A Practical Approach to Treating Patients With Chronic Diarrhea

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Although diarrhea is a common complaint, its evaluation and treatment can be challenging. Appropriately defining and classifying diarrhea provide the framework for approaching diagnostic and therapeutic options. Diarrhea can be defined based on frequency, consistency, and/or weight, and classified as acute or chronic with specific clinical characteristics and stool appearance. Colonoscopy is the most common diagnostic tool used in the evaluation of patients with chronic diarrhea. Other evaluation strategies include timed stool collections, evaluation of inflammatory markers, and hydrogen breath tests. A focused workup of chronic diarrhea may yield a specific diagnosis, including diarrhea-predominant IBS (dIBS), functional diarrhea, diabetic diarrhea, bile acid–induced diarrhea, and microscopic colitis. Ideally, therapeutic decisions are specifically tailored to target the underlying pathophysiology, including, for example, gluten restriction for celiac disease, rotating antibiotics for small bowel bacterial overgrowth, budesonide therapy for collagenous colitis, and loperamide for treatment of functional diarrhea. It is also important to assess the role of diet and medications in chronic diarrhea. However, if no specific causes are identified following workup, empiric therapy with simple opiate antidiarrheals such as loperamide may be effective. If this proves unsuccessful, the use of more potent agents, including codeine and opium, may be considered.

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Diarrhea is a common clinical complaint. However, the evaluation and treatment of diarrhea can be perplexing and challenging. Although there have been considerable advances in the understanding of fluid and electrolyte transport, motility, and epithelial biology, translating that knowledge to the clinical arena has been difficult and far from straightforward.
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Diarrhea is a symptom, not a disease, and, unfortunately, not necessarily a very precise symptom. There is a wide spectrum of what may be classified as diarrhea, from the voluminous fecal effluent, dehydration, and vascular collapse of cholera to the occasional postprandial bloating and loose stools associated with a particular dietary indiscretion. Therefore, defining and classifying diarrhea are necessary prerequisites for evaluation and treatment.

Defining Diarrhea
Diarrhea can be defined based on frequency, consistency, and/or weight. There is a considerable variability in what might be classified as a normal stool frequency, anywhere from 2 to 3 times per day to 3 to 4 times per week. For most individuals, a change from baseline would be considered “diarrhea.” Thus, an increase in an individual from once every other day to thrice daily may prompt a visit to the doctor for an evaluation, whereas for someone whose baseline is 2 to 3 times per day, that would be considered “normal.”

A change in consistency may be considered another manifestation of diarrhea. Because of the difficulties many individuals face in accurately describing the appearance of their stool, a pictorial scale may be very useful. The Bristol scale is a helpful aid in accurately characterizing consistency. It provides 7 pictorials that patients can select. In this case, 7 pictures are truly worth a thousand words.

Measuring stool weight provides perhaps the most objectively quantifiable measure of diarrhea. Unfortunately, it is the most difficult to obtain, in part because of patient resistance, but also because of laboratory misadventures. Nevertheless, it can prove to be very useful in directing both diagnostic and therapeutic choices. There are geographic variations in what may be considered normal; for the most part, in Western societies, stool weight of up to 150 g/day in women and 200 g/day in men is considered normal.

Classifying Diarrhea
There are several overlapping classifications of diarrhea. The most important classification in driving a diagnostic workup is acute versus chronic. Acute diarrhea lasting less than 2 weeks generally implies an infectious etiology. Chronic diarrhea (> 4 weeks) is much less likely to have an infectious etiology. For this review, we will restrict ourselves to evaluation and treatment of chronic diarrhea.

One of the more useful classifications divides diarrhea into 3 categories based on clinical characteristics and stool appearance: watery, fatty, and inflammatory. Watery diarrhea can be further divided into secretory and osmotic. Diarrhea with a fatty or greasy character suggests malabsorption. Inflammatory diarrhea may have blood and/or pus and be characterized by frequent small movements associated with tenesmus (see Figure 1). This classification provides a framework for approaching both the diagnostic and therapeutic options associated with diarrhea.

Diagnostic Strategies in Chronic Diarrhea
In an ideal clinical world, physicians would be able to synthesize a constellation of symptoms, signs, and laboratory tests to come up with a specific diagnosis that would lead to a targeted therapy. Unfortunately, in the real world, that is not necessarily the case. Sometimes symptoms, signs, and laboratory test results can lead to a diagnosis for which there is no good therapeutic alternative (see Figure 2). Another scenario is that even the most diligent workup does not yield a diagnosis; however, empiric therapies may be available to treat the symptoms. In the evaluation of chronic diarrhea, this scenario is a frequent outcome. At some point, depending on the severity of the symptoms and patient decisions, it may be prudent to consider therapeutic trials.

How Valuable Is Colonoscopy in Working Up Chronic Diarrhea?
The gastroenterologist’s reflex first step in evaluation of patients with chronic diarrhea is generally a colonoscopy. In our referral practice, it is rare to see a consultation without a prior colonoscopy. But, how effective is colonoscopy in providing a diagnosis in patients with chronic diarrhea? The literature suggests, somewhat surprisingly, that a specific diagnosis may be found in 15% to > 30% of patients.1,2 Perhaps the most common diagnosis is microscopic colitis (including “lymphocytic” and collagenous colitis), which may be found in up to 10% of cases. There is considerable disparity

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**Figure 1. Classification of diarrhea.**

- Chronic diarrhea
  - Watery
    - Osmotic
    - Secretory
  - Inflammatory
  - Fatty
    - Malabsorption
    - Malnutrition
in the frequency of finding inflammatory bowel disease (IBD) in this setting, with a range from 3% to 10%. This probably reflects patient referral patterns and selection bias.

Whether flexible sigmoidoscopy can suffice in the workup of chronic diarrhea remains somewhat controversial. Although Fine and colleagues concluded that 99% of diagnostic pathology was within the reach of the flexible sigmoidoscope, others have argued that microscopic colitis may only be apparent on the right side of the colon and that there are some significant findings noted on the intubation of the terminal ileum. In general, the trend is toward colonoscopy rather than flexible sigmoidoscopy (see Tables 1 and 2). One important variable not sufficiently emphasized is the necessity to take an adequate number of biopsies, even with a normal endoscopic mucosa.

Occasionally, endoscopic pathology can confuse rather than clarify the evaluation of chronic diarrhea. Two specific findings are particular pitfalls that may be associated with the use of a phospha soda prep: aphthoid ulcers and focal active colitis (FAC). Most endoscopists are sensitized to the association of aphthoid ulcers in patients who have received a Fleet’s prep, which may suggest Crohn’s disease. This may occur in 2.5% of patients. Additionally, FAC may occur in 3.5% of patients with endoscopically normal mucosa who were prepped with a phospha soda. The conventional interpretation of FAC is either early IBD or an intestinal infection. However, in addition to Fleet’s, FAC has been associated with irritable bowel syndrome (IBS), antibiotics, diabetes, nonsteroidal anti-inflammatory drugs, and immunosuppression. Thus, the finding of FAC on an endoscopic workup of chronic diarrhea may have confounding interpretations. In this setting, it would be prudent to not confer a diagnosis of IBD on an individual unless it can be confirmed by other components of the clinical picture.

**Timed Stool Collections**

Timed stool collections over 48 to 72 hours are a basic component of the workup of chronic diarrhea. There are 3 significant pieces of data that these studies may yield: 1) quantification of the diarrhea, 2) evaluation for steatorrhea, and 3) categorization of secretory versus osmotic diarrhea. In our experience, the first 2 pieces of information are valuable in the evaluation, whereas the third is somewhat problematic.

In our practice (unpublished observations), about 20% to 25% of patients referred for evaluation of chronic diarrhea will have normal stool weights. Such patients may have hyperdefecation (increased stool frequency) or a change in stool consistency. In a series of patients with low volume, low-consistency diarrhea, Wenzl and colleagues ascribed the stool changes to a decreased water holding capacity of the stool. An increase in dietary fiber, a somewhat paradoxical recommendation for individuals with diarrhea, appears to increase the water-holding capacity and improve the consistency of the stool. Confirming a stool weight of greater than 500 g/day (again, about 20% to 25% of referred patients) clearly suggests a nonfunctional etiology of diarrhea and channels the diagnostic workup. For those patients with increased stool weights but less

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**Table 1**

**Chronic Diarrhea: Yield of Colonoscopy**

- 168 patients (142 with ileoscopy)
- Specific histological diagnosis: 31%
  - Crohn’s disease 6%
  - Ulcerative colitis 4%
  - Lymphocytic 6%
  - Collagenous 2%
  - Ischemic 2%
  - Infectious 4%
  - Ileoscopy 3%

Data from Shah RJ et al.

**Table 2**

**Chronic Diarrhea (CD): Yield of Colonoscopy**

- 809 pts w/CD, 99% to cecum, 67% ileum
- Approximately 15% abnormal histopathology
  - Microscopic colitis 10%
  - Crohn’s disease 2.8%
  - Microscopic melanosis 1%
  - Ulcerative colitis 0.6%
- 99% of pathology within reach of flexible sigmoidoscopy

Data from Fine KD et al.
than 500 g/day, further evaluation is important, but may be negative and lead to a diagnosis of functional diarrhea. Although a Sudan stain of a random stool sample may detect steatorrhea, the gold standard remains a timed stool collection. A major pitfall of the test is that interpretation is based on the assumption of a diet containing 100 g/d of fat. Because that amount of dietary fat may not be consumed, borderline results should be interpreted with caution.

The classification of secretory and osmotic diarrheas on the basis of an analysis of the stool electrolytes and osmotic gap has provided a marvelous heuristic device for the understanding of the pathophysiology of watery diarrhea. However, there are few studies that have confirmed the utility of this diagnostic algorithm in the clinical arena.\(^7,8\)

### Inflammatory Markers

Fecal leukocytes have been considered the classic test for inflammatory diarrhea. However, over the last several years other markers have been demonstrated to be accurate indicators of inflammatory diarrhea. Calprotectin and lactoferrin are proteins found in leukocytes; they are relatively stable and, therefore, have fewer pitfalls in processing than fecal leukocytes. Additionally, these markers may be indicators of small bowel inflammation as well as colonic inflammation. They have proven useful in separating functional and inflammatory diseases of the gastrointestinal tract.\(^9\)

### Hydrogen Breath Tests

Hydrogen breath tests have assumed an increasing role in the evaluation of chronic diarrhea. Despite concerns about the sensitivity and specificity of these tests,\(^10\) they have been used to establish a diagnosis of bacterial overgrowth in the setting of a diagnosis of functional bowel disease. Accurate interpretation of these tests has significant implications for our understanding of the pathophysiology and function of diarrhea, and may also guide therapeutic options.

A hydrogen signal depends on the interaction of the test carbohydrate with luminal bacteria. The 2 main variables that may affect the results of a hydrogen breath test are intestinal transit and bacterial metabolism. A false negative test may occur if the bacterial flora are unable to metabolize the test sugar, either because of prior antibiotic therapy or occasionally because of the lack of necessary metabolic pathways. A more common and troubling problem is a false positive secondary to rapid intestinal transit. Interpretation of breath tests are generally based on the assumption that orocecal transit time (OCTT) is greater than 1 hour. For example, the breath test shown in Figure 3 using lactulose as the test sugar would generally be interpreted as consistent with bacterial overgrowth.

However, in fact, rapid intestinal transit may commonly occur. A simultaneous nuclear medicine intestinal transit scan can provide a more accurate interpretation of hydrogen breath tests.\(^11\) The OCTT in the case above\(^10\) was less than 10 minutes, suggesting that this was not a case of small bowel bacterial overgrowth. This is an important clinical distinction since therapeutic decisions will vary depending on the diagnosis. Lactulose breath tests performed without an intestinal transit scan should be interpreted cautiously because of the great variability of small bowel transit times.

### Specific Diarrheas

A focused workup of chronic diarrhea may yield a specific diagnosis. Among the most common are diarrhea-predominant IBS (dIBS), functional diarrhea, diabetic diarrhea, bile acid
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malabsorption, and microscopic colitis. The presentation and therapeutic options for these specific diarrheas are considered below.

dIBS

Functional bowel disease is exceedingly common. There have been multiple, extensive reviews of the etiology and clinical spectrum of IBS; however, discussion of these aspects of IBS is beyond the scope of the present article. Therapy remains problematic and, in large part, depends on the predominant symptoms. Medications that may be efficacious for constipation-predominant IBS (cIBS) would not be appropriate for dIBS and vice versa. Therefore, an initial necessity in selecting appropriate treatment of IBS is to categorize the type of disease and the severity of differing symptoms, including abdominal pain and bloating.

Several lines of evidence suggest that dIBS may have an inflammatory component, including the recognition of postinfectious IBS and the measurement of increased cytokines in IBS patients. Although this has prompted a reevaluation of the pathophysiology of dIBS, it has not yet been translated into new therapeutic options.

Despite considerable efforts to develop novel therapies for IBS, the treatment of dIBS remains problematic. Traditional smooth-muscle relaxants have stood the test of time and have been shown to be effective in relieving the abdominal pain associated with IBS. Dicyclomine may be better suited for patients with cIBS and its effectiveness may be limited by anticholinergic side effects. More selective anti-muscarinic agents have fewer side effects, but may not target the appropriate symptoms of dIBS.

Alosetron, a specific 5-hydroxytryptamine antagonist, has been shown to be effective in controlling the diarrhea and abdominal pain in women with dIBS. Unfortunately, it has been associated with significant side effects, including ischemic colitis. A recent trial using lower dose alosetron again proved the drug’s efficacy in controlling symptoms, but it was also associated with rare episodes of ischemic colitis. Another promising serotonin antagonist for dIBS, cilansetron, has also had some troubling side effects.

Loperamide has been shown to be both safe and effective in the treatment of dIBS. Loperamide increases intestinal transit time, but, interestingly, does not appear to decrease stool volume. Its major clinical effects are decreased stool frequency and increased consistency. Its effect on the abdominal pain of IBS is less clear; although there is a general consensus that it does not have a beneficial effect on pain, most of the randomized controlled studies report some improvement. As expected, loperamide was of little benefit in cIBS and in alternating IBS. Somewhat surprisingly there is little information on the role of diphenoxylate in IBS.

Functional Diarrhea

Functional diarrhea is the neglected stepsister of IBS. It is probably less common and certainly has not been nearly as well characterized or studied compared with dIBS. Manning and colleagues make only passing reference to functional “painless” diarrhea in their description of IBS, but a fuller definition appears in the Rome criteria. The clinical presentation overlaps with IBS, with 1 major exception: pain is not a major component of the clinical picture. Although intermittent cramping or discomfort may occasionally occur, it does not reach the significance of IBS. There is some difference of opinion on whether normal stool volumes are a necessary component of functional diarrhea. Although some experts would argue that an increased stool weight implies organic disease, others have assumed that modest increases in stool weight (< 500 g/day) may still be consistent with functional diarrhea after a negative workup for a specific etiology. Unfortunately, there are few studies of functional diarrhea (or, in fact, dIBS) that have quantified stool weight; thus, this remains an untested diagnostic issue. Functional diarrhea generally responds very well to loperamide. Because abdominal pain is not a component of functional diarrhea, other pharmacologic therapies for IBS that target abdominal pain may be less effective and less appropriate for patients with functional diarrhea.

Diabetic Diarrhea

Although constipation is a more common gastrointestinal complaint in diabetic patients, diarrhea is certainly more clinically significant and troubling. Conventional wisdom suggests that there are at least 2 mechanisms for the development of diabetic diarrhea: 1) impaired adrenergic regulation of fluid and electrolyte transport secondary to decreased $\alpha_2$ adrenergic input, and 2) slow intestinal transit and subsequent bacterial overgrowth. However, multiple other factors must be considered in the clinical evaluation of diabetic diarrhea (see Table 3).
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Table 3
Etiologies of Diabetic Diarrhea and Therapeutic Implications

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Therapeutic Implications</th>
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<tbody>
<tr>
<td>Rapid intestinal transit</td>
<td>Antidiarrheal/Clonidine</td>
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<tr>
<td>Bacterial overgrowth</td>
<td>Antibiotics</td>
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<tr>
<td>Diabetes medications</td>
<td>Alternative medications</td>
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<tr>
<td>Artificial sweeteners</td>
<td>Dietary modifications</td>
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<tr>
<td>Celiac disease</td>
<td>Gluten-free diet</td>
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<tr>
<td>Incontinence</td>
<td>Anorectal evaluation</td>
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</table>

Clonidine has been utilized to correct the presumptive deficits in adrenergic input; it has been shown to be effective both in animal models and a limited number of diabetic patients. However, its use may be limited by its concomitant hypotensive effects.

Although it is commonly assumed that small bowel transit is slowed in diabetes, leading to bacterial overgrowth, rapid intestinal transit may, in fact, be more common. Somewhat paradoxically, and going against conventional wisdom, rapid gastric emptying is not uncommon in diabetics and may be a factor in the diarrhea. A combination of hydrogen breath testing and nuclear scintigraphy has provided a more accurate assessment of the relationships among small bowel transit, nutrient absorption, and small bowel bacterial overgrowth.

Additional diagnostic considerations in diabetic diarrhea include associated celiac disease, medications, and fecal incontinence. Celiac disease may occur in approximately 5% of type 1 diabetics. Serologic testing followed by small bowel biopsy may be appropriate. Metformin is the most common medication associated with diabetes in this population, but there may be other culprits, including newer medications such as acarbose and miglitol. The use of artificial sweeteners as a mainstay of a diabetic diet may contribute to an osmotic component of “diabetic diarrhea.” Especially in the elderly patient, fecal incontinence may be described as diarrhea; therefore, it is important to characterize the exact nature of the diarrhea. Although pancreatic insufficiency and islet cell tumors are often considered as potential causes of diabetic diarrhea, it is not clear whether they actually occur more frequently than in the general population.

Bile Acid–Induced Diarrhea

Bile acids are frequently cited as the culprit in chronic diarrhea. Although it is clear that dihydroxy bile salts such as chenodeoxycholic acid can induce colonic secretion in a number of experimental settings, it is less clear how often bile salts actually cause clinically significant chronic diarrhea. The diagnosis is usually entertained in the appropriate clinical setting (ileal disease or resection, postcholecystectomy) or after a successful therapeutic trial with a bile acid–binding resin such as cholestyramine. Specific diagnostic tests are limited. The SeHCAT test quantifies the malabsorption of a radiolabeled bile acid. Unfortunately, SeHCAT testing is not available in the United States. Additionally, although the test does indeed quantify bile acid malabsorption, it does not delineate whether this is a primary or secondary transport event (ie, an epiphenomenon) in the etiology of diarrhea. Bile acid malabsorption has been found concurrently with other diarrheas (eg, microscopic colitis), further clouding the issue of specificity.

Bile acid malabsorption due to a specific loss of ileal transporters occurs, but is incredibly uncommon. In contrast, postcholecystectomy diarrhea is common, probably occurring in 10% of patients after surgery. The most consistent change is a decreased colonic transit time. It is unclear why removal of the gall bladder should lead to bile acid malabsorption. Perhaps because bile acids spend more time in the intestinal lumen after the loss of the gall bladder reservoir, bacterial dehydroxylation leads to more diarrheagenic bile acids. There are no data that address this issue. What has been termed idiopathic bile acid malabsorption (IBAM) occurs in multiple clinical settings, including IBS, microscopic colitis, and intestinal infections. It may be transient. There is no suggestion of an epithelial transport defect per se in postcholecystectomy diarrhea or IBAM.

A therapeutic response to bile acid–binding resins is putatively specific for bile acid malabsorption, although this class of medicine is generally constipating in normals. Although there is some controversy over how effective it is in postcholecystectomy diarrhea, it is a reasonable, but far from specific, diagnostic and therapeutic strategy.

Microscopic Colitis

Microscopic colitis is the most frequent diagnosis made on endoscopic evaluation of chronic diarrhea, occurring in approximately 10% of most published series. Clinically,
microscopic colitis presents as a watery diarrhea, most frequently in middle-aged women. The diarrhea is generally mild, but occasionally will be severe enough to lead to dehydration and hospitalization. Microscopic colitis has been associated with multiple medications, although the specific pathogenic mechanism linking any drug with the characteristic mucosal changes is not clear. The diagnosis is made by biopsy in endoscopically normal appearing colonic mucosa. Histologically, but not clinically, microscopic colitis can be differentiated into either collagenous colitis or microscopic colitis. Although there are some uncertainties about where and how many biopsies need to be taken, in general 6 to 12 random biopsies throughout the colon should suffice. Some experts have suggested that biopsies from the right colon have a greater yield. The significance of differentiating between microscopic and collagenous colitis is not clear.

Budesonide is effective short-term treatment for collagenous colitis. There have been limited studies focusing specifically on treatment of microscopic colitis, but given the similarity between the 2 entities, it seems reasonable to also treat individuals with budesonide for lymphocytic colitis. Long-term management is less clear; stopping budesonide, even with a tapering dose, often leads to relapse.

**Therapeutic Options in Chronic Diarrhea**

Ideally, therapeutic decisions should be specifically tailored to target the underlying pathophysiology (eg, gluten restriction for celiac disease or rotating antibiotics for small bowel bacterial overgrowth). Budesonide has emerged as the treatment of choice for collagenous colitis. Cholestyramine is a reasonable option in well-documented bile acid malabsorption, but may also have some nonspecific effects. Clonidine may be considered in diabetics, but its potential side effects are a limitation. Differentiation of rapid-transit diarrhea from slow-transit diarrhea in IBS and diabetes is important. Obviously, antibiotic treatment is appropriate for slow transit with overgrowth, whereas rapid-transit diarrhea may be more effectively treated with more conventional antimotility drugs such as loperamide. Octreotide may be considered when those rare endocrine tumor–induced diarrheas or severe dumping syndromes are encountered, but its limited efficacy and cost are constraining factors for more general use.

It is important to consider the role of diet in diarrhea. Poorly absorbed carbohydrates (lactose, but also fructose and sorbitol) may be contributing factors. In our hypercaffeinated society, excessive ingestion of coffee (ie, Starbucks® diarrhea) is an additional consideration. Medications should not be overlooked as a contributing factor.

If no specific cause is identified, empiric therapy with simple opiate antidiarrheals (eg, loperamide) is a reasonable starting point. If this proves unsuccessful, the use of more potent agents such as codeine and opium should be considered.

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**Main Points**

- A wide spectrum of symptoms exist that may be categorized as diarrhea. Defining and classifying diarrhea are necessary prerequisites for appropriate evaluation and treatment.

- Ideally, physicians synthesize symptoms, signs, and laboratory tests and provide a specific diagnosis for chronic diarrhea, leading to a targeted therapy. Unfortunately, results often offer a diagnosis for which no good therapeutic alternative exists; sometimes the most diligent workup yields no diagnosis at all.

- Generally, the first step in evaluation of patients with chronic diarrhea is a colonoscopy, utilized more frequently than flexible sigmoidoscopy. Other valuable diagnostic tools include timed stool collections over 48 to 72 hours, assessment of inflammatory markers, and hydrogen breath tests used to diagnose bacterial overgrowth.

- A focused workup of chronic diarrhea may successfully yield specific diagnoses, including diarrhea-predominant irritable bowel syndrome, functional diarrhea, diabetic diarrhea, bile acid malabsorption, and microscopic colitis.

- Ideally, therapeutic decisions for chronic diarrhea will be specifically tailored to target the underlying pathophysiology (eg, budesonide for the treatment of collagenous colitis or rotating antibiotics for small bowel bacterial overgrowth). It is also important to consider the roles of diet and medication as contributing factors to diarrhea.

- When no specific cause for chronic diarrhea is identified, empiric therapy with simple opiate antidiarrheals such as loperamide is a reasonable starting point of treatment. If this proves unsuccessful, however, the use of more potent agents such as codeine and opium may be taken into consideration.
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References


