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LARGE INTESTINE (B CASH, SECTION EDITOR)

Update on Chronic Diarrhea: A Run-Through for the Clinician

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Abstract Chronic diarrhea is a common patient complaint, with an estimated prevalence of 5 %. Diarrhea is defined as >200 g/day of stool with decreased consistency, and chronic diarrhea is defined as lasting more than 4 weeks. The purpose of this review is to guide the clinician's diagnostic evaluation and management of chronic diarrhea, rather than providing a textbook comprehensive review of the subject, focusing on the patient in developed countries and excluding the immune suppressed patient. While the investigation and treatment of chronic diarrhea can be challenging due to its myriad causes, when the clinician employs a practical approach, dividing chronic diarrhea into bloody, fatty, and watery causes, it simplifies and streamlines the work-up and management plan and leads to improved patient outcomes.

Keywords Chronic diarrhea · Diagnosis diarrhea · Management diarrhea · Inflammatory bowel disease · Infectious diarrhea · Bile acid malabsorption · Pancreatic insufficiency · Celiac disease · Small intestinal bacterial overgrowth · Irritable bowel syndrome

Introduction

Chronic diarrhea is a common complaint, with an estimated prevalence of 5 % [1]. Diarrhea is defined as >200 g/day of stool with decreased consistency. It is chronic if it lasts more than 4 weeks [1]. The purpose of this review is to guide the clinician's diagnostic evaluation and management of chronic diarrhea, rather than to provide a textbook comprehensive review of the subject. Focus is directed at the patient from developed countries and excludes the HIV-positive patient and other immunocompromised populations.

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Classification

For the purposes of the clinician, chronic diarrhea is most easily classified into inflammatory, fatty, and watery, although some overlap exists (see Table 1 for a list of etiologies, with the most common causes listed toward the top).

Initial Evaluation

A thorough history and physical examination is essential. One should ask about the consistency and frequency of the stool and the duration to confirm that diarrhea has indeed lasted for more than 4 weeks. "Red flag" symptoms such as nocturnal diarrhea, weight loss, and gross blood in the stool should be sought out, as should systemic symptoms such as fevers, rashes, or joint pains, which can indicate IBD, celiac disease, or infections such as Whipple's disease. A travel history should be obtained, and one should inquire about dietary triggers (lactose) and about a family history of IBD, colon cancer, or celiac disease. A review of the patient's medications is of the utmost importance, since there are several medications well known to cause diarrhea, such as metformin (see the Watery Diarrhea section for a comprehensive list). Over-the-counter medications, such as laxatives, can occasionally be abused. Recent antibiotic use should be noted, which, if positive, raises the suspicion for antibiotic-associated diarrhea or *Clostridium difficile*

Table 1 Classification and causes of chronic diarrhea

- Inflammatory
  - Inflammatory bowel disease (IBD)
  - Ischemic colitis
  - Medications such as NSAIDs, isotretinoin
  - Segmental colitis associated with diverticular disease (SCAD)
  - Radiation enteritis or colitis
  - Infectious
    - Bacterial
      - *Clostridium difficile*
      - *Salmonella*
      - *Aeromonas*
      - *Plesiomonas*
      - *Yersinia*
      - *Mycobacterium tuberculosis*
    - Parasitic
      - *Amoebiasis*
      - *Strongyloides stercoralis*
      - *Schistosomiasis*
      - *Trichuris trichuria*
  - Diversion colitis
- Fatty
  - Luminal causes
    - Small intestinal bacterial overgrowth
    - Pancreatic exocrine insufficiency
    - Bile salt deficiency
  - Mucosal causes
    - Celiac disease
    - Crohn's disease
    - Infections
      - *Giardiasis*
      - *Cryptosporidium*
      - *Cyclospora*
    - Postsurgery
      - Postvagotomy
      - Intestinal resection/ short-bowel syndrome
    - Postradiation
    - Chronic mesenteric ischemia
  - Rare causes
    - Whipple's disease
    - Collagenous sprue
    - Eosinophilic enteritis
    - Lymphoma
    - Amyloidosis
- Watery
  - Medications
  - Osmotic causes
    - Magnesium-based laxatives
    - Carbohydrate malabsorption (lactose, fructose)
  - Irritable bowel syndrome, diarrhea predominant (IBS-D)
  - Bile salt malabsorption
  - Diabetes related
  - Neoplasia
    - Colorectal adenocarcinoma
    - Lymphoma
    - Villous adenoma
  - Mucosal diseases
  - Infectious (as per "bloody diarrhea") but additionally:
    - Parasitic
      - *Giardia*
      - *Cryptosporidium*
      - *Cyclospora*
      - *Isospora*
  - Hormonal
  - Vasculitis
  - Factitous diarrhea

infection. On physical examination, one should assess for fevers, orthostasis, a decrease in weight, and abdominal tenderness or masses, any of which, if present, should alert the clinician to a pathological process other than functional cause, such as irritable bowel syndrome (IBS).

The typical initial investigation for chronic diarrhea should include basic blood tests for anemia, leukocytosis, inflammation, dehydration/renal insufficiency, protein loss, and thyroid abnormalities (CBC, ESR, CHEM 7, TSH, and albumin) [2]. Stool studies to consider include an enteric bacterial culture, *Clostridium difficile* toxin, ova and parasites, fecal leucocytes, and fecal occult blood tests (FOBT) [2]. Referral to a gastroenterologist should be considered whenever a patient has any red flags in their history, a positive FOBT or fecal leucocytes, persistent symptoms without explanation or if there is a need for endoscopy. Patients with chronic diarrhea who are young (<40 years) and without red flag symptoms or signs (no anemia, negative FOB, no weight loss, and no nocturnal diarrhea) most likely have a functional etiology of their symptoms, such as IBS with diarrhea (IBS-D), and the diagnostic Rome III criteria for this condition are described in Table 2. IBS can be a difficult condition to adequately treat. Common approaches include establishing rapport with, educating, and reassuring the patient, as well as avoiding dietary triggers or initiating dietary modifications such as the FODMAP diet, which is based on a low-carbohydrate diet and elimination of fermentable oligo-, di-, and monosaccharides and polyols [3]. Serotonergic antagonists, antispasmodics, antidiarrheals, and psychoactive drugs can also be tried [4].

In addition to the initial history and exam as above, the gastroenterologist should inquire about the response of

Table 2 Rome III diagnostic criteria for irritable bowel syndrome

Recurrent abdominal pain or discomfort[a] at least 3 days/month in the last 3 months[b] associated with two or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of the stool
3. Onset associated with a change in form (appearance) of stool

[a] Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.

[b] Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

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diarrhea to fasting, since diarrhea persistence while fasting is suggestive of a secretory diarrhea. One should specifically ask patients to describe stool consistency, since fatty diarrhea is hard to flush, malodorous and has oily droplets. If steatorrhea is suspected, ask about signs or symptoms of fat-soluble vitamin deficiency, such as easy bruisability (vitamin K), night blindness (vitamin A), and osteoporosis or osteopenia (vitamin D). The volume of stools is also important; voluminous diarrhea suggests a small-bowel origin, as opposed to a colonic origin [1]. One should ask about additional dietary triggers such as sorbitol and whether a strict lactose avoidance trial has been pursued. Inquire about fecal incontinence, which can occur with diarrhea or alone as a separate entity; patients will often not mention this unless specifically asked. The patient with proctitis will often complain of urgency and dyschezia. Question the patient about prior response to antibiotics, which suggests small intestinal bacterial overgrowth (SIBO), previous therapies, and additional systemic symptoms, such as flushing or heat intolerance.

The past medical and surgical history, especially with regard to abdominal surgeries, should be reviewed. Postcholecystectomy diarrhea is suggestive of bile acid malabsorption. Does the patient lack an ileocecal valve, suggesting that diarrhea could be due to SIBO? Note any gastric surgery, including esophageal fundoplication or vagotomy, as well as intestinal resection, especially if extensive. Ask about the presence and duration of diabetes, a disease that causes diarrhea by several mechanisms (described below), and about a history of radiation, which can cause enteritis or colitis. Ask specifically about alcohol intake over the patient's lifetime, since excessive alcohol use can cause diarrhea as a result of metabolism, as well as through chronic pancreatitis. Note the patient's ethnicity; for example, Ashkenazi Jews have a higher risk of Crohn's disease [5].

In addition to the physical exam as described above, evidence of a systemic process resulting in diarrhea, such as joint swelling (from IBD, Whipple's disease), rashes (Celiac disease, neuroendocrine tumors, IBD), exophthalmos, and tremor (hyperthyroidism) should be sought. Evidence of nutritional deficiencies such as glossitis, angular cheilitis, conjunctival pallor, and koilonychia from B vitamin and iron deficiency should also be looked for, since their presence can provide some clues as to the origins and severity of the diarrhea.

Inflammatory Diarrhea

If laboratory evaluation suggests that inflammation or fecal leucocytes have returned positive, the next diagnostic step is typically colonoscopy to distinguish between the many etiologies of inflammatory diarrhea (see Table 1). A normal colonoscopy with terminal ileal (TI) intubation and random biopsies excludes inflammatory causes and microscopic colitis and is useful for distinguishing IBD from infection [6]. Colorectal biopsies of IBD patients will often demonstrate abnormal architecture and crypt distortion, features of acute and chronic inflammation in the lamina propria, and basilar plasmacytosis and lymphoid aggregates, especially with ulcerative colitis. These changes may be less common with CD, because it is patchy in distribution. In contrast, infectious colitis will generally show preserved architecture, mucosal acute inflammation without chronic features, and no basal inflammation [7]. Mucin depletion and crypt abscesses are nonspecific indicators of inflammation [6].

An esophagogastroduodenoscopy (EGD) may be indicated for the work-up of inflammatory diarrhea if the patient has concomitant upper gastrointestinal (GI) symptoms such as nausea, vomiting, regurgitation, heartburn, dyspepsia, or melena that require investigation. Sometimes, a unifying cause for inflammatory diarrhea and upper GI symptoms is Crohn's disease, which affects the upper GI tract in only 3 % of adults, as compared with 50 % of children with the disease [8]. If IBD is found on colonoscopy and pathology, detailed management recommendations are beyond the scope of this article, but treatment is typically dependent on disease distribution, severity, and whether induction or maintenance of remission is desired [9•]. If history, blood tests, stool studies, and endoscopy exclude an inflammatory diarrhea, clinicians should consider the evaluations for fatty or watery diarrhea, as described below.

Fatty Diarrhea

Fatty diarrhea can be broadly classified into luminal causes and mucosal causes. There are additional uncommon causes that the clinician should be aware of (see Table 1 for details). Fatty diarrhea may be suspected from the history as

described above. Screening can be achieved with a qualitative fecal fat using the Sudan stain. Fewer than 20 drops per high-powered field is normal. If abnormal, one should order a 24-h quantitative fecal weight and fat, which requires the patient to collect stool for 24 h while consuming 100 g fat daily for 3 days prior to the collection [2]. Normal stool weight is less than 200–300 g/day, and normal stool fat is less than 7 g in 24 h [2]. Typically, pancreatic exocrine insufficiency (PEI) will cause a very fatty diarrhea and will demonstrate a ratio greater than 9.5 g of fat/100 g stool [10]. PEI can be caused by chronic pancreatitis, cystic fibrosis, or pancreatic or ampullary tumors obstructing the main pancreatic duct [11]. Since quantitative stool tests are critical in determining whether fatty diarrhea is present, the clinician should be aware of caveats; for example, stool weight is increased by a high-carbohydrate diet to ~300–400 g, voluminous stools in general will raise fat excretion up to 14 g/24 h, and false positives are common with olestra and Brazil nuts.

Luminal Causes

There is no single useful test available if PEI is suspected. The secretin test, which is a direct test of function, is invasive, cumbersome, and used mainly for research purposes [12]. Indirect tests are not very sensitive or specific, especially for early PEI, and include serum trypsin, fecal chymotrypsin, and fecal elastase-1. Fecal elastase-1 is more sensitive and specific than fecal chymotrypsin, especially in severe PEI [13], but false positives can occur with a number of comorbid diseases, such as diabetes [14], celiac disease, and short-bowel syndrome [15]. Thus, the most clinically useful diagnostic test is also a therapeutic maneuver—the administration of pancreatic enzymes. Prescribe a high dose and monitor the patient's weight (which will increase) and the fecal fat (which will decrease). If the patient responds, pancreatic imaging should be performed. There are a number of modalities to choose from (ultrasound, MRCP, endoscopic ultrasound, and CT). Contrast-enhanced CT of the abdomen is widely available and noninvasive and also serves to exclude pancreatic malignancy (especially in the presence of abdominal pain), which can rarely present with PEI.

SIBO has myriad causes, including structural (small intestinal diverticulosis, strictures, surgical diversions, or lack of IC valve), dysmotility (scleroderma and intestinal pseudo-obstruction), or other causes, such as diabetes [16]. There has been much controversy over whether proton pump inhibitor (PPI) use predisposes to SIBO, but a recent large, retrospective study showed no association between the two [17]. Clinical clues for SIBO besides diarrhea, bloating, and flatulence include low vitamin B12 and high serum folate levels because of consumption and production, respectively, by luminal bacteria [18]. The diagnostic gold standard for SIBO is the small-bowel aspirate, which is not commonly performed due to difficulty obtaining an adequate aspirate, its invasive nature, contamination from oral flora, variations in interpretation, and the difficulty culturing some colonic bacteria [18]. Noninvasive breath tests such as the lactulose breath test are an option but are not standardized in their performance between laboratories and have poor sensitivity (68 %) and specificity (44 %) for diagnosing SIBO [19, 20]. A diagnostic and therapeutic trial of 2 weeks of antibiotics such as ciprofloxacin or rifaximin is also a reasonable approach [16].

Mucosal Causes

Celiac disease can present in multiple ways, with diarrhea, weight loss, iron deficiency anemia, infertility, recurrent fetal loss, abnormal liver enzymes, and microscopic colitis [21•]. Because of its relatively high population prevalence of nearly 1 % and increasing awareness of the disease, some primary care providers will pursue testing for celiac before referral to a gastroenterologist. Such testing should be accomplished with a high-sensitivity/high-specificity test, such as tissue transglutaminase antibody (TTG) IgA testing, which is the most sensitive and specific antibody test for this disorder [22]. This should be ordered along with a total serum IgA level, since 2 %–3 % of patients with celiac disease are IgA deficient, which could lead to a false negative TTG IgA [23]. An alternative test is the endomysial antibody IgA, which has a similar specificity and sensitivity to TTG IgA antibody. The older, antigliadin antibody test is not currently recommended due to variable sensitivity and specificity [22]. If celiac serology is positive, a duodenal biopsy via EGD should be pursued, since histology remains the gold standard for diagnosis and may be useful for subsequent monitoring. However, it should be noted that histologic distribution of celiac disease on duodenal biopsy alone can be patchy, so concurrent serological testing is recommended [23]. Moreover, the patient must be consuming gluten at the time of the above diagnostic tests for serology and histology to be positive. If serology is negative and a biopsy borderline, one can test for the HLA-class II alleles DQ2 and DQ8, which are nearly universally present in patients with celiac disease [23]. Optimal management of the patient with celiac disease requires total gluten elimination.

Other causes of fatty diarrhea to consider are parasitic infections such as *Giardiasis*, *Cryptosporidium*, *and Cyclospora*, as well as postgastric surgery or radiation changes, chronic mesenteric ischemia, and rare causes such as Whipple's disease, collagenous sprue, eosinophilic enteritis, lymphoma, and amyloidosis [2]. Further investigation depends on the etiology suspected, since a number of additional modalities for small bowel disease are available, including cross-sectional abdominal imaging, capsule endoscopy, or double-balloon endoscopy.

A recent paper showed a high yield (>90 %) of capsule endoscopy when used for investigation of abdominal pain, diarrhea, and elevated inflammatory markers combined, but capsule endoscopy was virtually useless in the patient with chronic diarrhea without pain or elevated inflammatory markers [24].

Watery Diarrhea

Again, the history is critical. Review the patient's medications and note any recent antimicrobials, PPIs, NSAIDS, sulfasalazine, SSRIs, psycholeptics, or colchicine, all of which have been linked to diarrhea [25]. Examine the diet for lactose, fructose, and sorbitol, which can cause osmotic diarrhea [26]. Diabetes is common and can lead to diarrhea via various routes—through autonomic neuropathy, SIBO, associated Celiac disease, pancreatic insufficiency, or excessive unabsorbed carbohydrates in the form of sugarless sweets [27].

Bile salt malabsorption is a common cause of watery and, occasionally, fatty diarrhea. Ninety-five percent of bile acids are reabsorbed in the ileum for recirculation into the enterohepatic circulation, but when this cycle is disturbed due to ileal Crohn's disease or ileal resection, for example, bile acids that spill into the colon cause excessive colonic electrolyte and water secretion, resulting in diarrhea [28]. Recently, primary bile acid malabsorption has been shown to be due to excessive bile acid secretion from impaired negative feedback by ileal fibroblast growth factor-19 [29•]. Diagnosis is difficult without selenium homocholic acid taurine (SeHCAT) testing, which is not available in the U.S. [29•]. Thus, cholestyramine, a bile acid binder, is the diagnostic and therapeutic tool in these patients when the diagnosis is suspected, such as postcholecystectomy [28].

A variety of mucosal diseases can cause watery diarrhea: Crohn's disease, microscopic colitis, colon cancer, celiac disease, and the rest of the small-bowel luminal causes as described above in the Fatty Diarrhea section [2]. Microscopic colitis can be diagnosed only by colonoscopy, with biopsies being critical to the diagnosis, since there are classically thought to be few to no macroscopic findings, although this mantra has been recently challenged [30]. With improving endoscopic technology, linear fissures and coarse, nodular mucosal texture have been increasingly appreciated with microscopic colitis [30]. The yield of terminal ileum biopsies when the terminal ileum appears macroscopically normal is low; for example, a recent study examining patients with normal-appearing terminal ileums on colonoscopy found that patients who complained of chronic diarrhea had abnormal histology in 6 % of cases versus 3 % of cases without diarrhea; although the difference was not statistically significant, it highlights the overall low yield of terminal ileum biopsies even in the symptomatic patient [31]. If microscopic colitis is found, management is tailored toward symptomatic control with a range of agents, including bismuth subsalicylate, budesonide, bile acid binders, aminosalicylates, prednisone, and immunomodulators [32].

Chronic infectious etiologies of watery diarrhea are rare but, if present, are usually parasitic. Some of the organisms below can cause an inflammatory diarrhea also (see Table 1). Suspect infection in the immunocompromised patient or the patient with a recent travel history. Causes include *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium*, *Cyclospora cayetanensis*, *Isospora belli*, *Strongyloides stercoralis*, *Schistosomiasis*, *Trichuris trichuria*, and *Blastocystis hominis* [33]. Stool ova and parasite testing is commonly ordered but has an unknown positive and negative predictive value and is somewhat dependent on observer skill [2]. Many of the above pathogens, if suspected, require special techniques, but at a minimum, ELISA for giardia-specific antigen should be performed [2]. *Clostridium difficile* and *Salmonella* are the more common bacterial etiologies in the U.S., while *Aeromonas*, *Yersinia*, and *Tuberculosis* are uncommon [33]. Fecal culture in the patient with chronic watery diarrhea is often low yield but should be considered during the work-up of chronic diarrhea. It should be noted that rare bacterial causes, such as *Aeromonas* and *Plesiomonas*, require special culture media and conditions [2].

Thyroid disease is a relatively common endocrine cause of diarrhea and should be excluded [34]. Other uncommon hormonal causes include neuroendocrine tumors that secrete excessive VIP, serotonin, gastrin, or calcitonin, all of which can cause a voluminous secretory diarrhea [2]. Addison's disease can also cause chronic diarrhea [1]. Rectal villous adenomas causing profuse watery diarrhea are rare but have been described [35]. Sometimes pseudomelanosis coli is found on colonoscopy, raising the suspicion for factitious diarrhea due to laxative abuse that is caused by an eating disorder, unintentional overuse, factitious disorder or engaged in for secondary gain [36].

If the above work-up is negative, and the patient is not thought to have IBS, consider ordering a stool sodium and potassium to calculate the osmotic gap and confirm a secretory diarrhea. This is calculated by the following equation: $290-[2(Na+K)]$ [37]. Secretory diarrhea has an osmotic gap of less than 50, while an osmotic diarrhea gap is often >125 [37]. A gap of >290 suggests contamination of stool with water or hypotonic urine [2]. If secretory diarrhea is confirmed, an exhaustive work-up is negative, and there is no response to antibiotics, consider the diagnosis of idiopathic secretory diarrhea [38]. In the study referenced, a thorough work-up prior to diagnosing idiopathic secretory diarrhea was considered to be a normal CBC, Chem 7, ESR, CRP, TSH, VIP, gastrin, calcitonin, urine 5-HIAA, stool studies including enteric cultures for *Clostridium difficile*, ova and parasites, fecal leucocytes, laxative screen, EGD, colonoscopy with

biopsies, and in some cases, CT abdomen/pelvis [38]. Idiopathic secretory diarrhea is often of sudden onset, with red flags such as nocturnal bowel movements, and can cause initial weight loss in a previously healthy person with no history of GI disease or surgery. It can last up to 2 years but, typically, is self-limited [38].

Conclusion

The investigation and management of chronic diarrhea can be challenging due to its long list of etiologies. When the clinician employs a practical approach, dividing chronic diarrhea into bloody, fatty, and watery causes, it simplifies and streamlines the work-up and treatment plan for the benefit of the physician and the patient. If the work-up is persistently negative, a careful repeated history is unrevealing, and the patient's symptoms and signs are reassuring, consider stopping investigation at this point and managing the patient as IBS-D, or consider empiric trials of cholestyramine, pancreatic enzymes, antibiotics, or antimotility agents as directed by the history [2]. It is unclear whether repeating an exhaustive work-up is beneficial to the patient [2]. It is important to understand the caveats of all diagnostic tests, however, and to consider repeating an essential test if the history is persistently and highly suggestive of a specific diagnosis.

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