Chronic diarrhea: four decades experience in resource-limited settings

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ABSTRACT

Objective: In view of the paucity of information in the literature, this article aims at providing a simplified and yet state-of-the-art approach for the management of chronic diarrhea in children in resource-limited settings. Resource and Design: Systematic review of literature supported with our own experience spread over four decades. Salient Features: Etiology of chronic diarrhea, implying diarrhea of 2 weeks or more, usually secondary to a malabsorptive cause, is exhaustive. However, in clinical practice in resource-limited settings, only a few conditions such as malnutrition, intestinal infestations, cow’s milk protein allergy (CMPA), celiac disease, cystic fibrosis and endemic tropical sprue monopolize the situation. Diagnostic evaluation needs to be step-by-step with good history-taking and clinical examination followed by select investigations depending on the individual merits of the cases. High index of suspicion is a forerunner in detecting CMPA. Mild to moderate steatorrhea is usually indicative of malnutrition, iron-deficiency anemia or intestinal parasites (L. giardia, A. duodenale). Gross steatorrhea is due to celiac disease, cystic fibrosis or tropical sprue. In cystic fibrosis, despite significant steatorrhea, D-xylose test is usually normal. Conclusion: A good idea about the pattern of etiology of chronic diarrhea/malabsorption in different regions together with an individualized approach and an adequate follow-up is likely to resolve a large majority of the diagnostic as well as therapeutic problems. Treatment depends on the etiology of chronic diarrhea.

Key words: Celiac disease, Chronic diarrhea, Cow’s milk protein allergy, Cystic fibrosis, D-xylose test, Jejunal biopsy, Protein-losing enteropathy

INTRODUCTION

Among three giant killers of infants and children, diarrheal diseases rank supreme with around a billion episodes and 3-5 million deaths annually across the world.1 Needless to say, an overwhelming chunk of morbidity and mortality occurs in resource-limited communities. Associated malnutrition (both as a predisposing factor and as a consequence) contributes to high morbidity and mortality.2 A recent meta-analysis of global English medical literature shows a considerable fall in mortality because of increasing use of ORS but only little decrease in the incidence of acute diarrhea.3 In case of prolonged diarrhea (both persistent and chronic), it is the morbidity with growth failure and allied problems that is a matter of concern.

In view of the paucity of documented literature in the field, this review proposes to provide a state-of-the-art update with special reference to diagnostic and therapeutic approach, on chronic diarrhea in children as relevant in resource-limited settings.

WHAT’S CHRONIC DIARRHEA?

During the last half a century, chronic diarrhea has been defined differently by various groups of investigators. The duration has ranged from 2 weeks through 3 weeks to 4 weeks.

Today, chronic diarrhea is defined as a diarrhea of 2 weeks or more duration or 3 attacks of diarrhea during the preceding 3 months, usually due to obvious malabsorption or an organic or other cause without obvious malabsorption.4,5 Though both, chronic diarrhea and persistent diarrhea, have a minimal cut-off duration of 14 days along with some overlap, a few differences are noteworthy (Table 1).

Table 1: Differences between persistent and chronic diarrhea

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Persistent Diarrhea</th>
<th>Chronic Diarrhea</th>
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<tbody>
<tr>
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Onset and etiology | As acute gastroenteritis i.e. acute episode of infectious diarrhea which goes on and on. | Insidious, usually secondary to a malabsorptive state*
---|---|---
Age | Usually around 1 year | Any age
Diarrheal dehydration | Frequent | Infrequent
Associated malnutrition | Considerable with wasting | Less pronounced; growth retardation with stunting

* Chronic nonspecific diarrhea is an exception

**PATHOPHYSIOLOGY**

A vast majority of the infants and children with chronic diarrhea suffer from osmotic diarrhea or secretory diarrhea.1,2 Nevertheless, a relatively small proportion may have such pathophysiological mechanisms as mutation defects, decrease in anatomical surface and alteration in intestinal motility.

**Osmotic diarrhea** is the outcome of malabsorption of water-soluble nutrients (lactose) and excessive consumption of carbonated fluids (cola drinks) or nonabsorbable solutes (sorbitol, lactulose). An excess osmotic load in the colon is the operative factor. This type of diarrhea shows good response to simple fasting.

**Secretory diarrhea** is the outcome of activation of intracellular mediators like cyclic adenosine monophosphate (Cholera, heat-labile E.coli, Shigella, Salmonella, C. jejuni, P. aeruginosa, hormones (vasoactive intestinal peptide, gastrin, secretin,), anion surfactants ( bile acids, ricinoleic acid), cyclic guanosine monophosphate (heat stable E.coli, Y.enterocolitica and intracellular calcium (Cl. difficile, acetylcholine, serotonin, bradykinin).

**Mutation defects** in apical membrane transport proteins (chloride-bicarbonate exchange and sodium-bile acid transporter) cause secretory diarrhea and failure to thrive (FTT) at birth.

**Decreased anatomical surface area** (short bowel syndrome following surgical resection in necrotizing enterocolitis, volvulitis, atresia) understandably leads to chronic diarrhea as a result of poor absorption from the gut.

**Alteration in intestinal motility** (malnutrition, diabetes mellitus, intestinal pseudo-obstruction syndromes, scleroderma) results in secretory diarrhea.

**ETIOLOGY**

Though a large number of conditions, involving intraluminal factors, mucosal factors, or both, can cause chronic diarrhea (Box 1), the scene is dominated by a limited number of conditions in clinical practice.8-11

**Box 1: Causes of chronic diarrhea in general**

I. **Intestinal Mucosal Causes**

**Altered Integrity**
Infections/infestations: Viral, bacterial, fungal, parasitic
Cow’s milk protein allergy (CMPA) /intolerance
Soy protein allergy/intolerance
Inflammatory bowel disease

**Altered Immune Function**
HIV/AIDS
Autoimmune enteropathy

**Altered Function**
Abetalipoproteinemia
Acrodermatitis enteropathica
Tropical sprue
Selective folate deficiency
Defects in Cl-HCO3-, Na+/H+

**Altered Digestive Function**
Cystic fibrosis

**Altered Surface Area**
Celiac disease
Malnutrition
Iron-deficiency anemia
Endemic tropical sprue
Hookworm infestation

**Altered Secretory Function**
Enterotoxin-producing bacteria
Vasoactive peptides-secreting tumors

**Altered Anatomical Structures**
Congenital megalocolon
Partial small bowel obstruction

**Altered Motility**
Malnutrition
Diabetes mellitus
Intestinal pseudo-obstruction
Scleroderma

II. **Intestinal Intraluminal Causes**

Excessive intake of carbonated drinks
Excessive intake of sorbitol, lactulose, magnesium salts
Carbohydrate malabsorption
Congenital monosaccharide malabsorption

III. **Pancreatic Causes**
Cystic fibrosis
Chronic pancreatitis

IV. **Bile-related Disorders**
Chronic cholestasis
Bacterial overgrowth
Prolonged use of bile acid sequestrants
Terminal ileum resection
However, extensive studies in India\textsuperscript{12-14} have shown that etiology of chronic diarrhea in Indian children is at considerable variance with descriptions from western countries (Box 2).

**Box 2: Causes of chronic diarrhea in Indian children**

<table>
<thead>
<tr>
<th>Clinical profile</th>
<th>Likely condition</th>
<th>Remarks</th>
</tr>
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<tbody>
<tr>
<td>Chronic diarrhea + abdominal discomfort</td>
<td>Worm infestation/irritable bowel syndrome (IBS)</td>
<td>Such infestations as giardiasis and ancylostomiasis are common; IBS as a psychosomatic illness is on an increase in children too</td>
</tr>
<tr>
<td>Chronic diarrhea starting following introduction of semisolids (wheat in particular)</td>
<td>Celiac disease</td>
<td>Though once believed to be nonexistent in India, CD is now being increasingly diagnosed in wheat-eating population.</td>
</tr>
<tr>
<td>Chronic diarrhea in preadolescent or adolescent + anemia + malnutrition</td>
<td>Tropical sprue</td>
<td>High index of suspicion is central to its diagnosis; usually diagnosis is by exclusion.</td>
</tr>
<tr>
<td>Chronic diarrhea and recurrent respiratory infections from early infancy + failure to thrive despite excessive appetite and dietary intake, salt line over forehead</td>
<td>Cystic fibrosis, pancreatic insufficiency</td>
<td>Children with recurrent respiratory infections with chronic/recurrent diarrhea and failure to thrive despite voracious appetite and food intake must have sweat chloride test.</td>
</tr>
<tr>
<td>Chronic diarrhea following introduction of cow milk, frank or occult blood in stool, rash, eczema</td>
<td>Cow milk protein allergy (CMPA)</td>
<td>Clinical picture is the gateway to detection of CMPA.</td>
</tr>
<tr>
<td>Chronic diarrhea+ recurrent fever+ abdominal masses (ileocecal node, lymph nodes), subacute intestinal obstruction</td>
<td>Abdominal tuberculosis</td>
<td>Clinical picture is highly suggestive</td>
</tr>
</tbody>
</table>

**EVALUATION** \textsuperscript{6,7}

As per norms, a good history and physical examination should be a forerunner to investigative workup. Table 1 presents clues to diagnosis in the history and physical examination.
Clinical profile | Likely condition | Remarks |
--- | --- | --- |
recurrent ascites |  | small intestinal biopsy. |
Chronic diarrhea + blood in stools, fistulas, weight loss | Inflammatory bowel disease (IBD) | An uncommon condition in children; High index of suspicion Is helpful in detecting cases. |

Following a good history-taking, investigative evaluation of the child with chronic diarrhea should be step-by-step (Box 3) rather than by a large number of investigations at a time. The individual merits of each case and the proper application of knowledge and experience of the attending pediatrician contribute to deciding the necessary investigations.

**Box 3:** Four phases of evaluation of the child with chronic diarrhea/malabsorption

**Step I**
- History and physical examination with special reference to onset of diarrhea and its relationship with various factors (excessive carbonated drinks/fruit juices, supplementary milk feeds, cereals), specific amount of fluids ingested/day, nutritional status, etc.
- Meticulous stool examination (ova and cysts, pH, reducing substances, fat globules)
- Stool culture
- Stool for Cl. difficile toxia
- Blood studies (CBC, ESR, electrolytes, BUN, creatinine)

**Step II**
- Fat balance studies for daily stool fat or steatocrit.
- D-xylene test,
- Sweat chloride test,
- Stool osmolality and electrolytes, phenolphthalein, magnesium sulfate, phosphate Breath H2 tests

**Step III**
- Barium meal/enema to exclude anatomic defects
- Small intestinal biopsy/colonic biopsy by endoscopic studies
- Sigmoidoscopy/colonoscopy

**Phase IV**
- Hormonal studies,
- Neurotransmittal studies (vasoactive intestinal polypeptide, gastrin, secretin, 5-hydroxyindoleacetic assays)
- Intestinal brush border enzymatic activities
- Motility and electrophysiologic studies

**CHRONIC DIARRHEA: A PRACTICAL PROBLEM-SOLVING APPROACH**

The following approach, based on our experience spread over the past 4 decades, is suggested for diagnosis and management of a child with chronic diarrhea and/or malabsorption in our set-up.

**I. Good history:** The importance of a carefully taken history cannot be overemphasized. Most valuable pointers and clues are likely to be obtained from answers to the following questions:

- Did the symptoms appear early in infancy (cystic fibrosis) or after the first six months of life (celiac disease)?
- Was there any relationship between onset of symptoms and introduction of supplementary milk feeds (lactose intolerance) or cereals (celiac disease)?
- Is there a family history of chronic diarrhea (cystic fibrosis, celiac disease, hereditary lactose intolerance)?
- Is there any history of intolerance to an item of food, i.e. wheat, barley, rye, oat (celiac disease) or milk (lactose intolerance)?
- Was the child failing to thrive from early infancy or started suffering from growth failure after introduction of a solid food? The latter situation is very much suggestive of celiac disease.
- How is the appetite? It is generally increased in cystic fibrosis and in some children suffering from giardiasis. In celiac disease, it is almost always poor. Mothers of celiacs often express surprise “as to how children who eat so little can pass such voluminous stools”.
- Does the mother feel that the child eats like a glutton but, despite all that, he has not been growing well? This strongly suggests cystic fibrosis. We have encountered this situation in some children suffering from symptomatic giardiasis as well.
- What do the stools look like? Large, pale, frothy and very foul-smelling stools are highly suggestive of steatorrhea. Characteristically white, fatty stools with plenty of undigested material are most often a feature of giardiasis.
- Was the prolonged diarrhea preceded by an attack of acute gastroenteritis? The situation is highly indicative of secondary lactose intolerance. This condition is fairly common and the stools in it are watery, profuse, accompanied by excess of flatus and have extremely foul smell. The perianal area appears raw and red in a great majority of these children.
- Is the child consuming excessive amounts of carbonated drinks or fruit juices (over 150 ml/kg/24 hours) and yet has normal growth and height parameters (nonspecific chronic diarrhea)? The problem usually resolves following reduction in fluids (under 90 ml/kg/24 hours).
- Is the child having excessive intake of nonabsorbable nutrients such as sorbitol, Mg(OH)2 or lactulose? A corrective action often controls the chronic diarrhea.

**II. Physical Exam**

- How is the nutritional status? If it is poor and there are weight loss and nutritional deficiencies, especially in the presence of steatorrheic stools, malabsorption should be suspected.
III. Laboratory Investigations

**Stool microscopy:** Microscopic examination of stools for evidence of parasitic infestations is of definite value. At least three meticulous stool examinations on successive days are essential before one rules out the presence of intestinal infestation. The presence of numerous large fat globules, after staining with Sudan-3 or eosin, is indicative of steatorrhea. However, this is a rough screening test.

**Daily stool fat:** Chemical examination of stools for fat content is the next important investigation. The child is placed on a diet that provides at least 50 g of fat per day over a period of six days. During the last three days all the stools passed by the child are collected and analyzed chemically. The 24-hour fat excretion is calculated. A fat excretion of more than 5 g/24 hours is regarded as indicative of steatorrhea.

**Steatocrit test:** This is a semiquantitative new simple, inexpensive, rapid, accurate and reliable alternative to the gold-standard “fecal fat balance studies” for steatorrhea. The method comprises microcentrifugation of fecal homogenate. In view of the complexities associated with conventional fecal fat studies, it has by and lasrge replaced it.

IV. D-xylene test

In older children, D-xylene excretion in a 5-hour urine sample, after administration of the pentose in a dose of 1.0 g/kg of body weight, dissolved in water, is estimated. An excretion of less than 20% indicates malabsorption. Infants and young children present difficulties in collection of urine. D-xylene tolerance test is, therefore, preferred in their case. Here, D-xylene is administered in the same dose and blood samples are taken at 0, 30, 60, 90 and 120 minutes by finger prick. Estimation of the pentose in these small samples is done by a micromethod. The peak level of less than 30 mg% is considered indicative of absorptive defect of the small bowel.

A child with steatorrhea but normal D-xylene test is said to be suffering from steatorrhea of nonteogenous origin as is the case with cystic fibrosis and, in our experience, with giardiasis also.

V. Endoscopic jejunal biopsy

In view of the nonspecific results obtained from this investigation, its use may be reserved for difficult cases. Only in a few conditions like intestinal lymphangiectasia, abetalipoproteinemia, amyloidosis and intestinal lymphoma is the interstinal histology pathognomonic. In celiac disease, endemic tropical sprue, PEM, iron deficiency anemia and ancylostomiasis, similar types of villous atrophy occur and differentiation on the basis of histologic changes is nearly impossible. Peroral jejunal biopsy (multiple specimens) may be carried out with the aid of an endoscope.

VI. Radiology

Barium meal examination, using a nonflocculable medium may reveal abnormalities like intestinal dilatation, flocculation, segmentation and atypical mucosal pattern. These are indicative of malabsorption but fail to differentiate one condition from another, especially the ones that are responsible for most of the tropical malabsorption in infants and children. This investigation is of value in detecting anatomic defects.

VII. Other investigations

Schilling test, sweat chloride estimation, tryptic activity, lactose tolerance test, etc. may be performed under special circumstances, depending on the individual merits of a case. These, like jejunal biopsy and radiology, need not be done in every child suffering from chronic diarrhea/malabsorption.

Infrequently, flexible sigmoidoscopy and colonoscopy may be warranted in such cases as suggestive of inflammatory bowel disease or functional chronic diarrhea.

**MANAGEMENT**

Undoubtedly, the list of causes responsible for chronic diarrhea/malabsorption is rapidly expanding. Extensive studies in north India have made it exceedingly clear that etiology of chronic diarrhea is tropical children is much different from what is described in the textbooks from the western countries. In fact, in practice only a few of the conditions appear to monopolize the situation.

In our experience, stool fat signifying mild to moderate steatorrhea is usually indicative of malnutrition, iron-deficiency anemia or intestinal parasitic infestation. Gross steatorrhea is generally due to cystic fibrosis, celiac disease or tropical sprue.

The diagnosis of cystic fibrosis is best confirmed by sweat chloride estimation (sweat chloride is very high in this condition, always above 60 mEq/L) and tryptic activity.

A patient with gross steatorrhea, in whom the diagnosis of cystic fibrosis has been excluded, may be put on gluten-free diet. If he shows amelioration of symptoms, this regimen is continued and absorptive tests (and jejunal biopsy, if done earlier) are repeated after a period of 10 to 12 weeks. If found normal, the patient is challenged with gluten to see if the intestinal abnormality returns. This is now considered adequate to confirm the diagnosis of celiac disease.

If, on the other hand, 3 months of gluten-free diet fails to benefit, the patient’s record is reviewed to find, if he could be a case of tropical sprue. A Schilling test is indicated in this situation. If it is abnormal, he should be put on folic acid as such or along with vitamin B₁₂ and/or tetracycline therapy.

Symptomatic control of diarrhea, as the diagnostic tests are in progress, is desirable.

Last but not the least, it is worthwhile to have a clear idea about the pattern of chronic diarrhea/malabsorption in a particular region. This, together with an individualized approach and an adequate follow-up, solves a vast majority of the diagnostic problems. Indian Academy of Pediatrics has rightly argued for Fig. 1 provides an algorithmic approach for management of chronic diarrhea.
Fig 1: Algorithmic approach to chronic diarrhea in pediatric practice.

OUTCOME AND PROGNOSIS
Outcome and prognosis is dictated by the determination of the causative condition for chronic diarrhea/malabsorption and appropriateness of the treatment.

- Antiparasitic therapy for such conditions as giardiasis and ancylostomiasis along with supportive measures is usually followed by excellent results.
- Appropriate nutritional correction in malnutrition or IDA-related chronic diarrhea brings about good outcome.
- Strict gluten-free diet is crucial in celiac disease.
- Pancreatic enzyme therapy forms the core therapy in cystic fibrosis.
- Endemic tropical sprue responds well to folic acid/ vitamin B12, improvement in nutrition and antibiotic (tetracycline) therapy.

SUMMARY AND CONCLUSIONS
Chronic diarrhea in resource-limiting settings needs a different clinical and approach than that adopted in the prosperous settings in view of the etiology that is at variance. A significant number of cases may well be just the outcome of malnutrition, intestinal parasitosis like giardiasis or ancylostomiasis and cow-milk protein allergy. In view of the paucity of diagnostic advanced tests, there is a need for availability of sophisticated investigations for other etiologies. A good idea about the pattern of etiology of chronic diarrhea/malabsorption in different regions together with an individualized approach and an adequate follow-up is likely to resolve a large majority of the diagnostic as well as therapeutic problems. Undoubtedly, etiology dictates the therapeutic approach.

TAKE-HOME MESSAGES
- Though etiology of chronic diarrhea is exhaustive, in clinical practice, only a few conditions monopolize the
situation.

- Diagnostic evaluation needs to be step-by-step with good history-taking and clinical examination followed by stepwise investigations depending on the individual merits of the cases.
- Mild to moderate steatorrhea is usually indicative of malnutrition, iron-deficiency anemias or intestinal parasites (Giardia, A. duodenale).
- Gross steatorrhea is usually due to celiac disease, cystic fibrosis or tropical sprue.
- In cystic fibrosis, despite significant steatorrhea, D-xylene test is usually normal.
- Understanding of the etiologic pattern of chronic diarrhea/malabsorption in different regions together with an individualized approach and an adequate follow-up is likely to resolve a large majority of the diagnostic as well as therapeutic problems.

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