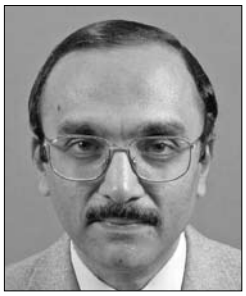

Approach to The Patient with Chronic Diarrhea

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Diarrhea is generally defined clinically as increased frequency and liquidity of the stool. This may vary from person to person, and attempts have made to define scientifically as increased stool weight.[1] In Western populations, daily fecal weight does not exceed 200g, but in Indians this figure is somewhat higher and up to 400g per day may be acceptable. Since the stool is composed principally of water, diarrhea generally implies an excessive loss of water in feces. There is no consensus on when diarrhea becomes chronic, but the shortest duration after which diarrhea may be termed chronic is probably 4 weeks.[2]

Diarrhea is a common symptom in the general population and 3-5% of the population may have chronic diarrhea without any abdominal pain. In practice, the most common cause of chronic diarrhea is likely to be the irritable bowel syndrome (diarrhea-predominant IBS). The diagnosis can usually be made clinically, and needs to be excluded before beginning detailed investigation for the cause of diarrhea. The other common causes of chronic diarrhea include intestinal parasitic infections, intestinal tuberculosis, malabsorption syndrome and inflammatory bowel disease. Malabsorption in turn could be due to tropical sprue, celiac disease, pancreatic insufficiency, intestinal parasitic infections and small bowel bacterial overgrowth.

Diarrhea that persists for weeks to months needs to be first evaluated with a good history and clinical examination. A history of frequent bowel movements of normal consistency, small caliber stools, abdominal discomfort accompanying defecation, mucus in the stool, and a sense of incomplete bowel evacuation are fairly typical of irritable bowel syndrome. This cluster of symptoms is typical and should be sought by questioning. Nocturnal diarrhea, where the patient wakes up at night to go to toilet, usually signifies organic disease. Persistent and sometimes severe abdominal pain is a prominent feature in diseases characterized by partial bowel obstruction (such as tuberculosis or Crohn's disease) and in inflammatory conditions of the bowel, and needs to be differentiated from the abdominal pain accompanying defecation that is a feature of the irritable bowel syndrome.

In the past, diarrhea was classified as being predominantly small bowel or large bowel in type. In small bowel diarrhea, the stool volume is large with characteristics of either steatorrhoea or of large volume watery diarrhea; pain, when present, tends to be located around the umbilicus. In large bowel diarrhea, the stool volume is small, there is blood and/or mucus in the stool, and pain tends to occur in the right and left iliac fossa, and is often related to bowel movement. The advantage of this simple clinical classification is that it allows investigation to be primarily targeted at the small bowel or large bowel. There are many patients, however, where clear categorization is not possible.

Physical examination should attempt to elicit evidence of organic disease. The presence of pallor and edema suggest a malabsorption syndrome or ulcerative disease of the intestine. The state of general nutrition including height, weight and body mass index must be recorded. In children it is necessary to record height for age and weight for height on appropriate charts. Evidence of goiter, tachycardia, tremor, specific nutrient deficiencies including glossitis, cheilitis, angular stomatitis, corneal xerosis and Bitot's spots, must be sought. The presence of abdominal tenderness, mass or ascites must be noted. Rectal examination is essential to assess the mucosa, and the presence of rectocele or occult intussusception. Signs of sphincter weakness such as perianal excoriation or moisture and a patulous anus must be sought. Spurious diarrhea may occur in patients who are constipated with retention and overflow incontinence, and is generally confined to children (encopresis) or those in the geriatric age group.

In approaching a patient with chronic diarrhea, the first step is to make a clinical diagnosis of irritable bowel syndrome (IBS) in those patients with this disease. Irritable bowel syndrome may present with diarrhea, constipation or alternating constipation and diarrhea. Patients with diarrhea-predominant IBS can often be diagnosed on clinical grounds based on the presence of pain during and after bowel movement, mucus in the stool and a feeling of incomplete bowel evacuation. Patients with IBS usually need only limited investigation – blood counts, erythrocyte sedimentation rate, stool examination to exclude parasites and presence of occult blood, and possibly liver function tests – in order to exclude significant organic disease. Stool examination for parasites and occult blood must be done on at least three occasions in all patients with chronic diarrhea, to increase the diagnostic yield. Detection of occult blood in the stool, nowadays commonly done using the Hemoccult or equivalent test, usually signifies an inflammatory or neoplastic cause for the diarrhea, although it may sometimes be positive even in malabsorption syndromes such as tropical sprue or celiac disease. Protozoan parasites that cause chronic diarrhea in immunocompromised individuals often require the use of special staining methods for their detection. The presence of neutrophils in the stool indicates the presence of an inflammatory condition of the intestine such as *C. difficile* colitis or inflammatory bowel disease. Presence of fecal

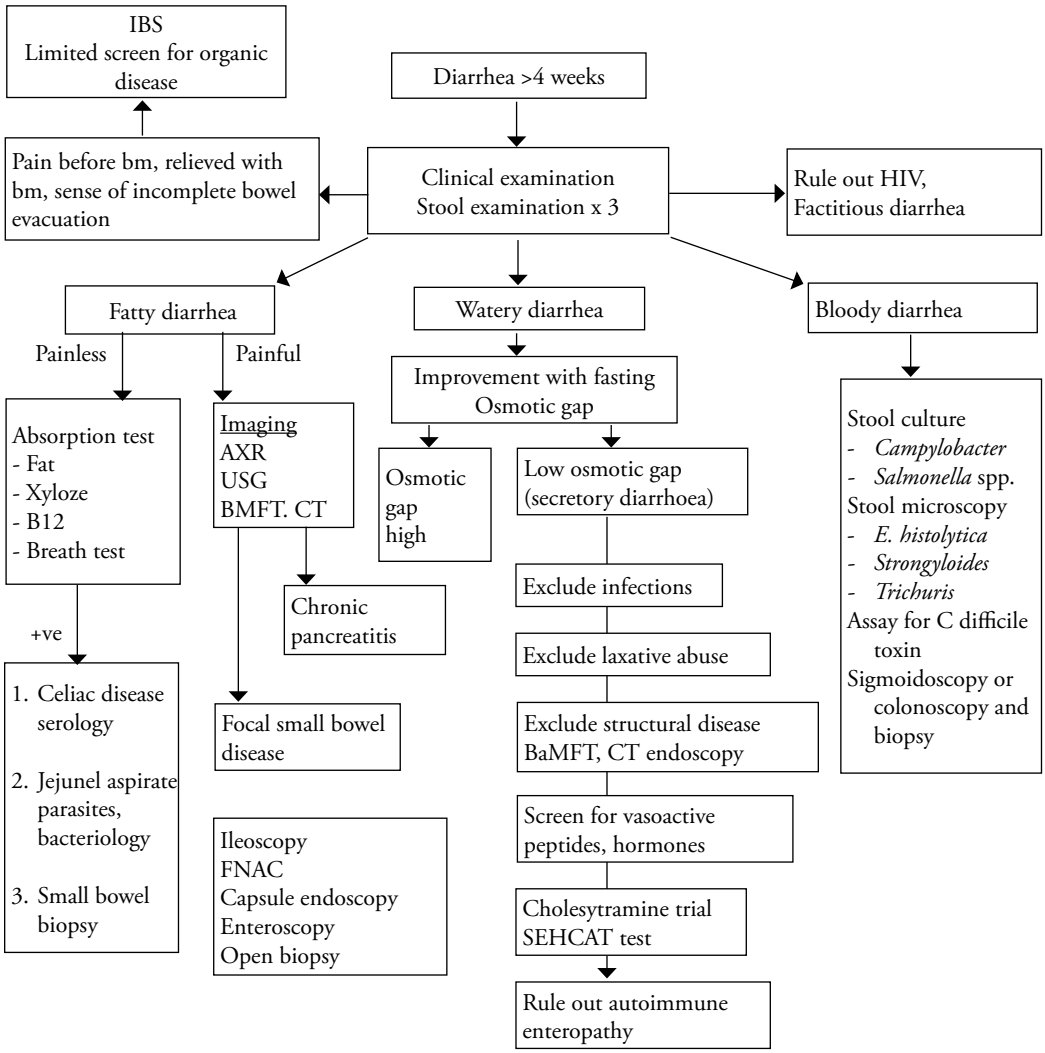

Fig. 1 : Algorithm for investigation of chronic diarrhea:

lactoferrin (detected by slide agglutination) has also been used to detect inflammatory diarrhea with great sensitivity.[3] Examination of fecal smears after staining with Sudan III stain may give an indication of fat malabsorption by detecting significant numbers of fat globules in the stool. Examination of the blood for other parameters such as serum electrolytes, renal function, and serum calcium and phosphorus may also be appropriate in many patients with chronic diarrhea, particularly where an organic cause is suspected.

Factitious diarrhea, where the patient apparently suffers from diarrhea, but has no evidence of any discomfort or nutritional impairment from apparently intractable diarrhea, is occasionally encountered in practice. Diagnosis requires close observation and monitoring, usually in the setting of a hospital admission. Dilution of stool by added water may be detected in an occasional patient, for secondary gain. This diagnosis is suggested by a low stool osmolality, less than 290 mOsm/kg.[4] Laxative abuse also falls into the category of factitious diarrhea, but may sometimes mimic secretory diarrhea due to pancreatic endocrine tumors. Patients with the diagnosis of factitious diarrhea will require psychiatric assessment and management.

It is often necessary to exclude HIV infection in patients with chronic diarrhea of organic causation. The history should include sexual history, use of intravenous drugs, and history of blood transfusion. A history of significant weight loss, symptoms of pulmonary disease, or symptoms of painful swallowing and dysphagia (suggesting esophageal candidiasis) should raise the suspicion of HIV infection. Chronic diarrhea is very common in patients with advanced HIV infection, and is usually due to infection of the small bowel with opportunistic pathogens such as *Isospora belli*, *Cryptosporidium parvum*, *Cyclospora cayatenensis*, microsporidia and *Mycobacterium avium intracellulare*.[5] Diagnosis of these requires special techniques for examination of the stool, and may sometimes require small bowel biopsy. These pathogens are also responsible for chronic diarrhea in other immunocompromised patients such as those receiving immunosuppressive medication. In addition to the above, it is also necessary to exclude more common pathogens such as *Strongyloides stercoralis* in such situations.

A number of recent articles present guidelines for investigation and management of chronic diarrhea.[8-11] One such algorithm for the diagnosis of chronic diarrhea is presented in Figure 1. It is

Table 1 : Causes of chronic diarrhea

Irritable bowel syndrome
Factitious diarrhea HIV and AIDS
Drug-induced diarrhea
Malabsorption syndromes
Tropical sprue
Celiac disease
Lymphoma
Post-gastrectomy malabsorption
Small bowel strictures
Intestinal parasites
Short bowel syndrome
Chronic pancreatitis
Carbohydrate malabsorption
Secretory diarrhea
Pancreatic endocrine neoplasm
Laxative abuse
Collagenous colitis
Lymphocytic colitis
Idiopathic bile acid malabsorption
Congenital chloridorrhea
Inflammatory diarrhea
Ulcerative colitis
Crohn's disease
Tuberculous enterocolitis
Amoebiasis
Cytomegalovirus
Whipworm infestation
Ischemia
Mesenteric ischemia
Vasculitis
Mesenteric vein thrombus
Endocrine
Thyrotoxicosis
Medullary carcinoma of thyroid
VIPoma
Gastrinoma
Neuroendocrine tumors
Carcinoid syndrome
Neural
Diabetic autonomic neuropathy
Chronic intestinal pseudoobstruction
Scleroderma
Neoplasia
Carcinoma
Lymphoma

first useful to diagnose those patients with chronic diarrhea where the illness is secondary to irritable bowel syndrome, HIV illness, or factitious diarrhea. Many commonly used drugs can also cause chronic diarrhea, and a partial list of such drugs is given in Table 1. It is helpful to classify the remaining patients as having one of three diarrhea patterns - fatty diarrhea, watery diarrhea, or bloody diarrhea. Fatty diarrhea is where the stool has characteristics of steatorrhoea, being large volume, pale, frothy, foul smelling and sometimes containing oil. Bloody diarrhea is diagnosed when the stool contains blood admixed, with or without mucus and/or pus. The remaining patients are classified as having watery diarrhea.

Fatty diarrhea is typical of patients with malabsorption syndrome. The common causes of malabsorption syndrome in our country include tropical sprue, celiac disease (more common in children), small bowel strictures with bacterial overgrowth and pancreatic insufficiency due to chronic pancreatitis or other diseases of the pancreas.[6] Malabsorption may also result after surgery of the gastrointestinal tract particularly after ulcer surgery. Short stature, weakness, anemia, bone pain and spontaneous fractures due to vitamin D and calcium malabsorption, bruising and bleeding due to vitamin K malabsorption, flatulence and bloating due to carbohydrate malabsorption, and edema from protein and albumin loss, are all features of malabsorption. Most patients with malabsorption syndrome do not have significant abdominal pain. The diagnosis is usually established by absorption testing. Fecal fat measurement in a 48 or 72 hour stool collection continues to be the gold standard of measurement, but is usually available only in reference laboratories.[4] Other tests of absorption include measurement of D-xylose excretion in a 5 hour urine specimen, after a 5g oral dose. Malabsorption of D-xylose usually signifies reduced mucosal surface area of the intestine rather than carbohydrate malabsorption. In patients who are unable to collect urine quantitatively or in those with fluid retention, measurement of blood xylose one hour after oral xylose is more accurate. Other tests of absorption are fairly specific for specific nutrients and could include vitamin B12 absorption and bile acid absorption testing. When a diagnosis of malabsorption syndrome has been made, barium meal follow through of the small bowel is indicated to exclude structural lesions of the small bowel such as tuberculosis and Crohn's disease. In the absence of focal lesions, small bowel biopsy is necessary for diagnosis. Small bowel biopsy is now usually accomplished by endoscopic biopsies from the third or fourth part of the duodenum. These biopsies need to be oriented correctly for proper diagnosis. Peroral capsule biopsy of the jejunum is still occasionally done using the modified Watson biopsy capsule placed in the jejunum under fluoroscopic guidance. In patients with malabsorption and no focal disease, further testing to establish the etiology is in order, and will include testing for antibodies characteristic of celiac disease,[7] and jejunal aspirate and culture for diagnosis of small bowel bacterial overgrowth. Currently we use anti-tissue transglutaminase antibody assay for diagnosis of celiac disease. Elderly individuals may also have bacterial overgrowth of the small bowel related to primary disturbances in motility, or related to jejunal diverticulosis.

Chronic diarrhea and malabsorption due to intestinal parasites in immunocompetent individuals is quite rare, but strongyloides and capillariasis may occasionally be responsible. Patients with significant pain will require imaging to exclude chronic calcific pancreatitis and focal small intestinal disease. Plain abdominal radiographs are useful to detect calcification and bowel dilatation, while ultrasound scan is useful for diagnosis of pancreatic disease, lymph node enlargement, liver disease and bowel masses. Barium meal follow through is gradually being replaced by CT abdominal scan for the diagnosis of focal small intestinal disease. Since these modalities do not provide a histological diagnosis, patients will eventually undergo gastroscopy with duodenal biopsies and ileocolonoscopy with ileal and colonic biopsies. Very often this is done with a view to excluding inflammatory bowel disease, particularly Crohn's disease, where the possibility

Table 2 : Drugs that commonly cause diarrhea

Gastrointestinal drugs
Magnesium containing antacids
Laxatives
Cisapride
Olsalazine
Cardiac drugs
Digitalis
Quinidine
Procainamide
Hydralazine
Beta-blockers
ACE inhibitors
Diuretics
Antibiotics
Clindamycin
Ampicillin
Amoxycillin
Erythromycin
Cephalosporins
Chemotherapeutic agents
Hypolipidemic agents
Clofibrate
Gemfibrozil
Lovastatin
Neuropsychiatric drugs
Lithium
Fluoxetine
Alprazolam
Others
Aminophylline
Salbutamol
Non-steroidal anti-inflammatory drugs
Thyroid hormones
Colchicine

of detecting mucosal inflammation by biopsy of endoscopically normal mucosa is about 10-20%. In patients with enlarged and necrotic lymph nodes, fine needle aspiration is obtained for cytological examination and AFB culture. In patients in whom the diagnosis remains obscure, laparotomy and open biopsy used to be the procedure of choice, but is now gradually being replaced by laparoscopy and lap-assisted enteroscopy and biopsy. Video capsule enteroscopy of the small bowel is increasingly being used for the diagnosis of focal small bowel disease in the setting of chronic diarrhea, but suffers from the disadvantage that histological sampling is not possible.

Watery diarrhea may be either osmotic or secretory. Chronic watery diarrhea may sometimes result from an infection including *Aeromonas* and *Pleisomonas*, which may both be diagnosed by stool culture. In patients with watery diarrhea, it is useful to measure the fecal osmotic gap. This is calculated from the following formula: (290–2x (sodium+potassium concentration)). Fecal sodium and potassium concentrations are measured in stool water after homogenisation and centrifugation. The osmotic gap of fecal fluid can be used to estimate the contribution of electrolytes and non-electrolytes to retention of water in the intestinal lumen. In secretory diarrhea, unabsorbed electrolytes retain water in the lumen while in osmotic diarrhea non-electrolytes cause water retention. Thus the osmotic gap should be large (>125 mosmol/kg) in osmotic diarrhea and small (<50 mosmol/kg) in secretory diarrhea. Further differentiation of osmotic and secretory diarrhea may be provided by a trial of a 48 hour fast (usually as an inpatient). Continuation of diarrhea despite this implies a secretory or factitious cause while cessation of diarrhea during the fast is highly suggestive of osmotic diarrhea. Osmotic diarrhea occurs when an orally ingested solute is not fully absorbed in the small intestine, thus exerting an osmotic force that draws fluid into the intestinal lumen. Malabsorption syndromes usually present with fatty diarrhea, but may occasionally masquerade as watery diarrhea, especially where the malabsorption is due to lactose intolerance, or ingestion of unabsorbed carbohydrates such as chewing gum or sweets containing sorbitol or fructose. Lactose intolerance may occasionally cause diarrhea in adults, but more commonly causes flatulence due to fermentation of lactose by colonic bacteria. Secretory diarrhea results from intestinal and colonic fluid secretion induced by the effects of bile acids (ileal disease or resection), free fatty acids (malabsorption), or hormones (Zollinger-Ellison syndrome, carcinoid syndrome, VIPomas). Documentation of the extent of stool loss in a 24 hour period is often helpful, since pancreatic endocrine tumors causing watery diarrhea usually are associated with stool volumes in excess of one litre per day. Idiopathic bile acid malabsorption is a specific entity that has been recognized in other countries, but is not usually diagnosed in India very much. The diagnosis usually requires specific demonstration of bile acid malabsorption using the SeHCAT test. Alternatively, a trial of cholestyramine, a bile acid binding resin, may help in demonstrating resolution of chronic diarrhea and confirm the diagnosis. Diarrhea following cholecystectomy may also be due to bile acids, and a trial of cholestyramine may be useful in resolving this possibility. Collagenous and lymphocytic colitis are relatively recently recognized disorders that are associated with watery diarrhea. Diagnosis requires demonstration of a thick subepithelial band of collagen or of lymphocytic infiltration in the lamina propria of the colon in affected patients, and diagnosis is usually made by colonoscopy and biopsy of the colon. Diabetic diarrhea is a somewhat special entity related to autonomic neuropathy in this disease. The diagnosis is usually made by the concomitant presence of peripheral neuropathy in a longstanding diabetic, and autonomic function testing is useful in establishing the diagnosis. The diarrhea is due to intestinal secretion secondary to loss of proabsorptive neural influences in the gut, although in some patients a motility disorder with secondary bacterial overgrowth may be responsible. A number of other endocrine disorders may cause chronic diarrhea including thyrotoxicosis, parathyroid disease and adrenal disease. These diseases are usually diagnosed by the associated setting and symptoms.

Bloody diarrhea usually signifies inflammation and ulceration of the colon, and is common in inflammatory bowel disease (ulcerative colitis, Crohn's colitis, and rarely tuberculous colitis). Certain infective causes of chronic bloody diarrhea must be considered first. Examination of wet fresh stool mounts to exclude *E. histolytica* infection is mandatory. Stool examination by concentration techniques will also diagnose *Trichuris trichura* (whipworm) infestation that may occasionally cause bloody

diarrhea, as well as infection with *Strongyloides stercoralis* that may cause extensive involvement of the gut with bloody diarrhea if the colon is involved. In patients with bloody diarrhea who have a history of previous antibiotic use, the diagnosis of *Clostridium difficile* infection and colitis is to be considered and can be established by testing for the toxin in stool. Other infections to consider in chronic bloody diarrhea include *Campylobacter coli* infection and cytomegalovirus infection. The former is diagnosed by stool culture while the latter may be diagnosed by histology showing characteristic inclusion bodies, IgM antibodies to CMV in the serum, and PCR of blood monocytes or of tissue. In most patients however, these tests do not show up a diagnosis, and the patient is most likely suffering from inflammatory bowel disease affecting the colon. The differential diagnosis includes ulcerative colitis, Crohn's colitis and indeterminate colitis. In patients who have undergone radiation to the pelvis for cancer, radiation proctitis and colitis needs to be considered. These conditions usually require large bowel endoscopy (sigmoidoscopy or colonoscopy) with biopsy for establishment of the diagnosis.

The management of chronic diarrhea depends on the cause, which should be identified and treated appropriately. Nonspecific dietary measures include the use of easily digestible foods, avoiding unabsorbed carbohydrates and excessive sweets, avoidance of milk in subjects with lactose intolerance, and avoidance of excessive dietary fat in patients with steatorrhoea. Opiate antidiarrheal agents such as loperamide, codeine or tincture of paregoric, may be used to control symptoms of diarrhea, but are contraindicated in diarrhea due to infectious agents or in severe inflammatory bowel disease. Racecadotril, an agent used to block serotonergic receptors with resultant proabsorptive and antisecretory effects, may reduce the intensity of acute watery diarrhea, but studies in chronic watery diarrhea are not available. Octreotide may be used to control diarrhea in the carcinoid syndrome and other neuroendocrine tumors. Clonidine, an alpha2-adrenergic agonist, is sometimes useful in the treatment of diabetic diarrhea. Proton pump inhibitors are useful in treating the diarrhea of Zollinger-Ellison syndrome. Indomethacin, phenothiazines and calcium channel blockers may be useful in some neuroendocrine tumors as well as unexplained secretory diarrhea. Cholestyramine is the drug of choice in bile salt-induced diarrhea. The treatment of chronic diarrhea usually rests on the identification and treatment of the underlying cause. Tropical sprue is usually treated with long term antibiotics and folate and vitamin B12 supplements, while pancreatic steatorrhoea is treated with pancreatic enzymes and acid suppression. Bacterial overgrowth is managed with antibiotics, sometimes given cyclically; where possible surgical reversion of the cause is helpful. Management of other specific conditions will not be dealt with here. In conditions of chronic diarrhea characterized by fat malabsorption, it is necessary to also supplement fat soluble vitamins and calcium.

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