

Chronic and Persistent Diarrhea in Infants and Young Children: Status Statement

PEDIATRIC GASTROENTEROLOGY CHAPTER, INDIAN ACADEMY OF PEDIATRICS

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Justification: Diarrhea that lasts for more than two weeks is a common cause of mortality and morbidity in infants and children. There is a need to update the information available on this subject in Indian context.

Process: This review has analyzed the available published data on the subject with particular focus on developing countries. It has also outlined the current diagnostic and management practices in India based on the experience of the participants from major hospitals in different parts of the country.

Objectives: Problem areas in both persistent and chronic diarrhea have been identified and remedial measures relevant to India are presented.

Recommendations: Micronutrient supplementation, algorithm based diet regimens, and good supportive care are sufficient in most children above 6 months of age with persistent diarrhea. Paucity of diagnostic facilities limits evaluation of chronic diarrhea in most parts of the country and regional laboratories need to be set up urgently. Lack of awareness regarding cow's milk protein allergy, celiac disease and immunodeficiency associated diarrhea is of particular concern.

Key words : *Chronic diarrhea, Consensus, Malabsorption, Malnutrition, Persistent diarrhea.*

Most acute diarrheal episodes subside by 7 days; few last up to 14 days. Persistent diarrhea and chronic diarrhea are defined when the duration of diarrhea lasts for more than two weeks. Etiology and management of prolonged diarrhea in western countries has changed significantly but there is little information available from India on this subject in the last two decades. A group of experts from Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics met in Calicut, Kerala on 10th October 2009 and analyzed recent published literature on the subject from developing countries, identified the problems currently faced in management, and discussed possible solutions to them.

PERSISTENT DIARRHEA

Persistent diarrhea (PD) is an episode of diarrhea of presumed infectious etiology, which starts acutely but lasts for more than 14 days, and excludes chronic

or recurrent diarrheal disorders such as tropical sprue, gluten sensitive enteropathy or other hereditary disorders [1].

Epidemiology

WHO estimates that while persistent diarrhea accounts for only 10 percent of diarrheal episodes, as much as 35 percent of deaths from diarrhea in children under 5 years of age occur from it. Community studies show that for every 100 children below 4 years, seven cases of persistent diarrhea occur every year [2] and that it is responsible for one-third to half of all diarrhea related mortality [3-5]. Twenty per cent of acute diarrheal episodes in malnourished children persist beyond two weeks. Sixty per cent of PD occurs before 6 months and 90% below 1 year of age [6].

Pathogenesis

The pathogenesis though not well understood, is

believed to be multifactorial - persistent mucosal injury due to specific pathogens (*E. coli*, Shigella, Salmonella, Campylobacter), sequential infections with multiple pathogens, and host factors (macro, micronutrient deficiency and compromised immune system). In a recent study, 23% of children with shigellosis developed persistent diarrhea [7]. The risk of an acute diarrhea becoming persistent is many fold more in malnourished children and in those with secondary carbohydrate malabsorption [8]. Other risk factors include very young age, previous infections, recent introduction of animal milk, irrational usage of antibiotics, and lack of breast feeding [1]. In persistent diarrhea, chronic inflammation and defective intestinal repair result in abnormal mucosal morphology, leading to poor absorption of luminal nutrients and increased permeability of the bowel to abnormal dietary or microbial antigens [9]. The severity of these changes is greater in younger children due to delayed intestinal mucosal maturation.

Micronutrient deficiencies contribute to poor intestinal repair and zinc deficiency may result in prolongation of mucosal injury and delayed intestinal repair mechanisms [10]. The role of immune deficiency in persistent diarrhea is not well understood [11]. Micronutrient deficiency itself may cause transient immune deficiency which could be an important risk factor for persistent diarrhea [12]. Persistent diarrhea is being increasingly recognized as a manifestation of HIV infection and cryptosporidiosis [13,14].

Treatment

Intestinal mucosal damage and consequent problems with nutrient absorption are common features in all children with persistent diarrhea and therefore nutritional management is the cornerstone of treatment [15-17]. Since persistent diarrhea often requires management in community settings, diets which are inexpensive are currently being used. Milk cereal mixes containing modest amount of milk are as efficacious as milk free diet in the early stages, when diarrhea is not severe. Milk free diet with simple or complex carbohydrates is ideal for those with severe disease. Monosaccharide based diet is required only for those who do not respond to these

measures. In a multi-centric study involving 560 children aged 4-36 months; the overall success rate with this regimen was 80% [18].

At admission, most patients have dehydration and electrolyte imbalance which will need correction. Evidence suggests that low osmolality ORS is efficacious in management of dehydration in persistent diarrhea [19,20].

The energy density of the feeds should be around 1 Cal/g and an intake of about 100 Cals/kg bodyweight should be aimed at. Micronutrients should be given for at least 2 wk; multivitamin (twice the RDA), folic acid (5 mg day 1, then 1 mg/day), zinc (2 mg/kg/day) and copper (0.3 mg/kg/day). Oral vitamin A (<6 months 50,000 IU, 6-12 months 100,000 IU) and a dose of parenteral Vitamin K should be given at admission. Severely malnourished infants require 50% magnesium sulphate 0.2 mL/kg/dose twice daily for 2 -3 days. After the infant has begun to improve and is gaining weight, 3 mg/kg/day of iron is added. Analysis of four large studies reported a beneficial effect of zinc in infants with persistent diarrhea [21].

Available evidence does not support the routine use of antibiotics directed against enteric pathogens. Published data is presently insufficient to recommend the use of probiotics. There is no role for racecadotril or steroids. Unusual enteropathogens, sucrase/isomaltase deficiency, severe glucose malabsorption, and severe systemic infection are reasons for failure to respond [22].

Problem Areas in Management

Infants less than six months of age continue to remain an area of concern, since most of the foods recommended cannot be used in them. They need extensively hydrolyzed 100% bovine casein infant formulas and elemental amino acid formulas which are currently not available in India. Another major problem is the inability to manage unresponsive children in most health care settings. Regional centers equipped to manage them are urgently needed. Current nutritional management requires prolonged hospital stay and facilities to prepare special diets, which is a problem for many health-care settings. Diet regimens in general have poor

TABLE I BASIC TESTS IN THE DIAGNOSIS OF CHRONIC DIARRHEA

Type	Test	Availability in India	Diagnosis in India
Osmotic vs Secretory diarrhea	Stool pH, reducing substance Stool electrolytes Stool osmotic gap Breath hydrogen tests	Good Poor-Fair Poor Poor	Based only on stool pH, / reducing substance and response to keeping child nil orally.
Fatty diarrhea	Sudan stain Acid steatocrit 72 hr stool fat	Good Poor Poor	Based on fat globules in normal microscopy, and Sudan stain at some centers.
Protein losing enteropathy	Fecal Alpha-1- antitrypsin	Poor	Based on clinical picture, low serum albumin and by exclusion.
Pancreatic insufficiency	Fecal elastase/chymotrypsin Secretin test	Poor Poor	Based on ruling out other causes of fatty diarrhea.

acceptability among parents of the upper strata of society. Parent education and uniform protocols of management to be followed by all pediatricians in India may be a possible solution.

Preventive Strategies

Improvements in nutritional status of infants and children as well as prevention and rational management of acute diarrhea are keys to prevention of PD. Cost effective interventions in the community include promotion of exclusive breastfeeding, safe complementary feeding practices, promotion of safe drinking water, low osmolality ORS, zinc supplementation, avoiding unnecessary antibiotics and continued feeding during diarrhea [23].

CHRONIC DIARRHEA

Diarrhea which lasts for more than 14 days, is usually non infectious and associated with malabsorption is labeled as chronic diarrhea.

Epidemiology

The true incidence of chronic diarrhea in India is not known. There are many causes for chronic diarrhea and with better facilities these are being increasingly diagnosed in India [6,24]. In a study on 137 children with chronic diarrhea, celiac disease was documented in 26%, parasitic infections in 9% and tuberculosis in 5% of children [25].

Diagnostic Approach

Infants with chronic diarrhea require a two stage

evaluation. The first involves assessing the type of diarrhea, and the second to determine the specific etiology. **Table I** illustrates the basic tests required for the first stage and the current scenario in India.

Specific Etiology

There is limited capability of most settings to investigate children with chronic diarrhea primarily due to the poor availability of diagnostic tests in India. Some of the more common causes and the basis of their diagnosis in India are:

1. *Cow's milk protein allergy (CMPA)*: It typically causes colitis with blood and mucus in stools. Immunoglobulin profile and proctosigmoidoscopy with biopsy are diagnostic and can be done in many centers.
2. *Celiac disease*: It is being increasingly recognised in parts of North India(26). Serological studies and intestinal biopsy are widely available in many centers in North India. Characteristic histological changes in the duodenal biopsy (Marsh grade \geq III), a positive serological test (IgA antiendomysial antibody of tissue transglutaminase antibody) and response to gluten free diet by 8-12 weeks, is essential for diagnosis. Serological test for celiac disease should be done in all cases of chronic diarrhea.
3. *Giardiasis/Amebiasis*: Microscopic examination of a freshly passed stool on three consecutive days is recommended for detection of Entameba

and *Giardia* trophozoites. Endoscopic duodenal aspirate or biopsy can also be used.

4. *Immunodeficiency associated diarrhea*: Both congenital and acquired immunodeficiencies can cause chronic diarrhea. Immunoglobulin profile, and tests for HIV as well as for the enteric pathogens (*Shigella*, *Salmonella*, *Cryptosporidium*, *Campylobacter*) are widely available.
5. *Cystic fibrosis*: Sweat chloride estimation is available in a few centers, but mutation studies are not being done. Currently diagnosis is based on the clinical picture and a positive sweat test.
6. *Intractable diarrhea of infancy*: They are broadly divided into two groups:
 - (a) Without villous atrophy: These include congenital transport defects, ileal bile acid receptor defect, congenital glucose galactose malabsorption etc. Stool electrolyte estimation is done in a few centers, while genetic studies are not. Currently diagnosis is based on serum electrolytes, clinical picture and response to available elimination diets.
 - (b) With villous atrophy: Includes congenital epithelial structure/function defects like microvillous inclusion disease, tufting enteropathy and autoimmune enteropathies. Electron microscopy of intestinal biopsy, anti enterocyte and anti colonic antibodies and genetic studies for diagnosis are available in very few centers .
7. *Hormone mediated secretory diarrhea*: Serum gastrin, VIP, somatostatin, and calcitonin are done in very few centers. Tumor localisation with CT or MRI is possible but difficult.

Management

CMPA, celiac disease, giardiasis and lactose intolerance are easily treatable. CMPA is now being increasingly recognized in India [27]. These children need extensively hydrolyzed 100% bovine casein infant formulas or elemental amino acid formulae that are currently not available in India. Soy formulations are not recommended, particularly in

those below 6 months of age. Gluten free diet for celiac disease is successfully being practiced in many centers, but the food industry needs to be sensitized to this disease. Patient support groups are currently being formed in some cities. Lactose free formula for secondary lactose intolerance is freely available, but they are probably being over-used. Elemental formulae are essential in the management of intractable diarrhea of infancy. Response to steroids or immuno-suppression confirms autoimmune enteropathies. Small intestinal transplantation is currently not available in India.

Parenteral nutrition has a major role to play in management of chronic diarrhea. However it involves considerable cost, expertise and infrastructure and cannot therefore be suggested as a viable treatment option

Problem areas in management

There is very little awareness about CMPA, Celiac disease and immunodeficiency associated diarrhea among pediatricians. The practice of giving a trial of gluten free diet without duodenal biopsy and serological tests is becoming widespread. Creating awareness among primary care physicians is the only solution for these problems. The lack of availability of many specific diagnostic tests and their prohibitive cost in most parts of the country is also a problem. Regional laboratories need to be urgently established to overcome this limitation.

CONCLUSIONS AND RECOMMENDATIONS

1. Persistent diarrhea is still prevalent in India, since unhygienic living conditions and under-nutrition coexist with HIV and poor access to quality health care. However, there is paucity of recent data on persistent diarrhea and there is an urgent need for well designed epidemiological and outcome studies.
2. Micronutrient supplementation, step-wise diet based regimens and good supportive care is sufficient in most children above 6 months of age. Special infant formulas are required in those who do not respond.
3. Promotion of exclusive breastfeeding in early infancy, safe complementary feeding practices,

access to safe drinking water and scientific management of acute diarrhea can significantly reduce the incidence of persistent diarrhea.

4. Specific diagnostic tests to evaluate the etiology of chronic diarrhea are not readily available in India. There is a need to have regional laboratories where these tests could be done. Celiac disease, cow's milk protein allergy and immunodeficiency associated diarrhea are being increasingly recognized in India.
5. Special formulas like extensively hydrolyzed 100% bovine casein infant formulas and elemental amino acid formulas need to be made available in India. However, administrative steps need to be taken to ensure that they are not misused or overused.

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Funding: None.

Competing interests: None stated.

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Annexure

Participants at the meeting

- Convener : John Matthai (Coimbatore)
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