

# CLINICAL MANAGEMENT

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## Chronic Diarrhea

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### Clinical Case

A 51-year-old woman presented with a 6-month history of diarrhea. She had 6–7 loose stools a day without bleeding or pain. The patient had not lost weight, and complete blood count and chemistry panel were unremarkable. Multiple stool tests for white blood cells, occult blood, and pathogens were negative, and a flexible sigmoidoscopy by her internist was normal.

### Background

Even experienced clinicians shudder a bit when confronted with a patient who has chronic diarrhea. The differential diagnosis is vast, and sorting through the pertinent history can be time-consuming. Although the evaluation can be taxing, making an accurate diagnosis is rewarding, because effective therapy is available for many of the conditions that cause chronic diarrhea.<sup>1</sup>

Chronic diarrhea is a common condition. By one estimate, diarrhea lasting more than 4 weeks occurs in up to 3%–5% of the population.<sup>1</sup> Other estimates place the prevalence of chronic diarrhea at closer to 1%.<sup>2</sup> Many patients do not seek medical attention unless their diarrhea is associated with other symptoms, such as weight loss, fecal incontinence, rectal bleeding, or abdominal pain. Unlike acute diarrhea, which is mostly self-limited, chronic diarrhea often persists unless some therapy is instituted; this makes an accurate diagnosis central to effective management.

The effect of chronic diarrhea on quality of life and health-care expenses is considerable. Especially if accompanied by urgency of defecation or fecal incontinence, diarrhea has a devastating effect on self-confidence and employability. The economic impact of chronic diarrhea on society can be estimated from the American Gastroenterological Association Burden of Illness study that showed direct costs of chronic diar-

rhea at \$524 million per year and indirect costs of at least \$136 million per year.<sup>2</sup> Even more important is the burden on individuals: many sufferers have to quit jobs and become recluses for fear of accidents in public.

The fundamental pathophysiology of all diarrhea is incomplete absorption of water from the lumen either because of a reduced rate of net water absorption (related to impaired electrolyte absorption or excessive electrolyte secretion) or because of osmotic retention of water intraluminally.<sup>3</sup> Reduction of net water absorption by as little as 1% may be sufficient to cause diarrhea, and thus even relatively modest compromise of absorptive function can lead to loose stools. It is no wonder, therefore, that many conditions can be associated with diarrhea (Table 1).

### Potential Management Strategies

Three different strategies can be applied to the management of chronic diarrhea: (1) test and treat; (2) categorize, test, and treat; and (3) empirical therapy. Selection of the appropriate strategy depends on the specific presentation of the patient.

#### Test and Treat

After a thorough interview and examination of the patient, one could opt for developing a differential diagnosis and then testing for each possibility in turn until a diagnosis is made. Specific treatment could then be applied. The effectiveness of this approach depends on the pretest probability that the proposed diagnosis is correct and the operating characteristics of the diagnostic tests used.<sup>4</sup> In some cases this approach may be appropriate, but in most cases it is impractical.

**Table 1.** Differential Diagnosis of Chronic Diarrhea Classified by Typical Stool Characteristics

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Watery diarrhea
Osmotic diarrhea
Mg <sup>2+</sup> , PO <sub>4</sub> <sup>-3</sup> , SO <sub>4</sub> <sup>-2</sup> ingestion
Carbohydrate malabsorption
Secretory diarrhea
Laxative abuse (nonosmotic laxatives)
Congenital syndromes
Bacterial toxins
Ileal bile acid malabsorption
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Microscopic (lymphocytic and collagenous) colitis
Diverticulitis
Vasculitis
Drugs and poisons
Disordered motility
Postvagotomy diarrhea
Postsympathectomy diarrhea
Diabetic autonomic neuropathy
Hyperthyroidism
Irritable bowel syndrome
Neuroendocrine tumors
Gastrinoma
VIPoma
Somatostatinoma
Mastocytosis
Carcinoid syndrome
Medullary carcinoma of thyroid
Neoplasia
Colon carcinoma
Lymphoma
Villous adenoma
Addison's disease
Epidemic secretory diarrhea
Idiopathic secretory diarrhea
Fatty diarrhea
Malabsorption syndromes
Mucosal diseases
Short-bowel syndrome
Postresection diarrhea
Mesenteric ischemia
Maldigestion
Pancreatic insufficiency
Bile acid deficiency
Inflammatory diarrhea
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Diverticulitis
Ulcerative jejunoileitis
Infectious diseases
Ulcerating viral infections
Cytomegalovirus
Herpes simplex
Ischemic colitis
Radiation colitis
Neoplasia
Colon cancer
Lymphoma

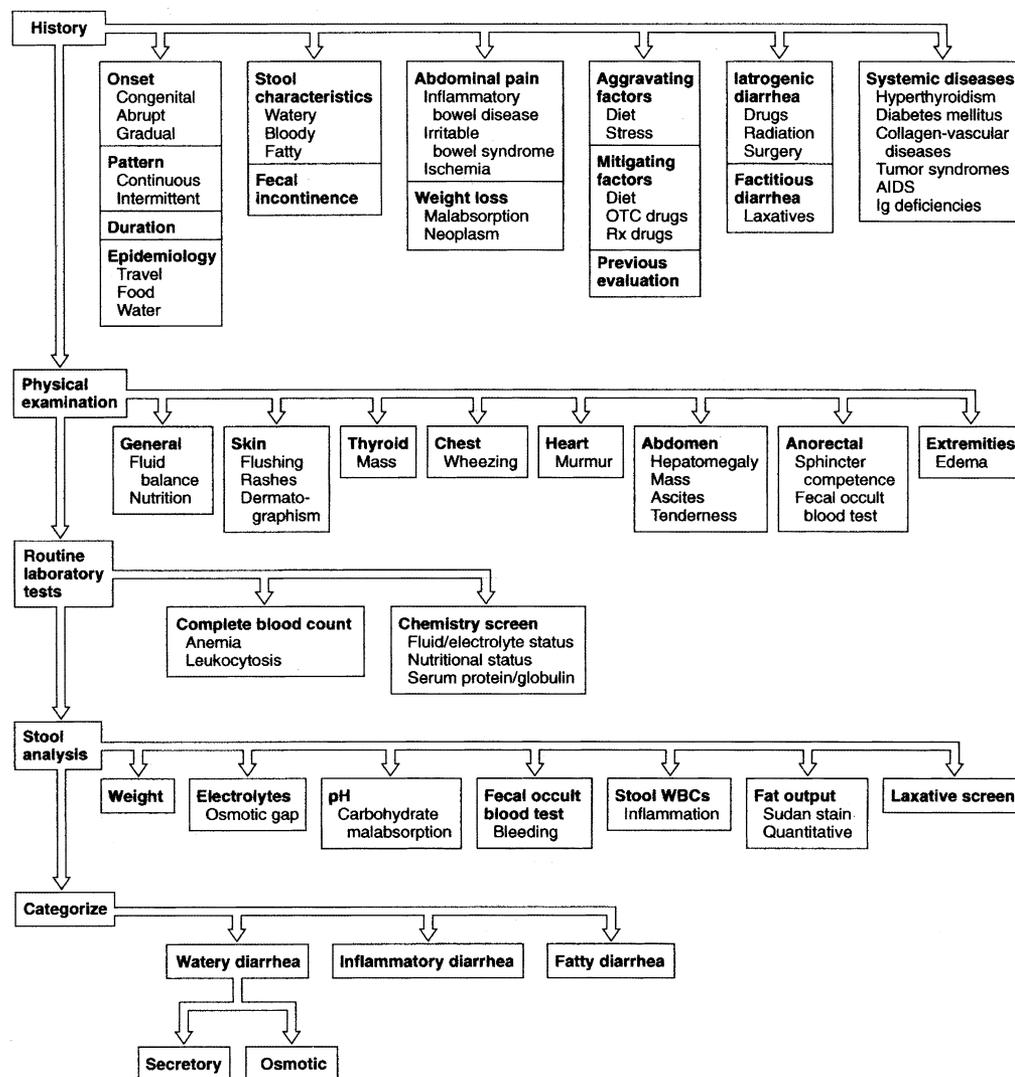
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For example, the pretest probability that a person in the population in general has a carcinoid tumor causing diarrhea is something in the order of 1 in 500,000 on the basis of the prevalence of this tumor syndrome

in the population.<sup>5</sup> In any patient with chronic diarrhea, the probability will be higher, perhaps 1 in 5000, on the basis of the prevalence of chronic diarrhea in the general population. Thus, testing every patient with chronic diarrhea for carcinoid tumor would yield a true-positive result only once for every 5000 patients tested (there would be many more positive tests, but these would be false-positive tests). However, testing a patient with chronic diarrhea who presents with flushing, a heart murmur, and a large liver is much more likely to yield the right diagnosis because the pretest probability of having a carcinoid tumor would be much higher given that particular scenario. If the patient in the clinical case had a history or physical findings more characteristic of a specific diagnosis, this might be the preferred approach.

### Categorize, Test, and Treat

An alternative and frequently more useful approach to diagnosis is to perform a series of preliminary tests to narrow down the possibilities.<sup>4</sup> This is preferable in most patients with chronic diarrhea because—as in the patient presented in this article—the history often is nonspecific, and physical findings are lacking. The basis for this approach is properly categorizing the diarrhea as watery, fatty, or inflammatory. Although gross inspection of stool can help with this distinction, analysis of a stool sample is usually definitive. The tests that can be performed on a stool sample to distinguish watery, fatty, and inflammatory diarrheas are stool sodium and potassium concentration, fecal occult blood test, fecal leukocytes (or, alternatively, fecal lactoferrin, an enzyme found in leukocytes), and measurement of stool fat, either quantitative (on a timed collection) or qualitative (Sudan stain).<sup>1</sup> A timed collection of stool (for 48 or 72 hours) is relatively easy to do and yields specific information about stool weight and fecal fat excretion. In situations in which this is difficult to do, a spot stool collection can give almost as much information and allows for accurate categorization. Once the diarrhea is categorized, the differential diagnosis becomes more manageable, and a more focused series of investigations can be pursued.<sup>1,3</sup> Examples of a scheme for investigation of chronic diarrhea based on this strategy of classifying the type of diarrhea to facilitate diagnosis are displayed in Figures 1 and 2, which also include additional suggestions for the evaluation of chronic diarrhea.



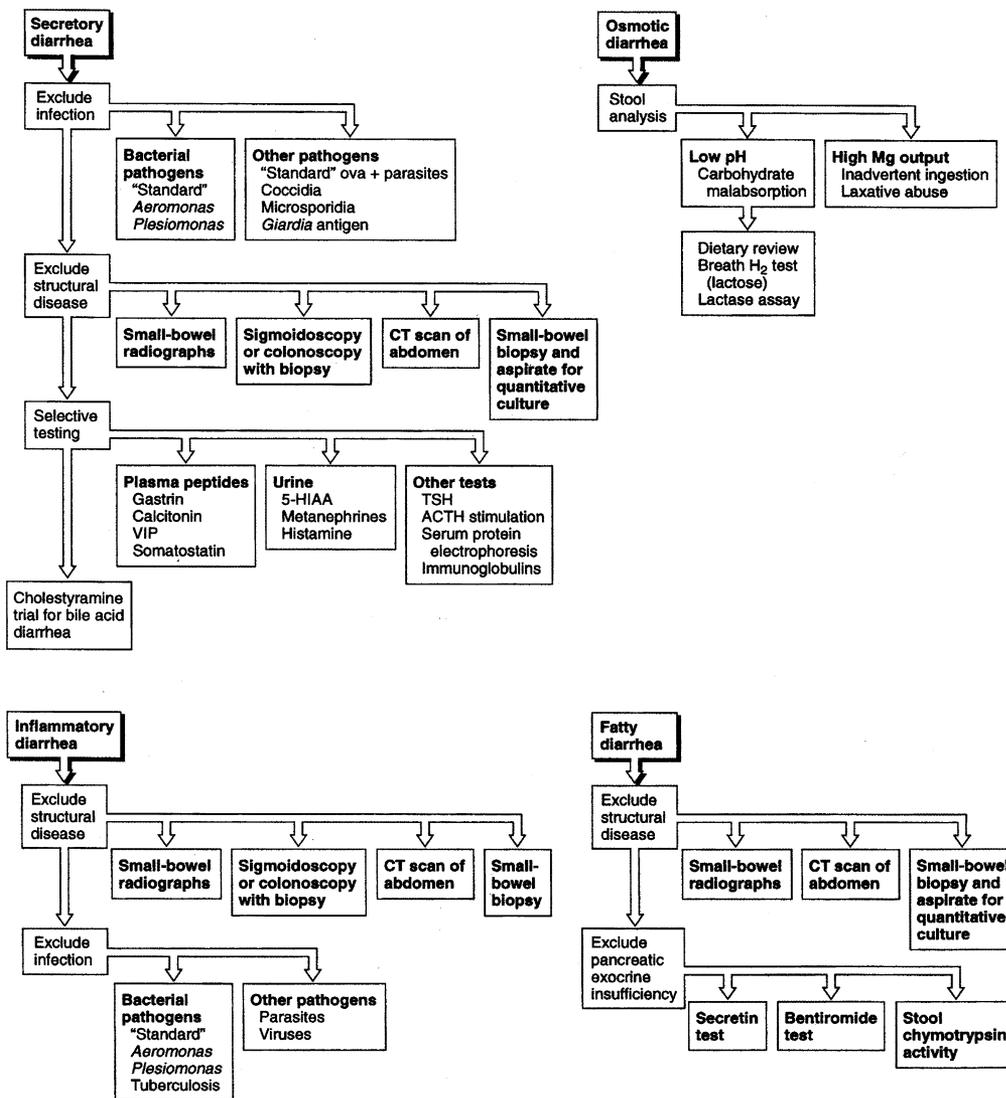
**Figure 1.** “Mind map” for the initial evaluation and classification of chronic diarrhea.<sup>1</sup> AIDS, acquired immunodeficiency syndrome; Ig, immunoglobulin; OTC, over the counter; Rx, prescription; WBC, white blood cell.

### Empirical Therapy

Another strategy avoids proving a diagnosis at all. The physician could treat diarrhea empirically with either nonspecific antidiarrheal drugs or a series of more specific treatments without making a definite diagnosis. This strategy makes sense only if life-threatening and specifically treated conditions can be excluded by history, physical examination, and relatively simple tests, leaving only functional or self-limited conditions as possibilities. Whereas many of the conditions in the differential diagnosis of chronic diarrhea (Table 1) are functional or self-limited, some are not, and these cannot always be distinguished by simple means from those that are. This makes this strategy potentially perilous for the patient and could delay specific curative treatment in some cases. However, many causes of chronic diarrhea are nonfatal or self-limited conditions that do not have any specific

treatment, so empirical antidiarrheal therapy may be appropriate at times. For example, irritable bowel syndrome can be diagnosed on the basis of history and simple tests to look for alarming findings that warrant further investigation. If a patient meets diagnostic criteria for irritable bowel syndrome and lacks alarming findings, it is very unlikely that any other diagnosis will be made in follow-up.<sup>6</sup> Thus, empirical treatment might be very suitable in that setting. If an empirical treatment strategy is adopted, however, it is essential that the patient be observed closely.

The selection of an appropriate management strategy depends on the specific situation of the patient and the physician’s confidence that the patient has a specific diagnosis or is likely to have a functional or self-limited problem. When a specific diagnosis is likely because of the history, physical findings, or setting, the test-and-treat strategy is likely to be the



**Figure 2.** “Mind maps” for the further evaluation of secretory, osmotic, fatty, and inflammatory diarrheas.<sup>1</sup> CT, computed tomography; VIP, vasoactive intestinal polypeptide; 5-HIAA, 5-hydroxyindoleacetic acid; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone.

most cost-effective. If a functional or self-limited disorder is likely, empirical therapy without much diagnostic evaluation may be the best strategy. For all other situations in which no specific diagnosis is very likely and the possibility of a specifically treatable condition is more than vanishingly small, the categorize, test, and treat strategy should minimize the expense of diagnostic testing and get to the right answer expeditiously.

### Recommended Management Strategy

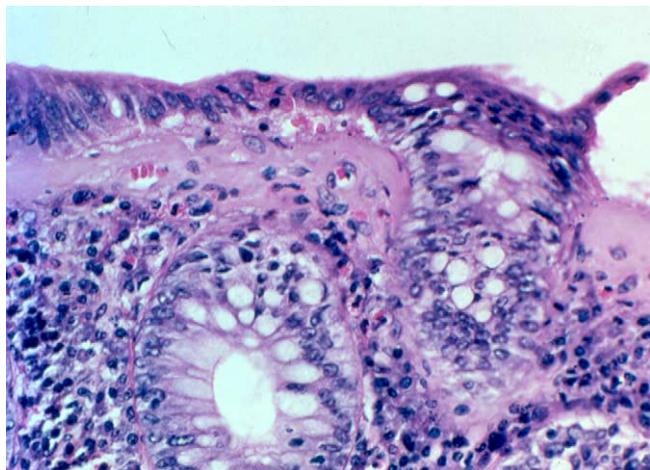
In this patient, the history and physical examination were nonspecific, so the test-and-treat strategy would not be efficient. She also did not meet diagnostic criteria for irritable bowel syndrome<sup>6</sup> and had the potential of having a specifically treatable condition, making the empirical ther-

apy approach less likely to be successful. This left the categorize, test, and treat strategy as the best approach.

The first goal should be to categorize the diarrhea as being watery, inflammatory, or fatty. The laboratory tests performed by her internist were of some value in this regard: the absence of fecal leukocytes, fecal occult blood, and mucosal changes on sigmoidoscopy excluded chronic inflammatory diarrhea from the differential diagnosis. Additional preliminary studies needed included stool electrolytes to sort out secretory and osmotic forms of watery diarrhea and a measure of fecal fat excretion to exclude steatorrhea. A more focused diagnostic evaluation could then follow.

### Evolution of Case

Additional tests were performed and included stool sodium concentration (80 mmol/L),



**Figure 3.** Photomicrograph of colon biopsy specimen.

stool potassium concentration (55 mmol/L), and qualitative fecal fat (Sudan stain; negative). Colonoscopy with biopsies from throughout the colon was performed next. The mucosa of the terminal ileum and colon appeared normal. A representative biopsy specimen from the colon is shown in Figure 3.

### Subsequent Management

The absence of excess fecal fat eliminated chronic fatty diarrhea as a potential diagnostic category. This left chronic watery diarrhea as the remaining category. Determining whether this was a case of chronic osmotic diarrhea or chronic secretory diarrhea could best be performed by calculation of the fecal osmotic gap.<sup>7</sup> The principle behind this calculation is that in secretory diarrhea, water is held intraluminally by incompletely absorbed electrolytes, whereas in osmotic diarrhea, electrolyte absorption is normal, and water is held intraluminally by the poorly absorbed, osmotically active substance. Thus, secretory diarrheas have high electrolyte concentrations, and osmotic diarrheas have low electrolyte concentrations. The contribution of electrolytes to stool osmolality is calculated by doubling the sum of the sodium and potassium concentrations to account for the anions accompanying these cations. This product is then subtracted from 290 mOsm/kg, the osmolality of intraluminal contents in the gut (the small bowel and colon are too permeable to water to allow a substantial difference in osmolality between the lumen and plasma; measured stool osmolality increases rapidly *in vitro* because of bacterial metabolism and therefore should not be used in this calculation). This is the fecal osmotic gap. Values <50 mOsm/kg are consistent with secretory diarrhea, and values >50 mOsm/kg are consistent with osmotic diarrhea.<sup>7</sup>

In our case, the stool sodium concentration was 80 mmol/L, and the stool potassium concentration was 55 mmol/L, making the fecal osmotic gap equal to  $290 - 2 \times (80 + 55)$  or 20 mOsm/kg, clearly in the range of a secretory diarrhea. The most likely diagnoses in a middle-aged woman with a history of new-onset secretory diarrhea without evidence of systemic disease, infection, or inflammation would be microscopic colitis syndrome (lymphocytic colitis or collagenous colitis) or chronic idiopathic secretory diarrhea. On the basis of the referral population of patients with chronic diarrhea seen in a tertiary referral center, the prevalence of both microscopic colitis syndrome and chronic idiopathic secretory diarrhea is approximately 10%–20% each.<sup>8,9</sup>

The next test should be one that can distinguish between these 2 possibilities. Biopsy of the colon can do that. The main issue is whether to perform sigmoidoscopy or colonoscopy to obtain the biopsy samples.<sup>9</sup> Colonoscopy affords the opportunity to examine the entire colon, and, in some situations, such as diarrhea in a patient with acquired immunodeficiency syndrome, this may be valuable. For finding microscopic colitis, biopsy samples from any portion of the colon are likely to be positive (<10% of patients with microscopic colitis will have negative rectosigmoid biopsy results), so the decision about what test to perform depends on other factors.<sup>10</sup> In this patient a full colonoscopy could be justified on the basis of a need for colon cancer screening. Were that not a factor, biopsy specimens from the rectosigmoid colon would most likely be adequate for diagnosis.

The histological picture of the colon biopsy specimen (Figure 3) was characteristic of collagenous colitis.<sup>11</sup> The key findings were a plasmacytic infiltrate in the lamina propria, little evidence of crypt destruction, an increase in intraepithelial lymphocytes, loss of regularity of the columnar epithelium, and, of course, thickening of the subepithelial collagen table, which gives this condition its name. It is important to note that although mucosal inflammation was present, the diarrhea produced in this condition is categorized as secretory and not inflammatory. This is because the mucosa stays intact; there usually is no bleeding or pus in the stools. These patients have reduced water and electrolyte absorption in the colon because of the inflammatory changes<sup>10</sup> and so have excess stool water.<sup>12</sup>

### Management of Collagenous Colitis

The fundamental causes of collagenous colitis are not known. Most patients with this diagnosis are women with autoimmune problems, such as arthritis, thyroid disease, or diabetes, so it may have an autoimmune basis.<sup>11,13</sup> Many patients with collagenous colitis have

HLA-DQ types similar to those of patients with celiac disease, raising the possibility that the condition relates to antigen presentation by the immune system (although the antigen is not likely to be gluten).<sup>14</sup> We do not at present have any proven dietary advice or management for this condition.

Nonspecific treatments also have a limited role. Stool weight rarely exceeds 800 g/24 hours, so dehydration is not a major issue unless access to salt and water is restricted. Therefore, oral or intravenous hydration usually is not needed. Antidiarrheal drugs have a mixed record in these patients. In some, regular use of opiate antidiarrheal drugs can reduce diarrhea sufficiently; in others, they are ineffective. They may be of most use in patients with coexisting fecal incontinence, but this has not been established.<sup>15</sup>

When microscopic colitis syndrome was first being defined in the 1980s, therapy was based on treatments for more established forms of inflammatory bowel disease, such as ulcerative colitis and Crohn's disease.<sup>11</sup> The initial treatments used included 5-aminosalicylate drugs and corticosteroids in doses similar to those used for ulcerative colitis. Many reports of response to these and other agents were published, but it has been difficult to judge effectiveness in the absence of controlled trials. This is particularly true in this condition, because it tends to have spontaneous remissions.<sup>16</sup>

In most published series of cases, use of 5-aminosalicylate drugs resulted in mitigation of diarrhea in up to 40% of patients.<sup>11</sup> There was little effect on histology when this was evaluated, and relapse was frequent. There was no clear advantage to any of the various 5-aminosalicylate drug preparations when used in standard doses. Nevertheless, because these drugs have an enviable safety and tolerance record, they are often tried first by many experienced clinicians.<sup>17,18</sup> Results should be apparent within 1 month.

Anomalously high doses of systemic corticosteroids are needed to control symptoms in microscopic colitis syndrome as compared with ulcerative colitis.<sup>11</sup> Typically, 60–80 mg of prednisone daily may be required. One recent small study from Denmark suggested that prednisolone 50 mg/day for 2 weeks induced an incomplete remission in patients with microscopic colitis, although statistically not more often than placebo.<sup>19</sup> Because many patients with microscopic colitis are older, the risk of complications with high-dose steroids may be prohibitive. Results should be seen within 1 month, but diarrhea may recur as the steroid is tapered.

Other immunosuppressive drugs have been tried and reported in isolated case reports.<sup>11</sup> These include 6-mer-

captapurine and azathioprine. Patients respond to low doses, but it may take several months for any effect to be seen. These drugs could be considered when patients cannot be weaned from corticosteroids.

Because of its anti-inflammatory and antibacterial effects, bismuth subsalicylate was tried in microscopic colitis syndrome. In one series, 90% of patients had a clinical remission, and 80% had histological improvement.<sup>20</sup> This effect was duplicated subsequently in a small controlled trial, suggesting that this agent has a real place in treatment.<sup>21</sup> Most patients who will respond have had a clinical response within 1 month. It is recommended that responders continue treatment for an additional month to increase the chance of a durable remission. Because bismuth subsalicylate is inexpensive, well tolerated, and associated with a high response rate, it is the initial therapy of choice for microscopic colitis.

Two agents have been subjected to larger controlled clinical trials: cholestyramine and budesonide. Cholestyramine was better than placebo at controlling diarrhea and inducing histological remission in one European study.<sup>22</sup> It was useful not only in the subset of patients with bile acid malabsorption (as defined by a radioisotope retention method), but also in patients without coexisting bile acid malabsorption, suggesting that the resin may have been binding some other intraluminal substance that was causing the problem. Bile acid-binding resins are difficult to take regularly, so compliance may be an issue when these drugs are prescribed.

Budesonide is a corticosteroid that has a high hepatic first-pass metabolism, which effectively limits it to a topical effect in the intestine. It has been used topically for allergic rhinitis and for asthma, with a good safety record. Ingested budesonide can produce systemic corticosteroid side effects when used chronically, so the drug should be tapered as soon as feasible. Individual studies<sup>23–25</sup> and a meta-analysis<sup>26</sup> show that budesonide is superior to placebo in inducing both clinical and histological remission in microscopic colitis. Of all the available treatments, it has the best evidence basis for efficacy.

In choosing therapy for an individual patient, the physician must balance the peculiarities of a particular patient, the potential benefit and risks of a given drug, and the costs involved. In most patients with microscopic colitis, it makes sense to use opiate antidiarrheal drugs for their symptomatic benefit, to try bismuth subsalicylate for 1 month with an additional month of therapy for responders, and to reserve budesonide for those who do not respond to 1 month of bismuth therapy. Cholestyramine and 5-aminosalicylates should be

reserved for those who do not respond to budesonide or who relapse quickly when it is tapered and withdrawn.

## Conclusion

Chronic diarrhea is a challenging condition to evaluate and treat. By approaching each case individually and selecting an appropriate management strategy, a long differential diagnosis can be made more manageable, and the appropriate treatment can be ordered. Microscopic colitis is a common cause of chronic diarrhea. Although its etiology remains unknown, effective treatments are available.

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