

An Approach to Chronic Diarrhoea

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Diarrhoea is a universal human experience. It is both a symptom and a sign.

On symptoms it is defined as abnormal passage of three or more loose or liquid stools per day. As a sign, diarrhoea is an increase in stool weight (or volume) of more than 200 grams (or mL) per 24 hours on a Western diet. Previous studies have suggested that stool weight is higher in Indians, and the upper limit of normal daily stool weight for Indians is thus kept at 400 g.

Diarrhoea should not be defined solely in terms of fecal weight because fecal consistency and weight correlate best with the ratio of water-holding capacity of insoluble solids to the total water present.

Diarrhoea is generally considered acute when it lasts less than two or three weeks. Chronic diarrhoea is defined if symptoms persist for more than four weeks.

Chronic diarrhoea is a common clinical problem. Prevalence of chronic diarrhoea in the general population ranges between 3-5%. WHO has stated it could be between 5-20%. Unlike acute diarrhoea which is mostly self-limited, chronic diarrhoea often persists, unless some therapy is instituted. This makes an accurate diagnosis central to effective management. Effect of chronic diarrhoea on quality of life and health care expenses are considerable.

Understanding Diarrhoea

Diarrhoea is usually due to an excess of stool water rather than a decrease in water holding capacity of fecal solids, implying an abnormality in water transport within the gut. Diarrhoea results when there is a reduction of water absorption by as little as 1% by small or large bowel. Water itself is not actively transported but moves across the intestinal mucosa secondary to

osmotic forces generated by the transport of solutes, i.e. electrolytes and nutrients. Molecular pathways of ion and nutrient transport across the mucosa have been well characterized. Identification of 5 specific congenital diarrhoeal disorders (Table 1) has confirmed the importance of certain ion transporter mechanisms in health and disease.

Table 1: Congenital diarrhoeal disorders

S. No		Defective transport mechanism	Mutated gene
1.	Congenital chloride diarrhoea	Chloride bicarbonate exchange	DRA
2.	Glucose galactose malabsorption	Glucose stimulated sodium absorption	SGLT – 1
3.	Congenital sodium diarrhoea	Sodium hydrogen exchange	NHE 3
4.	Congenital bile acid diarrhoea	Sodium dependent bile acid Absorption	ABAT
5.	Congenital lactase deficiency	Lactase phlorizin hydrolase	LCT

Congenital Diarrhoea Disorders

Diarrhoea is often classified pathophysiologically as osmotic or secretory.

Osmotic diarrhoea is due to presence of poorly absorbed cations and anions (magnesium, sulfate, phosphate), or poorly absorbed sugar or sugar alcohols (mannitol, sorbitol, lactulose) in bowel in excess, as these are poorly absorbed or transport mechanisms are saturated at low intra-luminal ion concentration, leading to water retention. Lactose intolerance, due to lactase deficiency, is the most common clinical syndrome which results in osmotic diarrhoea.

Osmotic diarrhoea typically disappears with fasting or cessation of ingestion of the offending substance. Also as electrolyte absorption is not impaired, the electrolyte concentrations in stool water may be quite low.

Secretory diarrhoea has many causes, it is either due to net secretion of chloride or bicarbonate, or inhibition of net sodium absorption. The stimulus for secretion may come from the lumen (enterotoxins), the subepithelial space or systemic circulation (vasoactive intestinal peptide, calcitonin, histamine, inflammatory cytokines). Secretory diarrhoea may also result from absence of a specific absorptive pathway (congenital chloridarrhoea), significant loss of surface area (extensive small bowel mucosal disease, as in celiac disease, inflammatory bowel disease, resective surgery etc), abnormal motility (diabetes mellitus, post-vagotomy diarrhoea) where the contact time between luminal contents and epithelium is insufficient.

Since there is a secreto/absorptive defect in secretory diarrhoea, the stool electrolyte concentration is high and the diarrhoea persists on fasting.

The classification of diarrhoea as secretory or osmotic is helpful; pure secretory or pure osmotic diarrhoeas are uncommon. Most clinically significant diarrhoeas are complex, rather than being produced by a single pathophysiological mechanism.

Recently a new variety of diarrhoea has been described due to mutant neurogenin – 3, a transcriptor factor pivotal to development of pancreatic beta cell. Features of this disorder are that, diarrhoea ceases in the fasting state, is induced when anything other than water is ingested, mucosa of small intestine is normal, except for absence of enteroendocrine cell and there is no inflammatory component. The exact mechanism still remains unclear.

Differential Diagnosis of Chronic Diarrhoea

Clue to the site of diarrhoea can be obtained on the basis of volume of individual stools. When left side of colon, including the rectosigmoid, is involved the stools are frequent, small in quantity, and may be painful. If the source of diarrhoea is upstream in right colon or small bowel stools are large volume, and less frequent.

Another schema for classifying diarrhoea is based on characteristic of stool produced—watery, fatty and inflammatory.

Watery stools are typically runny and lack pus, blood or fat. Watery diarrhoea is subdivided into secretory or osmotic depending on stool electrolyte concentration. Fatty stools have an excess of fat, which can be shown

by qualitative testing with Sudan stain or by quantitative analysis of a timed stool collection for fat. Inflammatory diarrhoea typically contains blood or pus; these characteristics may be detected by a fecal blood test or, staining for neutrophils in stool or lactoferrin, a neutrophil-derived protein.

Differential Diagnosis of Chronic Diarrhoea by Stool Characteristics

I. Watery Diarrhoea

- a. Osmotic diarrhoea—osmotic laxatives (Mg, Phosphates, Sulfates)
Carbohydrate malabsorption
- b. Secretory diarrhoea
 - Congenital syndromes (Congenital chloridarrhea)
 - Bacterial toxins
 - Bile acid malabsorption.
 - Inflammatory bowel disease (Crohn's disease, microscopic colitis)
 - Drugs (most antibiotics, anti-neoplastic, antiarrhythmic, theophylline)
 - Laxative abuse
 - Disordered motility/regulation (postvagotomy, post-sympathetomy, diabetic autonomic neuropathy, irritable bowel syndrome)
 - Endocrine diarrhoea (hyperthyroidism, Addison's disease, gastrinoma, VIPoma, pheochromocytoma).
 - Other tumors (Colon cancer, lymphoma)
 - Idiopathic secretory diarrhoea.

II. Inflammatory Diarrhoea

- Inflammatory bowel disease (ulcerative colitis, Crohn's disease, ulcerative jejuno-colitis)
- Infections (pseudomembranous colitis, invasive bacterial infection like TB and Yersiniosis, ulcerating viral infection like CMV and Herpes simplex, invasive parasitic infections like amebiasis)
- Ischemic colitis
- Radiation colitis
- Neoplasia (colon cancer, lymphoma).

III. Fatty Diarrhoea

- Malabsorption syndromes
 - Mucosal disease (Celiac disease, Whipple's disease)
 - Short bowel syndrome

Small bowel bacterial overgrowth

Mesenteric ischemia.

Maldigestion

Pancreatic exocrine insufficiency

Inadequate luminal bile acid concentration.

Epidemiology of Chronic Diarrhoea in India

Chronic diarrhoea is a common problem in India. Most studies in India have classified the diarrhoea depending on site of involvement—small bowel and large bowel diarrhoea. In studies from south India in 1970s, tropical sprue was the commonest cause of chronic diarrhoea. It is now believed that frequency of TS is decreasing, possibly due to an improvement in standard of living, as also more frequent use of antibiotics.

In a recent study at a tertiary hospital in north India on malabsorption, the causes were tropical sprue (39%), Crohn's disease (9%), celiac disease (9%), giardiasis (8%), primary small intestinal bacterial overgrowth syndrome (6%), intestinal tuberculosis (4%), AIDS (2%), amyloidosis (2%), intestinal lymphangiectasis (1%), panhypogammaglobulinemia (2%). Under representation of tuberculosis in the study was possibly because empirical treatment with anti-tubercular medicines was a common practice among community physicians.

Celiac disease was considered rare in India, it is being described frequently now, especially from northern India. The prevalence in school children in Punjab is one in 310.

The causes of large bowel diarrhoea in India are ulcerative colitis (25%), microscopic colitis (7%), colorectal malignancies (4%), intestinal polyps (4%) and irritable bowel syndrome (45%).

Speaking to the Patient

A careful medical history is key to the evaluation of chronic diarrhoea. Stool frequency is the easiest characteristic for patients to define. Patients have poor notion of stool volume; watery stools suggest an osmotic or secretory process. Physician should ask about relationship to meals or fasting, as continuation of diarrhoea during fasting is one of the criteria for secretory diarrhoea. Presence of blood or pus in stools signals possibility of malignancy or inflammatory bowel disease, although blood is frequently due to hemorrhoids in patients with frequent evacuations. Presence of oil droplets or food particles in stools is suggestive of malabsorption, maldigestion or intestinal hurry. Excess

flatulence suggests increased fermentation of carbohydrates by colonic bacteria, caused by ingestion of poorly absorbed carbohydrate or malabsorption of carbohydrate by small intestine.

Other coexisting symptoms such as abdominal pain, bloating, fever and weight loss should be enquired. There should be a thorough enquiry of drugs, previous surgery, radiation therapy, nutritional remedies, herbal medicines etc. Diet should be reviewed for ingestion of large quantities of poorly absorbable carbohydrates in fruit juices, soda pop, sugar-free candies, chewing gum etc.

History is essential to differentiate patients with functional bowel disorders, like irritable bowel syndrome (IBS) which may be suggested by abdominal pain with defecation, long history usually dating to adolescence or young adulthood, excess mucus, exacerbations with stress etc. Factors against the diagnosis of IBS are recent onset symptoms, older age group, nocturnal diarrhoea, weight loss, blood in stool and stool weight > 400 g/day.

Examining the Patient

Physical examination may provide more direct evidence of cause of diarrhoea. Characteristic skin changes may be seen in celiac sprue (dermatitis herpetiformis), Addison's disease (heightened pigmentation), amyloidosis (waxy papules, pinch purpura), carcinoid syndrome (flushing), glucagonoma (migratory necrotizing erythema). Peripheral neuropathy and orthostasis may give clue to amyloidosis/diabetic autonomic neuropathy. Thyroid nodule with cervical adenopathy may suggest medullary carcinoma. Lymphadenopathy may suggest lymphoma, tuberculosis or HIV infection. Arthritis may be noted in inflammatory bowel disease, Whipple's disease and some enteric infections. Tremors and other signs of hyperthyroidism may be present.

Preliminary Evaluation of Chronic Diarrhoea

Analysis of stool sample can be used to categorize the diarrhoea and thereby limit the number of conditions to be considered in differential diagnosis. Stool analysis can be timed (i.e. 24-48 hour stool sample) where stool weight, output of various components such as fat, electrolytes can be measured accurately. Random stool sample can still provide clues when evaluated for sodium, potassium, pH, testing for occult blood, searching for WBCs or determining surrogate marker for WBC i.e., fecal lactoferrin. It is important to send

multiple samples if parasitic infestation like strongyloidosis or giardiasis is suspected.

Stool osmotic gap is calculated by subtracting twice the sum of sodium and potassium from 290 mOsm/kg, the osmolality of stool within the body. The osmotic gap is small (< 50 mOsm/kg) in secretory diarrhoea and a large osmotic gap (100 mOsm/kg) is seen in usually due to Osmotic diarrhoea. If pH of stool is acidic < 6 it is supportive of carbohydrate malabsorption.

Occult blood and fecal leucocytes are seen in inflammatory diarrhoeas.

Stool fat concentration can be measured quantitatively, by chemical means on a timed (48-72 hr) collection. Steatorrhea is defined as excessive loss of fat in the stool > 7 g or 9% of fat intake for 24 hours. For a valid study patients should consume 70 to 100 g of fat per day for three days before and during the timed collection. When a random sample is available semi-quantitative estimation of fat excretion by means of a Sudan stain of fecal smear is helpful, if fat excretion is more than 14 g/day.

Evaluation of Chronic Watery Diarrhoea

Secretory diarrhoea—has a broad differential diagnosis. Infections should be ruled out by stool cultures and special tests for other organisms. HIV status should be clarified. Some organisms like *Aeromonas*, *Plesiomonas*, coccidia, microsporidia, etc. require special microbiological techniques like PCR. *Giardia* and strongyloidosis can be detected by distal duodenal mucosal biopsy examination. Small bowel bacterial overgrowth which can cause secretory diarrhoea by toxins can be screened by glucose breath hydrogen test. But the standard test is to document >10⁶ bacteria by quantitative culture of a small bowel aspirate.

Structural diseases such as short bowel syndrome, gastrocolic or enterocolic fistula, mucosal disease, inflammatory bowel disease and tumors including lymphoma should be sought by radiographic and endoscopic techniques. Small bowel series/radiographs are helpful for small bowel structural diseases. CT scan helps in visualizing not only bowels, but also extrinsic problems like pancreatic diseases.

Small bowel mucosa visualization by endoscopy or enteroscopy can be used to take biopsy and detection in Crohn's disease, giardiasis, celiac sprue, intestinal lymphoma, eosinophilic gastroenteritis, tropical sprue, Whipple's disease, lymphangiectasia, abetalipoproteinemia, amyloidosis, mastocytosis and various infectious diseases.

Sigmoidoscopy/colonoscopy is used to visualize and take biopsy of colonic mucosa as in melanosis coli, tuberculosis, tumors, Crohn's disease, ulcerative colitis and amebiasis. Conditions where the colonic mucosa appear normal endoscopically, but which can be diagnosed histologically include microscopic colitis, amyloidosis, Whipple's disease, granulomatous infections and schistosomiasis.

Testing for peptide secretory tumors like carcinoid, Zollinger Ellison syndrome, mastocytosis should be based on pretest probability depending on clinical and radiographic /endoscopic possibility and not as a screening tests.

Endocrine tests like a fasting blood sugar in suspected diabetics, TSH in hyperthyroidism, ACTH stimulation tests in patients with clinical suggestion of Addison's disease should be asked for.

In spite of all investigation 25% of all cases of secretory diarrhoeas the cause remains unidentified and they are labeled as idiopathic secretory diarrhoeas.

Osmotic diarrhoea—It has limited differential diagnosis, usually due to ingestion of exogenous magnesium, consumption of poorly absorbed carbohydrates or carbohydrate malabsorption. Magnesium can be measured in stools by atomic spectrophotometry. Excretion of more than 30 mEq of magnesium daily or concentration in stool water of more than 90 mEq/L strongly suggest magnesium-induced diarrhoea. This may be intentional ingestion/accidental ingestion/therapeutic content in antacids or mineral supplements.

Low fecal pH is usually due to ingestion of poorly absorbed carbohydrates or carbohydrate malabsorption. Isolated carbohydrate malabsorption is seen in lactase deficiency. Poorly absorbed sugar alcohols are used as artificial sweeteners, sorbitol or mannitol. Excess fructose is also not absorbed. These patients complain of gas and bloating sensation. Breath hydrogen with lactose as sugar can confirm the diagnosis of carbohydrate malabsorption. Once a specific diagnosis has been proposed for osmotic diarrhoea therapeutic trial of an elimination diet can confirm the diagnosis.

Evaluation of Chronic Inflammatory Diarrhoea

Chronic diarrhoea patients with white blood cells or blood in stool are classified as inflammatory diarrhoea usually due to mucosal disruption and inflammation. Diagnostic considerations include inflammatory bowel disease, infections, pseudomembranous enterocolitis, ischemic/radiation enteritis and neoplasia. Mucosal examination and biopsy must be taken for making correct pathological diagnosis.

Infections causing chronic inflammatory diarrhoea are *Clostridium difficile*, cytomegalovirus, tuberculosis and amebiasis should be excluded by appropriate biopsies, cultures and serological tests.

Evaluation of Chronic Fatty Diarrhoea

Evaluation is designed to distinguish between mal-digestion (inadequate luminal breakdown of triglycerides) and malabsorption (inadequate mucosal transport of products of digestion). Fecal fat concentration provides a clue to the cause of steatorrhea. Mucosal disease is often associated with poor fluid and electrolyte absorption, and stool fat content is diluted by unabsorbed water. In addition, triglycerides are broken down to fatty acids in small intestine and pass into colon where they further inhibit water absorption. Mal-digestion due to pancreatic and biliary problems typically does not produce fatty acids and does not inhibit water absorption; this unabsorbed fat is dispersed in a smaller stool volume. Fecal fat contents greater than 9.5 g per 100 g strongly suggest pancreatic or biliary steatorrhea.

In evaluation of cause first step is to look for structural problems of small bowel which may include small bowel radiograph/CT scan and small bowel biopsy. CT scan of the pancreas is diagnostic in most cases of chronic pancreatitis which are associated with steatorrhea.

If no structural problems are found then pancreatic exocrine function should be evaluated. The secretin test, bentiromide test, fecal elastase, direct measurement of fecal chymotrypsin etc are tests available, but done only in research laboratories. But the best test for pancreatic exocrine insufficiency may be a therapeutic trial of pancreatic enzyme preparation with objective assessment. Possibility of inadequate bile salt, or solubilization of dietary fat can usually be inferred from

history of ileal resections, known enterocolic fistula. Supplementation of diet with exogenous bile acids should reduce steatorrhea, if bile acid deficiency is the problem.

CONCLUSION

Chronic diarrhoea is a challenging condition to evaluate and treat. By approaching each case individually, rationally directed by a careful history and physical examination, with simple triage tests, a long list of differential diagnosis can be made more manageable and appropriate treatment can be ordered.

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