactose free, and had a lower cereal and legume content. Each center designed its own Diet A to include locally available and culturally acceptable foods; > 9.5% of total calories as proteins; animal protein (milk or yogurt), and energy density of >65 kcal/100g (Table 2).

Micronutrient supplements were given to provide at least twice the US recommended daily requirements of vitamins and minerals (Table 3). The pills were crushed and mixed with the study diets. Children were allowed to eat at least six times per day to reach a caloric target of 150

kcal/kg/day, with no restrictions placed on children who wanted more food. Water was allowed as desired. Breast-milk feeding was freely allowed to children who were still being breastfed at the time that they were admitted to the study. Antimicrobial therapy was given for clinically or laboratory diagnosed infections, including dysentery (bloody diarrhea), cholera, and giardiasis, urinary tract infection, and acute lower respiratory infection.

A total of 460 children were enrolled at the six study centers. Admission characteristics were similar between groups and included mean age, weight, weight for age and weight for height z-scores, duration of diarrhea, and stool frequency on admission. Almost half of the children, (45%) required a stabilization period, and only 11% of all children were too ill to be stabilized within 24 hours and were transferred to intensive care or other hospital settings for treatment. The remaining 89% received Diet A with micronutrient supplementation and antimicrobial therapy (Figure 1). The overall recovery rate for these children was 80%, defined by cessation of diarrhea and either weight greater than admission weight, or two consecutive days of weight gain exceeding 20 g/day. Success varied from 65% in

Table 3. Recommended Micronutrient Intakes for Persistent Diarrhea and Severe Malnutrition

Micronutrient	Intake for Severe Malnutrition (per 100 kcal)	Intake for Persistent Diarrhea (per day)
Vitamin A	150 mg	400 - 1600 mg
Vitamin D	3 mg	10 - 40 mg
Vitamin E	2.2 mg	5 - 20 mg
Vitamin K	24 mg	15 - 60 mg
Vitamin C	10 mg	40 - 160 mg
Thiamin (B1)	70 mg	.7 - 2.8 mg
Riboflavin (B2)	200 mg	.8 - 3.2 mg
Niacin	1 mg	9 - 36 mg
Vitamin B6	70 mg	1 - 4 mg
Folic Acid	100 mg	50 - 200 mg
Vitamin B12	100 mg	.7 - 2.8 mg
Biotin	10 mg	20 - 80 mg
Pantothenic Acid	300 mg	3 - 12 mg
Potassium	160 mg	-
Calcium	80 mg	800 - 3200 mg
Phosphorus	60 mg	800 - 3200 mg
Magnesium	10 mg	80 - 320 mg
Iron	-	-
Zinc	2 mg	10 - 40 mg
Copper	.3 mg	1 - 4 mg
Iodine	12 mg	70 - 280 mg
Selenium	4.7 mg	20 - 80 mg
Manganese	300 mg	1.25 - 6.0 mg

Pakistan to 89% in India and Peru. The recovery among children evaluated after receiving Diet B, was 71%. Weight gain after correction of dehydration was achieved in 88% of cases. The 11 children who did not recover after receiving Diet A and Diet B required more intensive or prolonged hospital treatment for associated illnesses. Ten children (2%) died during the course of the study; 7 were critically ill with sepsis on admission and could not be stabilized, and 3 developed severe sepsis during the second week of treatment. Importantly, at the time of admission, the majority of children (312, 68%) had evidence of an associated illness.

These results indicate that treatment guidelines based on nutritional therapy using inexpensive, locally avail-

able foods, vitamin and mineral supplementation, and antimicrobial therapy for specific infections is successful for the short-term management of children with persistent diarrhea. The major advantages of this system are that it is highly effective, affordable, and accessible because it uses local foods—familiar to both children and parents, and not defined diets or formulae. Supplementation with vitamin and mineral tablets allows the use of local foods as nearly complete diets while avoiding the high cost of formula. Although Diet B is more expensive because it requires eggs and meats, it too costs much less than formula, and is only necessary for those children who fail on Diet A.

Support for enteral nutritional rehabilitation grew from experimental observation, which showed that lack of enteral stimulation delayed the intestinal mucosal recovery process and regeneration. In early studies by Greene et al.⁽³⁾, comparing the response to various forms of nutritional therapy in malnourished infants with persistent diarrhea, children receiving total parenteral nutrition (TPN) had a longer duration of hospitalization and a slower rate of recovery of intestinal brush border enzyme activity than those in another study receiving additional enteral feeds. In another study, Orenstein⁽⁴⁾ randomly allocated 13 infants with intractable diarrhea to either TPN or continuous enteral infusion of semi-elemental formula. Although the rate of recovery of malnutrition was similar in both groups, the group receiving enteral infusion had a significantly faster resolution of diarrhea (2.8 vs. 9.8 weeks). Clinical improvement of persistent diarrhea (as measured by stool losses) using the local dietary guidelines was usually evident in three to four days—a dramatic decrease in resolution time when compared with either TPN or continuous enteral feedings.

Although the study was only analyzed and published in 1996, the guidelines have already been implemented around the world. In Peru, the Instituto de Investigacion Nutricional has incorporated this approach in the training of its residents and students in order to familiarize them with current strategies in hospital management of persistent diarrhea. The Mexican Ministry of Health has adopted the chicken-based diet (Diet B) on a countrywide basis for the

treatment of children with malnutrition and persistent diarrhea. The treatment guidelines are also now part of the routine management of children admitted at the Children's Hospital No. 1 in Ho Chi Minh City, Vietnam and are now being progressively implemented in other hospitals throughout the country. In Bangladesh, the guidelines are practiced at Dhaka's Shishu Hospital and at the ICDDR,B Hospital with great success.

On a global scale, the persistent diarrhea guidelines are a part of the WHO Integrated Management of the Childhood Illness (IMCI) guidelines used by health workers throughout the world (Table 4). In health facilities, the IMCI strategy promotes the accurate identification of childhood illnesses in outpatient settings, ensures appropriate combined treatment of all major illnesses, strengthens the counseling of caretakers and the provision of preventive services, and speeds up the referral of severely ill children. The strategy also aims to improve the quality of care of sick children at the referral

level. In the home setting, it promotes appropriate care-seeking behaviors, improved nutrition and preventive care, and the correct implementation of prescribed care. The IMCI guidelines for persistent diarrhea emphasize appropriate feeding of the sick child with breastmilk, yogurt or nutrient rich semi-solid food, instead of other milk, or formula.

In conclusion, severe cases of persistent diarrhea can be safely and effectively treated using diets consisting of locally available foods, vitamin and mineral supplementation and specific antimicrobial therapy. The use of mostly local supplies and simple clinical guidelines without reliance on sophisticated medical technology indicates that these guidelines can be used in a wide range of hospital settings. WHO is also in the process of adapting the persistent diarrhea guidelines for community use in Sub-Saharan Africa. Continued research will undoubtedly lead to further refinements of the guidelines, and to improved case management of persistent diarrhea worldwide.

Table 4. IMCI Guidelines for Persistent Diarrhea

Classify		Identify Treatment	Feeding Recommendations
Diarrhea lasting less than 14 days	No Persistent Diarrhea	No additional treatment	
Diarrhea lasting 14 days of more AND No Dehydration	Persistent Diarrhea	Advise mother how to feed the child with persistent diarrhea Advise mother to return with child in 5 days	If still breastfeeding, give more frequent, longer breastfeeds, day and night. If taking other milk, replace with increased breastfeeding, OR replace with fermented milk products, such as yogurt OR replace half the milk with nutrient-rich semisolid food.
Diarrhea lasting 14 days of more AND Dehydration	Severe Persistent Diarrhea	Treat dehydration before referral unless the child is severely malnourished Refer to hospital	

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is published by the Child Health Research Project. For information, comments or more copies of this issue please contact: Laura Kelley 410-614-5439, (fax:) 410-614-1419 or e-mail: LKELLEY@JHSPH.EDU or visit our web site at <http://ih1.sph.jhu.edu/chr/chr.htm>. Synopsis Number 2, available in January, 1998, will feature *The Validation of IMCI*.

The Child Health Research Project is a project of the United States Agency for International Development, and represents cooperative agreements between USAID and WHO, Harvard University, the ICDDR,B: Center for Health and Population Research in Dhaka, Bangladesh, and Johns Hopkins School of Public Health.

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