Journal of Enam Medical College
Vol 11 No 2 May 2021

*Review Article*

# Chronic Diarrhea in Children

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Received: 4 April 2020 Accepted: 18 March 2021
doi: https://doi.org/10.3329/jemc.v11i2.65194

***Abstract***

*Chronic diarrhea (CD) is a common but challenging clinical scenario in pediatric medicine. It has several hundred disorders in the differential diagnosis and can create a complex situation for practitioners and families. Some of the disorders cause failure to thrive but some are not. This article focuses on important aetiologies of CD, their clinical features, diagnostic approach as well as treatment approaches.*

***Key words*****:** *Chronic diarrhea; Osmotic diarrhea; Secretory diarrhea*

J Enam Med Col 2021; 11(2): 120−127

## Introduction

Diarrhea is defined as stool volume >10 g/kg per day in infants and toddlers, and >200 g/day in older children.[1] Chronic diarrhea (CD) is one which lasts for more than 14 days, is usually noninfectious and associated with malabsorptive features. Some experts also refer CD for episodes lasting more than 4 weeks.[2] On the other hand persistent diarrhea (PD) is an episode of diarrhea of presumed infectious etiology, which starts acutely but lasts for more than 14 days and excludes recurrent diarrheal disorders such as tropical sprue, gluten sensitive enteropathy or other hereditary disorders.[3]

## Epidemiology

According to the World Health Organization, diarrheal illness is the second leading cause of death in developing countries in children younger than 5 years of age and is responsible for 1.7 million child morbidities and 760,000 child mortalities.[4] In 2002, the World Health Organization estimated that 13.2% of all childhood deaths worldwide were caused by diarrheal diseases, 50% of which were chronic diarrheal illnesses.[5] Among children aged 1 to 4 years, persistent diarrhea accounted for more than 25% of diarrheal deaths in Bangladesh, Ethiopia and Uganda.[6] Large-scale studies indicate that the prevalence of chronic diarrheal illnesses worldwide ranges from 3% to 20%, and the incidence is ≈ 3.2 episodes per child year.[7]

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## Pathophysiology

The basic pathophysiology of CD is incomplete absorption of water from the intestinal lumen. This occurs either because of a reduced rate of net water absorption (related to impaired electrolyte absorption or excessive electrolyte secretion) or because of osmotic retention of water in the lumen. Reduction of net water absorption as little as one percent is sufficient to cause diarrhea.[8]

The four principal pathophysiologic mechanisms of CD are osmotic, secretory, dysmotility associated, and inflammatory**.** Often, a single disorder may involve multiple overlapping mechanisms.

Osmotic diarrhea is caused by a failure to absorb a luminal solute. As a result, there are secretion of fluids and net water retention across an osmotic gradient. This may occur from either congenital or acquired diseases such as lactose malabsorption.[9]

Secretory diarrhea occurs when there is a net secretion of electrolyte and fluid from the intestine without compensatory absorption. Endogenous substances, often called "secretagogues," induce fluid and electrolyte secretion into the lumen even in the absence of an osmotic gradient. Typically, secretagogues affect ion transport in the large and small bowel both by inhibiting sodium and chloride absorption and by stimulating chloride secretion via cystic fibrosis (CF) transmembrane regulator activation. Multiple congenital diarrheal disorders associated with identified genetic mutations that affect gut epithelial ion transport are the example of secretory diarrhea.[10] Congenital chloride diarrhea (CCD) is one such disorder. Children with a pure secretory diarrhea will therefore continue to experience diarrhea even while fasting.

CD associated with intestinal dysmotility typically occurs in the setting of intact absorptive abilities. Intestinal transit time is decreased, the time allowed for absorption is minimized, and fluid is retained within the lumen. High-amplitude propagated contractions cause diarrhea predominant irritable bowel syndrome (IBS) in older adolescents and changes in small intestinal motility results chronic nonspecific diarrhea (CNSD) in toddlers.[11]

Inflammatory diarrhea may include all of the pathophysiologic mechanisms. Inflammation that results injury to the intestine may lead to malabsorption of dietary macronutrients which, in turn, creates a luminal osmotic gradient. Moreover, particular infectious agents may induce secretion of fluid into the lumen, and blood in the gut may alter intestinal motility. Diseases such as inflammatory bowel disease (IBD) and celiac disease are the example of this inflammatory mechanism.[9]

## Common causes of chronic diarrhea in children

Causes of chronic diarrhea can also be divided into following subgroups (Table II).

Table II: Causes of chronic diarrhea

| |
|---|
| Infective |
| Due to exogenous substances |
| Abnormal digestive processes |
| Nutrient malabsorption |
| Immune and inflammatory |
| Structural defects |
| Defects of electrolytes and metabolite transport |
| Motility disorders |
| Neoplastic |
| Chronic non-specific diarrhea |

Table I: Differences between osmotic and secretory diarrhea

| Variables | Secretory diarrhea | Osmotic diarrhea |
|---|---|---|
| Volume of stool | >200 ml/24 hours | <200 mL/24 hours |
| Response to fasting | Diarrhea continues | Diarrhea stops |
| Stool Na | >70 mEq/L | <70 mEq/L |
| Reducing substances | Negative | Positive |
| Stool pH | >6 | <5 |
| Stool osmotic gap {Stool osmolarity – 2 (stool $Na^+$ K )} | < 100 | >100 |

**Infective causes:** Infective causes of chronic diarrhea can be seen in any age and common organisms implicated includes *Salmonella, Yersinia, E.coli, Campylobacter, Aeromonas, Plesiomonas, Giardia, Cryptosporidium*, viral causes (Rota, Entero, Norwalk). They have associated fever, abdominal pain, exposure history, blood/mucus in stool. Giardia causes both osmotic and secretory diarrhea. Microscopic examination of a freshly passed stool on three consecutive days is recommended for detection of Giardia trophozoites. Antimicrobial therapy for giardiasis is metronidazole, tinidazole, or nitazoxanide. Non typhoidal Salmonella organisms typically cause gastroenteritis with diarrhea, abdominal cramping, and fever. Salmonella organisms typically are detected in routine stool culture for up to 5 weeks but may be excreted in stool for >1 year in 5% of patients.[12] Antibiotic therapy for uncomplicated nontyphoidal serotypes is not indicated as it does not shorten the disease duration but may prolong the duration of excretion of bacteria in the stool.[13] Antibiotic is indicated only for children younger than 3 months of age or those with immunosuppressive diseases.[14]

**Small bowel bacterial overgrowth:** There are overgrowths of aerobic and anaerobic bacteria in the small bowel such as in short bowel syndrome, bowel strictures, pseudo-obstruction, malnutrition. Osmotic diarrhea occurs due to enhanced bile acid deconjugation and fatty acid hydroxylation by bacteria. The patients present with abdominal pain and diarrhea. The diagnosis can be made by breath hydrogen with lactulose testing. Metronidazole or non absorbable rifaximin is the treatment of choice.[15]

**Whipple's disease:** Whipple's disease is caused by Gram +ve bacteria: Tropheryma whipplei. The patients have malabsorption, central nervous system, joints and cardiovascular involvement. It is a rare condition and carries a poor prognosis.

**Tropical sprue:** It is a rare condition in children and coliform organisms are implicated in its etio-pathogenesis.

## Abnormal digestive processes

### Cystic fibrosis

Pancreatic insufficiency is common in approximately 90% of patients with CF and this causes diarrhea in this disorder.[16] Loss of exocrine pancreatic function leads to malabsorption of carbohydrates, fat, and protein because of dysfunctional amylases, lipases, and proteases, respectively. Pancreatic exocrine function can be assessed by fecal elastase, and low levels indicating possible pancreatic insufficiency. Pancreatic enzyme replacement therapy may improve malabsorptive diarrhea in patients with CF.

### Nutrient malabsorption

**Carbohydrate malabsorption:** Intestinal lactase deficiency causes carbohydrate malabsorption that can be congenital, adult-onset and secondary lactase deficiency. Congenital lactase deficiency is a rare entity. Adult onset is relatively common and 'normal' for most humans. Secondary lactase deficiency is seen after infectious gastroenteritis or injury to small intestinal mucosa caused by gluten or other sensitizing substances, Crohn's disease, and other enteropathies.

Symptoms of lactose intolerance are independent of the cause. Incompletely digested lactose reaches the dense colonic microbial population, which ferments the sugar to hydrogen and other gases, thereby causing gassy discomfort and flatulence. The no absorbed lactose serves as an osmotic agent, resulting in an osmotic diarrhea. Diagnosis can be made by a successful lactose-free diet trial of 2 weeks or by hydrogen breath-testing. Minimizing lactose intake is the treatment of choice, as the symptoms are dose dependent and so complete removal of dietary lactose is not necessary.[17]

**Lipid malabsorption:** Lipid malabsorption is seen in diseases like cystic fibrosis, Shwachman- Diamond syndrome, Pearson syndrome, Johanson-Blizzard Syndrome, celiac disease, cholestatic liver disease, beta lipoproteinemia, lymphangectasia and short bowel syndrome.

**Protein malabsorption:** Protein malabsorption is seen in condition like pancreatitis, cystic fibrosis, trypsinogen deficiency, enterokinase deficiency, hartnup disease, lymphangectasia, lowes syndrome and lysinuric protein intolerance.

## Immune and inflammatory

**Celiac disease:** Celiac disease is an immune-mediated systemic disease that occurs due to gluten ingestion in a genetically susceptible individual. With its prevalence in adults and children approaching 1% worldwide.[18] It is most common cause of chronic diarrhea and malabsorption in more than 2 years age group patients.[19]

The typical presentation of celiac disease in children is failure to thrive, diarrhea and abdominal distension. The presence of raised anti-tissue transglutaminase antibody/anti endomysial antibody make the suspicion of celiac disease and is confirmed by histologic findings in the duodenum which is graded according to Marsh Criteria.[20] The management of celiac disease is lifelong restriction of food containing gluten in diet which includes wheat, rye, and barley. Multivitamin and mineral deficiency should also be managed appropriately.

**Cow's milk protein allergy (CMPA):** Cow's milk protein allergy presents in first year of life, but may present up to two years of age. The child present with streaks of blood and mucus in stool, in otherwise healthy infant. It typically occurs in child on top milk, however 0.5% may present in exclusive breast-fed infants. Withdrawal of cow's milk from diet is the treatment of choice.

## Inflammatory bowel disease[21]

Inflammatory bowel diseases (IBD) can present in children and adolescents with chronic diarrhea along with passage of blood or mucus in stools. The child can have weight loss, anemia, tenesmus, joint pains, and redness of eyes. In Crohn's disease, stool may contain microscopic blood but may not be grossly bloody. In ulcerative colitis, diarrhea is a more consistent presenting feature.

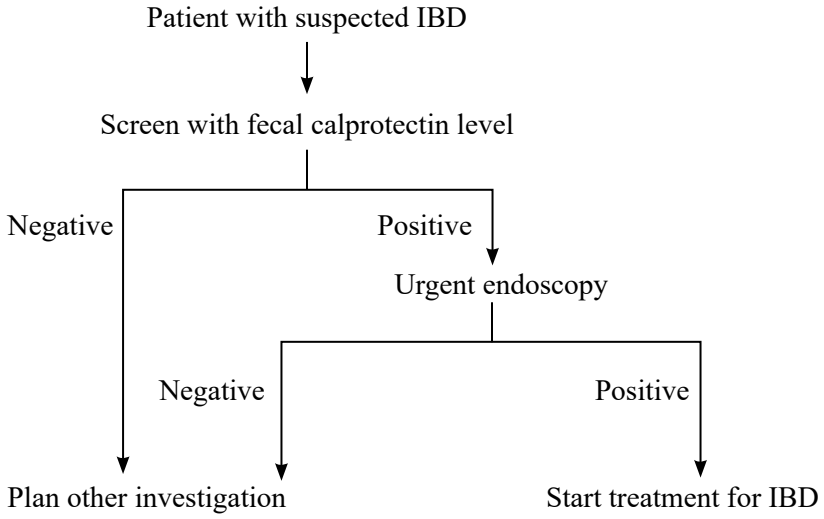


Fig 1. Workup for suspected inflammatory bowel disease (IBD) in adults[20]

Treatment includes anti-inflammatory agents like steroids, 5ASA, Azathioprine etc. Nocturnal diarrhea with urgency may be a sign of left-sided colonic inflammation in either Crohn disease or ulcerative colitis. Diarrhea associated with IBD typically improves with therapy as mucosal inflammation resolves.

**Autoimmune enteropathies:** Autoimmune enteropathies are rare disorders that may present as severe diarrhea during infancy or toddlerhood. The diarrhea may be isolated, or may occur in association with diabetes mellitus as part of the IPEX (Immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome. Diagnosis is made by documenting antienterocyte, anticolonocyte, or antigoblet cell antibodies in the blood. Treatment

is difficult but may be accomplished with immunosuppressive agents such as corticosteroids, 6-mercaptopurine, tacrolimus, and infliximab.

**Immunodeficiency:** Patient with chronic diarrhea should be evaluated for primary or secondary immunodeficiency such as HIV disease. In this case, the evaluation should focus on potential infectious causes of the diarrhea, particularly parasites and opportunistic infections such as Cryptosporidium, Isospora, and Cyclospora.[20]

**Structural defects:** These include disease like tufting enteropathy, microvillous inclusion disease, phenotypic diarrhea, lymphangiectasia, intergrin deficiency, heparan sulphate deficiency. These are rare diseases and cause neonatal diarrhea and carries a poor prognosis.

**Defects with effects of electrolytes and metabolite transport:** It includes congenital chloride diarrhea (CCD) and congenital sodium diarrhea (CSD), these disorders cause secretory diarrhea and present in 1−2 week of life and carry a poor prognosis.

### Chronic Nonspecific Diarrhea of Childhood or Infancy (CNSD)

CNSD is the most common form of chronic diarrhea in the first 3 years after birth.[21] The typical time of onset may range from 1 to 3 years of age and can last from infancy until age 5 years. It presents with varied stool frequency and consistency without blood or mucus and stool contain undigested food particles. There is no failure to thrive. Potential pathophysiologic mechanisms for CNSD include increased intestinal motility and osmotic effects of intraluminal solutes (e.g. carbohydrates).[12]

Reassurance is the cornerstone of therapy for CNSD. Treatment includes decreased fruit juices (fructose) and reassurance along with liberalization of fat to encourage normal caloric intake and to slow intestinal transit time is also important.[22]

## Motility disorders

### Irritable Bowel Syndrome (IBS)

According to Rome IV Diagnostic Criteria Irritable Bowel Syndrome must include all of the followings: 1. Abdominal pain at least 4 days per month associated with one or more of the followings: a. Related to defecation; b. A change in frequency of stool; c. A change in form (appearance) of stool; 2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome). 3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.[23]

Criteria fulfilled for at least 2 months before diagnosis treatment is often challenging. Antispasmodic agents, tricyclic antidepressants, and selective serotonin-reuptake inhibitors may improve symptoms. Some probiotics have been useful in adult and pediatric IBS, but results are not consistent.[24]

Among the causes of CD some are associated with failure to thrive and some are not (Table III).

Table III: Causes of chronic diarrhea

| Without failure to thrive | With failure to thrive |
|---|---|
| CNSD | IDI (Intractable Diarrhea of Infancy) |
| Infectious colitis | Allergic enteropathy |
| Lactose malabsorption | IBD |
| Small bowel bacterial overgrowth | Celiac disease |
| IBS | Immunodeficiency state (various diseases) |
| | Congenital secretory diarrhea (Chronic chloride and chronic sodium diarrhea) |
| | Tufting enteropathy |
| | Microvillous inclusion disease |
| | Autoimmune enteropathy |
| | CF |

## Evaluation of CD

### History and physical examination

For diagnosis of different causes of CD detailed history and examination is a must. Characteristics of the stool as well as feeding history are very important in assessing the cause and severity of the illness.

There are differences in pattern of stool in small and large bowel diarrhea. So, it is important to differentiate small bowel diarrhea from large bowel type of diarrhea. Small bowel diarrhea differs from large bowel diarrhea with its large volume, foul-smelling stools with undigested food particles and often it is associated with features of lactose intolerance like explosive diarrhea and bloating. On the other hand, large bowel type of diarrhea has blood, mucus, tenesmus, urgency and high frequency. In toddler's diarrhea children often have loose stools with undigested food particles. Frequent loose watery stools may indicate carbohydrate intolerance and pasty or loose foul-smelling stools indicate fat malabsorption. It is also necessary to take history of extraintestinal symptoms like presence or absence of weight loss, rash, fatigue, vomiting, joint aches, or oral ulcers. A detailed history of source of drinking water, family history, complementary feeding and whether onset of diarrhea after introduction of specific foods like seen in celiac disease and cow's milk protein allergy should be evaluated. There may be history of repeated infections in cystic fibrosis or immune deficiency syndromes.

In physical examination one should have to look for anthropometry assessment and status of dehydration. Clubbing may be seen in celiac disease and IBD. Extraintestinal manifestations of IBD like joint pain, swelling and erythema may also be found. There also may be signs of various nutrient and vitamin deficiencies like zinc, vitamin D,Vitamin A, Vitamin K and B complex. Distended abdomen may be seen in malabsorption syndromes or small bowel bacterial overgrowth. Rectal examination is also important as it may reveal perianal disease in IBD and perianal excoriation in carbohydrate malabsorption.

**Laboratory evaluation:** A detailed history and examination is needed so that unnecessary investigations are better avoided. Initial investigations include a complete hemogram to evaluate anemia, total counts and platelets. Stool routine and culture with urine routine should be done in all cases of chronic diarrhea. Stool may contain RBC, WBC and mucus indicating a mucosal inflammation in large bowel and analysis of the stool for electrolyte content and osmolarity may be helpful in distinguishing an osmotic from a secretory diarrhea. Serum electrolytes with renal function test should also be done. Serology for celiac disease, tTG with total IgA should be done in cases of small bowel diarrhea. Upper GI endoscopy and when required colonoscopy with mucosal biopsy are required in many diseases like celiac disease, IBD, eosinophilic enteropathy, microvillous inclusion disease, tufting enteropathy, giardiasis, Intestinal lymphangiectasia. In special cases, fecal fat estimation, fecal elastase, H2 breath test, hormonal assays may be required.

### Treatment

It depends on primary cause of chronic diarrhea; it may vary from just reassurance in cases of chronic nonspecific diarrhea to bowel transplant in structural enteropathies. In addition to specific disease-oriented therapy the patients should be given vitamin and mineral supplement. Disease like Cow's milk protein allergy, celiac disease, and giardiasis are easily treatable. Celiac disease management includes a lifelong strict adherence to gluten free diet and nutritional counseling. For CMPA, the ideal management it extensively hydrolyzed formula, unfortunately they are not still available in India and are to be imported thereby increasing their cost.

## Conclusion

Chronic diarrhea is important cause of morbidity in developing countries. Timely evaluation and management are of paramount importance to prevent complications. The patient should be referred to a tertiary care center in time for appropriate diagnosis and treatment.

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