

PRACTICAL APPROACH TO UNEXPLAINED DIARRHEA

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Learning Objectives

Upon completion of this session the participants should be able to:

- Develop a differential diagnosis of diarrhea by classifying as bloody, fatty or watery.
- Understand role of stool tests including fecal fat analysis in evaluation of chronic diarrhea and malabsorption.
- Understand how to develop a reasonable approach to evaluation of patients with chronic diarrhea.

Key Clinical Management Points

- Colonoscopy evaluation of diarrhea should include biopsy, even if normal mucosa, but probably avoiding the cecum because there may be increased inflammatory cells in normal individuals. Ileal biopsy has a low yield if mucosa looks normal grossly.
- A careful history may guide diagnosis and qualitative stool fat and 24 hour stool for fat and weight may be the only way to detect fat malabsorption.
- Some common overlooked causes of diarrhea include medications, diet (high carbohydrate), inadvertent laxative use, and occult infections.

Introduction

Chronic diarrhea is defined as diarrhea lasting longer than a month. Clues that diarrhea is organic rather than “functional,” i.e., irritable bowel syndrome, are the presence of gross or occult blood in the stools, waking the patient at night, and associated weight loss. The presence of mucus in the stools is usually normal and is of no diagnostic significance although its presence may alarm some patients. Daily normal GI intake is one to two liters, the GI tract produces only seven to eight liters and 1-1½ liters reach the colon. A decreased absorption by only 1% can lead to diarrhea. A reasonable approach is to guide evaluation by determining if diarrhea is bloody, fatty or watery.¹

Evaluation

History and Physical Exam

Evaluation is expedited by classifying the diarrhea as bloody or fatty or watery. Sometimes this can be accomplished by history, as in bloody diarrhea, or by examination of the stools for gross or occult blood. Fat malabsorption is suspected when stools look oily (i.e., fat globules floating in the toilet bowl water) and are hard to flush. Floating stools reflect methane or gas content, not excessive stool fat as is commonly believed. Associated symptoms of fat soluble vitamin malabsorption

associated with steatorrhea are relatively uncommon but it is still worth asking for easy bruisability (vitamin K deficiency) tetany or osteomalacia (vitamin D deficiency) or night blindness (vitamin A deficiency). Symptoms related to vitamin E deficiency are negligible.

Other questions in the history that may guide evaluation of chronic diarrhea include recent travel to developing countries (bacterial or parasitic infection), drinking well water or unpasteurized milk (some parasites or bacteria), recent antibiotic therapy (*C. difficile*), whether other household members or contacts are also sick (infectious etiology), presence of arthritic symptoms (IBD, *Yersinia*, Whipple’s disease), HIV infection (opportunistic infections), dietary history (lactose intolerance), family history (IBD, celiac sprue), prior gastric surgery (postvagotomy diarrhea, dumping syndrome), and medications (laxatives, sorbitol containing compounds etc.).

Stool Analysis

A Sudan stain is 100% sensitive and 96% specific when there are more than 100 globules of fat/hpf. If there are no clinical clues to guide evaluation it is reasonable to collect a 24 hour stool for fat and weight. In addition to defining steatorrhea, it also documents the presence of diarrhea, which is occasionally helpful. I instruct patients to eat a 100 gm fat diet daily for three days prior to the collection (one fast food meal a day usually is adequate). Then they collect all stools from 8:00 am one morning to 8:00 am the following morning. The lab should weigh the stool and quantitate its fat content.

A 24-hour stool weight is abnormal when greater than 200-300 grams, and steatorrhea is present when there is greater than 5 grams of fat in the 24-hour collection. A high carbohydrate diet can increase stool weight to 400 grams/24 hours. With large volume (secretory) diarrhea, fecal fat can be elevated to up to 14 g/24 hours. Be sure to correct for a low fat diet. Normally we absorb 90% of the fat we eat. False positives can be seen with ingested solid fats like nuts.

Normally the stool has an osmotic gap equal to 290-2 (Na + K). When the gap is less than 50, it suggests secretory diarrhea; when greater than 100, it suggests an osmotic diarrhea, i.e., lactose intolerance. A stool osmolarity greater than 375-400 suggests contamination of the specimen, for example by urine; less than 200-250 suggests it has been diluted by water or other liquids. It is better to use the calculated osmolarity rather than measured since the latter is

Table 1: Common Etiologies of Chronic Diarrhea

Bloody
Colitis
Infection
IBD
Ischemia
Malabsorption
Luminal
Pancreatic insufficiency
Mucosal
Celiac Sprue
Crohn's disease
Watery
IBS
IBD
Drugs
Antibiotics
NSAIDS
Cancer drugs
Cardiac drugs
Osmotic
Laxatives
Carbohydrates
Chronic Infection
Parasites
Bacterial overgrowth
Gastric or Small Intestine resection
Colon Cancer
Microscopic colitides
Diabetes
Neuropathy
Bacterial overgrowth
Celiac Sprue
Pancreatic insufficiency
Post cholecystectomy
Secretory
Endocrine
Idiopathic

altered by bacterial degradation of carbohydrate as the stool sits at room temperature.

Bloody Diarrhea

Bloody diarrhea almost always suggests a colonic process, usually colitis. Colon bleeding also suggests possible colon cancer or perhaps polyps. The differential diagnosis of colitis includes inflammatory bowel disease, infectious colitis (which is usually not chronic), ischemic colitis (usually acute), or radiation colitis (can be acute or chronic). When infection is suspected, check stool cultures for bacterial pathogens such as *Campylobacter*, *Salmonella*, *Shigella* or *E. coli* 0157:H7. The latter requires a special medium (Maconkey sorbitol) so alert your microbiology lab if they do not check for this routinely. *Yersinia* also requires a special cold enrichment medium and may take longer to grow. Only a few parasites cause bloody diarrhea, most commonly ameba, trichuris, and

Table 2: Infectious Causes of Chronic Diarrhea

<u>Bacteria</u>
Yersinia
Tuberculosis
Ameba
Aeromonas
Plesiomonas
Recurrent <i>C. difficile</i>
<u>Parasites</u>
Ameba
Giardia
Cryptosporidia
Cyclospora
Chronic epidemic diarrhea
i.e., "Brainerd" diarrhea
Henderson County diarrhea
Tropical sprue
Post infectious IBD
Post infectious IBS

schistosomias (in endemic areas). If diagnosis is not made by cultures, when indicated, evaluation of the colonic mucosa is suggested – either sigmoidoscopy or colonoscopy. Mucosal biopsy can be very helpful in diagnosing causes of colitis and differentiating infection from IBD. Barium enema lacks specificity. Likewise, abnormal CT scan can detect mucosal thickening but will rarely make a specific diagnosis. It can be helpful, however, when a complication such as abscess is suspected.

Fatty Diarrhea (Steatorrhea)

Fat malabsorption (> 5gm fat/24 hr in stools) suggest either a mucosal process (i.e., celiac sprue), or a luminal process (i.e., pancreatic insufficiency). Mucosal disease is best diagnosed by small bowel biopsy, best done at upper endoscopy. If pancreatic insufficiency is suspected, i.e., in the setting of chronic pancreatitis, with pancreatic damage, a trial of pancreatic enzymes can be given. Other objective tests of pancreatic function are not widely available.

Celiac sprue is the most common small intestinal mucosal disease, and is related to an immunologic reaction of the mucosa to the gluten protein gliadin. Antibody tests are a good screen. I order an IgA endomysial and/or IgA tissue transglutaminase (IgA-EMA or IgA-tTG) and a serum IgA level (up to 3% of sprue patients are IgA deficient). Small bowel biopsy and response to a gluten free diet are diagnostic. Serum antibody tests can be also used as an adjunct to biopsy and screen to family members – they will be positive in most sprue patients unless they are already on a true gluten free diet. The antigliadin antibody is no longer used due to poor sensitivity and specificity. Abnormal liver function

Table 3: Association of Parasites with Specific Clinical Syndromes**A. Malabsorption**

Coccidiosis
 Giardia
 Strongyloides
 Cryptosporidia
 Isospora belli
 Microsporidia

B. Diarrhea with Blood

Amebiasis (*E. histolytica*)
 Schistosoma sp
 Trichuriasis
 Strongyloides
 Balantidium coli

C. Occult Blood in Stools / Iron Deficiency Anemia

Hookworm
 Strongyloides

D. Chronic Tropical Diarrhea

Bacteria
 Salmonella
 Parasites
 Amoeba
 Post amebic dysentery
 Giardia
 Coccidiosis
 Cryptosporidia
 Isospora belli
 Tropical sprue

tests can be seen in up to 40% of patients; this normalizes with a gluten free diet. Nonresponsive sprue can be due to noncompliance, lymphoma, refractory or collagenous sprue or microscopic colitis.

Less common small bowel diseases include Whipple's disease and tropical sprue. Small bowel infection with cryptosporidia, giardia or cyclospora can cause mild fat malabsorption.

Whipple's disease is characterized by weight loss (90%) diarrhea (70%) and arthralgias (70%). Other presentations include congestive heart failure, pericarditis and lymphoedematous. Small bowel biopsy is diagnostic with PAS positive macrophages in the lamina propria. The cause is an organism *Trophoeryma whippelii*, a gram positive actinomycete. Treatment is six months of antibiotics. Crohn's disease causes malabsorption when there is small bowel disease or as a result of ileal resection (see below).

This is common in patient with Crohn's ileocolitis after surgery. Symptoms depend on amount of ileum resected, especially the terminal ileum. If less than one hundred centimeters is resected, bile salt absorption is decreased with resulting watery diarrhea due to choleric effects of bile salts in the colon. Symptoms are common after meals and treatment with

a bile salt binding resin like cholestyramine is helpful. When more than one hundred centimeters of ileum has been resected, decreased bile salt reabsorption results in steatorrhea due to decreased micelle formation in the proximal small bowel. Treatment includes low fat diet or rarely medium chain triglycerides.

Watery Diarrhea

Watery diarrhea has an extensive differential diagnosis. I usually go back to obtain more history, such as reviewing medications,² symptoms suggestive of lactose intolerance, chewing large amounts of sugarless chewing gum (with nondigestible sorbitol), inadvertent or surreptitious laxative abuse, prior gastric or bowel resection, and symptoms which suggest Crohn's disease or IBS. Colonoscopy can be helpful to exclude colon cancer, occult IBD, and the microscopic colitides collagenous colitis and lymphocytic colitis, which requires colon biopsy. Colonoscopic biopsy can also detect evidence of some infections and pseudomelanosis coli which suggests laxative abuse. Thus chronic diarrhea is an indication for colon mucosal biopsy even if the mucosa looks normal. Candida overgrowth has been described as a cause of chronic diarrhea in the elderly, but interpretation of the presence of yeasts in stool specimens is problematic. Bacterial infections rarely cause chronic diarrhea but those which can include *Yersinia enterocolitica*, *Aeromonas sp* and *C. difficile* (when recurrences occurs).

Entamoeba histolytica can cause chronic diarrhea. Diagnosis is made by detection of ova in stools or in colonic biopsies. Serologic tests are often helpful to differentiate pathogenic *E histolytica* from nonpathogenic *E dispar* (positive serology in former, negative in latter).

As mentioned previously, ileal resections of less than 100 cm can result in choleric diarrhea due to secondary bile acid malabsorption. There appears to be an entity of primary bile acid malabsorption which causes watery diarrhea. There are no good diagnostic tests for this in the U.S. A recent paper supports this entity as a cause of chronic diarrhea. Patients were identified, and found to have lower levels of a growth factor that the ileum produces in response to bile acid, suggesting a defect in bile acid synthesis with more bile acid in the colon causing choleric diarrhea.⁴

Epidemic chronic diarrhea has been reported in epidemics from Brainerd, MN (milk-related) and Henderson County, IL (water borne), no infectious agent was isolated but an organism seemed likely.³

Secretory diarrhea is diarrhea which persists even where there is no oral intake. This is usually best diagnosed by a short hospitalization with IV fluids while the patient is NPO. Se-

cretory diarrhea suggests hormone producing tumors often located in the pancreas. Others include carcinoid syndrome, Zollinger-Ellison syndrome (gastrinoma), Verner Morrison syndrome (VIP tumor; WDHA, watery diarrhea, hypokalemia, achlorhydria), medullary carcinoma of the thyroid and glucagonoma.

Treatment of Chronic Diarrhea

When a specific diagnosis is made, specific therapy can often be effective. Otherwise, antidiarrheal preparations can be given such as antimotility agents, which slow motility and allow more time for fluid absorption. These should be avoided in children with acute diarrhea or in adults with severe dysentery. Their use is generally safe in chronic diarrheal illnesses. Somatostatin analog can be used in refractory cases. Empiric antibiotics can be given when bacterial infection is likely. Otherwise, specific therapy relies on diagnosis of specific diagnoses.

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