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Bile Acids: An Underrecognized and Underappreciated Cause of Chronic Diarrhea



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Bile acid malabsorption is a common cause of chronic watery diarrhea; however, its role appears to be poorly appreciated among clinicians. As such, bile acid diarrhea remains an underrecognized cause of chronic diarrhea, resulting in many patients incorrectly diagnosed and interfering and delaying proper treatment. In this review, we briefly discuss the synthesis, enterohepatic circulation, and function of bile acids. We then focus on the role of bile acids in bile acid malabsorption including the diagnostic and treatment options. By recognizing that bile acid malabsorption is a relatively common cause of chronic diarrhea, we hope that more physicians will more effectively evaluate and treat patients with this condition.

INTRODUCTION

Diarrhea caused by bile acids was first recognized in 1967, when Alan Hofmann described this phenomenon as choleric enteropathy.¹ Despite more than 40 years since the initial report, bile acid diarrhea remains an underrecognized and underappreciated cause of chronic diarrhea. One recent report found that only 6% of British gastroenterologists investigate for bile acid malabsorption (BAM) as part of the first-line testing in patients with chronic diarrhea, while 61% consider the diagnosis only in selected patients or not at all.² As a consequence, many

patients are diagnosed with other causes of diarrhea or are considered to have irritable bowel syndrome or functional diarrhea by exclusion, thereby interfering with, and delaying proper treatment. The goal of this review is to raise awareness of this clinical condition so that it may be considered in the differential diagnosis of chronic diarrhea. We will first review bile acid synthesis and enterohepatic circulation, followed by a discussion of specific disorders involving BAM including their diagnosis and treatment.

Bile Acid Synthesis

Bile acids are produced in the liver as end products of cholesterol metabolism. Bile acid synthesis occurs by two pathways: the classical (neutral) pathway via

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microsomal cholesterol 7 α -hydroxylase (CYP7A1), or the alternative (acidic) pathway via mitochondrial sterol 27-hydroxylase (CYP27A1). The classical pathway, which is responsible for 90-95% of bile acid synthesis in humans, begins with 7 α -hydroxylation of cholesterol catalyzed by CYP7A1, the rate-limiting step (Figure 1).³ This pathway occurs exclusively in the liver and gives rise to two primary bile acids: cholate and chenodeoxycholate. Newly synthesized bile acids are conjugated with glycine or taurine and secreted into the biliary tree; in humans, most of the bile acids are conjugated to glycine.⁴ Conjugation is a very important step in bile acid synthesis converting weak acids to strong acids, which are fully ionized at biliary and intestinal pH, making them hydrophobic (lipid soluble) and membrane impermeable. These properties aid in digestion of lipids and also decrease the passive diffusion of bile acids across cell membranes during their transit through the biliary tree and small intestine.⁵ This allows maximum lipid absorption throughout the small intestine without sacrificing bile acid loss.

Enterohepatic Circulation

After their involvement in micelle formation, about 95% of the conjugated bile salts are reabsorbed in the terminal ileum and returned to the liver via the portal venous system for eventual recirculation in a process known as enterohepatic circulation; only a small proportion (3-5%) are excreted into the feces.^{6,7}

Enterohepatic circulation requires carrier-mediated transport by the terminal ileal enterocytes and the hepatocytes by means of both apical and basolateral transporters.⁸ First, the bile acids are actively transported from the intestinal lumen into the enterocyte via a network of efficient sodium-dependent apically located co-transporters (ileal bile acid transporters) (6,7) in the distal ileum up to 100 cm proximal to the ileocecal valve.⁹ The bile acids are then transported into the portal venous system via a basolateral transport system consisting of 2 proteins, organic solute transporter (OST)- α and OST- β , and returned to the liver. In the liver, they are efficiently extracted by basolateral transporters on the hepatocytes and added to the bile acid pool. The liver must then only replace the small amount of bile acids that are not recirculated and instead excreted into the feces (about 0.3-0.5 g/day). In humans, approximately 12 g of bile acids are secreted into the intestine daily. Efficient recycling allows the maintenance of a bile

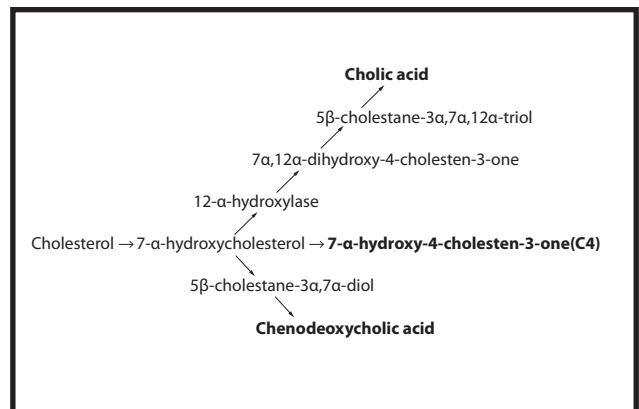


Figure 1. Classical pathway of bile acid synthesis. Note the production of the primary bile acids, cholic acid and chenodeoxycholic acid, and the intermediate, C4.

acid pool of about 2-3 g which typically cycles 4-6 times/day.¹⁰

The size of the bile acid pool is tightly controlled by a complex regulatory pathway. Bile acid synthesis is under negative feedback regulation by which bile acids downregulate their own biosynthesis by binding to the nuclear receptor, farnesoid X receptor (FXR), thereby inducing the synthesis of a repressor protein which downregulates the rate-limiting enzyme in bile acid synthesis, CYP7A1.¹¹ Recently, fibroblast growth factor 19 (FGF19), acting via FXR, was shown to be stimulated by bile acids in the ileal enterocyte.¹² FGF19 is then released from the enterocyte and travels to the liver where, acting together with β -klotho, it activates the FGF receptor 4 (FGFR4) on the hepatocyte leading to a phosphorylation cascade that downregulates bile acid synthesis (Figure 2).¹³

As previously noted, a small proportion of the secreted bile acids reach the colon where they are deconjugated (removing the taurine or glycine) and dehydroxylated (removing the 7-OH group) by bacteria to produce the secondary bile acids, deoxycholate and lithocholate. A small fraction of these secondary bile acids are absorbed by the colonic epithelium; however, most are eliminated in the feces.

Bile Acid Function

Bile acids play a key role in the absorption of lipids in the small intestine. Upon stimulation by a meal (via cholecystokinin release), bile acids are expelled from the gallbladder into the bile duct and then enter the lumen of the small intestine where they solubilize dietary lipids in a multistep process.¹⁴ First, they

emulsify the lipids, allowing the droplets to disperse and increasing the surface area for digestive enzymes. Next, they form micelles with the products of lipid digestion, allowing the normally hydrophobic lipids to dissolve into the aqueous luminal environment. The micelles then diffuse to the brush-border membrane of the intestinal epithelium whereby the lipids are released from the micelles and diffuse down their concentration gradients into the cells. Once released, the bile acids are left behind in the intestinal lumen until they are absorbed in the terminal ileum. Their presence in the intestinal lumen allows maximal absorption of lipids throughout the small intestine; however, the majority of fat absorption occurs in the proximal 100 cm of the jejunum.

Multiple other functions of bile acids have also been described,¹ including:

- Contributing to cholesterol metabolism by promoting the excretion of cholesterol
- Denaturing dietary proteins, thereby accelerating their breakdown by pancreatic proteases.¹⁵
- Having direct and indirect antimicrobial effects.¹⁶ In this capacity, recent evidence suggests bile acids are mediators of high-fat diet-induced changes in the gut microbiota.¹⁷
- Acting as signaling molecules outside of the gastrointestinal tract,¹⁸ thereby representing another mechanism by which the gut microbiota influences the metabolism of the host.

Role of Bile Acids in Diarrheal Disorders

Excess bile acids entering the colon contribute to the classical symptoms associated with BAM including watery diarrhea, bloating, fecal urgency and fecal incontinence by stimulating colonic secretion and motility. Bile acids stimulate secretion in the colon by activating intracellular secretory mechanisms, increasing mucosal permeability, inhibiting Cl^-/OH^- exchange and enhancing mucus secretion.¹⁹ Colonic water secretion depends on the concentration of bile acids, with concentrations typically above 3 mmol/L leading to secretion.²⁰ Bile acids stimulate motility by inducing propulsive contractions thereby shortening colon transit time, potentially worsening urgency and

diarrhea.^{21,22} Interestingly, a recent study suggests that low concentrations of bile acids downregulate colon secretion and promote fluid and electrolyte absorption.²³ In contrast, when colonic luminal concentrations of bile acids are high, as is seen in BAM, bile acids induce prosecretory and promotility effects, manifesting clinically as diarrhea.

Prevalence of Bile Acid Diarrhea

Due to the limited availability of diagnostic tests for BAM, its prevalence remains unclear. The availability of the ⁷⁵Selenium-homocholic acid taurine (SeHCAT) retention test (see below) in Europe has, nevertheless, allowed an estimate of its prevalence, at least in the Western world. A systematic review of studies that estimated the prevalence of primary bile acid diarrhea using the SeHCAT test in patients with chronic unexplained diarrhea [most of whom were classified as diarrhea-predominant irritable bowel syndrome (D-IBS)] identified 18 studies involving 1223 patients.²⁴ At the best confidence interval (<10%) for SeHCAT retention percentage, one-third of patients had an abnormal result suggesting BAM. Using this figure, these investigators have estimated the population prevalence of bile acid diarrhea based upon the population with D-IBS. For example, if it's estimated that approximately 90 million people worldwide suffer from IBS, approximately one-third, or 30 million, have D-IBS, of whom about one-third, or 10 million, will have bile acid diarrhea. In the United Kingdom, the prevalence in the general population has been estimated to be over 1%.²⁴ Therefore, although bile acid diarrhea is often considered rare, this appears not to be the case.

Diagnosis of Bile Acid Diarrhea

The diagnosis of BAM is difficult as measurement of fecal bile acids in a 24-hour stool collection, the definitive method, is unpleasant and is available only in a few research laboratories. Additionally, the SeHCAT test, a nuclear medicine test more appropriate for clinical practice that measures loss of bile acids in a simple and reliable manner, has never been approved for use in the United States and is not widely available in the rest of the world. This has clearly hindered the recognition of BAM in patients with chronic diarrhea. Another test of BAM that has fallen from favor and is more of historical interest is the ¹⁴C-glycocholate breath test.²⁵

In the SeHCAT test, first described in 1981, the selenium-labeled bile acid is administered orally and the

total body retention is measured with a gamma camera after 7 days.²⁶ A retention value of less than 10% is indicative of BAM and highly predictive of a successful therapeutic response to bile acid sequestrants.^{24, 27} This test has a sensitivity for diagnosing BAM of 80-90% and a specificity of 70-100%, and offers a low radiation dose to the patient.²⁸

More recently, the measurement of 7- α -hydroxy-4-cholesten-3-one (C4) levels in the plasma has been proposed as an indicator of BAM.²⁹ Plasma C4 levels increase when bile acid synthesis increases, and C4 levels are substantially elevated in BAM patients with a sensitivity and specificity of 90% and 77%, respectively for type 1 BAM (see below) and 97% and 74%, respectively for type 2 BAM (see below).³⁰ Furthermore, C4 levels have been shown to correlate well with SeHCAT retention.³¹ Despite its obvious advantages in the diagnosis of BAM, to our knowledge, at present, this test is available for research use only. Perhaps with the expanding availability of mass spectroscopy in diagnostic laboratories, this test will become more widely available.³²

Given the limited diagnostic testing for BAM currently available, particularly in the United States, a "therapeutic trial" with a bile acid sequestrant (see below) is often used as a diagnostic tool. If the treatment results in resolution or improvement of the diarrhea, the response is considered supportive evidence of BAM. This approach is supported by the pooled data from a report showing a dose-response relationship according to severity of malabsorption, as determined by SeHCAT retention, to treatment with a bile acid sequestrant.²⁴ Although this approach has the advantage of not requiring specialized investigations, as treatment is often poorly tolerated and response variable, this strategy is difficult to strongly advocate without a definitive diagnosis.

Bile Acid Malabsorptive Disorders

Many conditions cause BAM and may be divided into three types depending upon their etiology (Table 1).³³ Type 1 BAM results from terminal ileal resection/bypass or disease (e.g., Crohn's disease) which results in failure of enterohepatic recycling of bile acids and excess amounts entering the colon. Type 2 BAM, often referred to as primary (or idiopathic) bile acid diarrhea, occurs in the setting of otherwise normal (grossly and histologically) gastrointestinal and hepatobiliary systems. Potential mechanisms contributing to this type

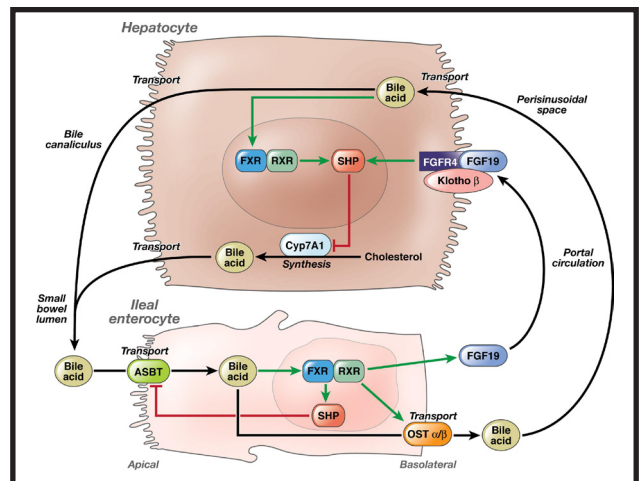


Figure 2. Molecular mechanisms responsible for the control of bile acid synthesis. See text for details.

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of BAM are discussed below. Finally, type 3 BAM includes causes of BAM not included with types 1 and 2 that may interfere with normal bile acid cycling, small intestinal motility or composition of ileal contents. A selection of specific causes of BAM is discussed further below.

Short Bowel Syndrome

Terminal ileum resection affects the reabsorption of bile acids into the enterohepatic circulation. Resection of less than 100 cm of terminal ileum will interrupt the normal feedback, resulting in increased bile acid synthesis and an increased concentration of unabsorbed bile acids entering the colon.^{27, 34} When more than 100 cm of distal ileum in adults is resected, the most common bowel anatomy in short bowel syndrome (SBS), the resulting reduction in bile acid absorption exceeds the liver's ability to synthesize adequate replacement. This ultimately results in a decreased bile acid pool with impaired micelle formation and fat digestion, and manifests clinically as steatorrhea and fat soluble vitamin deficiencies. Maximum bile acid synthesis (5-10 mmol/day) is less than daily bile acid secretion in healthy patients (about 25-30 mmol/day).³⁵

Further aggravating bile acid function in SBS is the common occurrence of small intestinal bacterial overgrowth which results in the deconjugation of bile

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acids in the small bowel.³⁶ Moreover, the absence of the ileum also contributes to the diarrhea because of both the loss of epithelial absorptive capacity and loss of the “ileal brake” resulting from diminished production of motility-inhibiting gut hormones (glucagon-like peptide 1 and peptide YY) that are produced in the L cells of the distal ileum and proximal colon.³⁷ In SBS patients with residual colon, the synthetic conjugated bile acid, cholylsarcosine, was shown to increase fat absorption and body weight without aggravating diarrhea.³⁸ Ox bile supplementation has also shown benefit in an uncontrolled case study.³⁹ Unfortunately, these products are not commercially available. The use of bile acid sequestrants, such as cholestyramine, may worsen fat digestion and should generally be avoided in the SBS patient.

Diarrhea-predominant Irritable Bowel Syndrome

BAM has been documented in up to 50% of patients diagnosed with functional diarrhea and D-IBS.^{40,41} Ileal perfusion of bile acids has been shown to result in greater ileal fluid secretion in IBS patients compared to healthy volunteers.⁴² In a small, randomized, double-blind, placebo controlled trial of colesevelam hydrochloride, a bile acid sequestrant, in patients with D-IBS, colonic transit at 24 hours was delayed in the ascending colon by an average of 4 hours compared with placebo. It was also associated with greater ease of stool passage and somewhat firmer stool consistency.⁴³ Recently, single nucleotide polymorphisms of FGFR4 and β -klotho were found that identified a subset of D-IBS patients who received a beneficial response to colesevelam.⁴⁴

Microscopic Colitis

Up to 43% of patients with microscopic colitis have evidence of BAM^{45,46} with a high response rate to treatment using a bile acid sequestrant suggesting a pathophysiological role of bile acids in this condition.⁴⁷ In a study of 51 patients with either lymphocytic or collagenous colitis, 22 (43.1%) patients were found to have BAM.⁴⁶ The frequency of BAM was higher in lymphocytic colitis than in collagenous colitis (60% vs 27%). Treatment with a bile acid sequestrant induced clinical remission in 19 of 22 patients with both microscopic colitis and BAM; no clinical remission was seen in patients without BAM. Therefore, BAM

Table 1. Causes of Bile Acid Malabsorption

Etiology of BAM	Consider BAM if Symptomatic
Type 1	<ul style="list-style-type: none"> Terminal ileal resection or bypass Terminal ileal disease (e.g., Crohn's disease)
Type 2	<ul style="list-style-type: none"> No definitive etiology No demonstrative ileal disease
Type 3	<ul style="list-style-type: none"> Small intestinal bacterial overgrowth Post-cholecystectomy Post-vagotomy Celiac disease Radiation enteritis Chronic pancreatitis

seems to be common in patients with microscopic colitis, particularly lymphocytic colitis, suggesting that idiopathic BAM and microscopic colitis are often concomitant conditions. In this setting, bile acid sequestrant use seems to be highly effective in stopping diarrhea.

Primary Bile Acid Diarrhea

Limitations of the data notwithstanding, as discussed earlier, it would appear that idiopathic or primary bile acid diarrhea (PBAD) is the most common cause of BAM and may account for at least 30% of individuals who would otherwise be labeled as having D-IBS or functional diarrhea. Importantly, the current definition of PBAD requires that there be a grossly and histologically normal ileum and good response to treatment with a bile acid sequestrant. Despite much investigation, until recently the pathogenesis of PBAD

Table 2. Commercially-available Bile Acid Sequestrants

Drug	Dosage	Side Effects	Comments
Cholestyramine (Questran®, Questran® Light, Prevalite®, LoCHOLEST®, LoCHOLEST® Light)	4-gram packet 1 to 6 times/day	Nausea, vomiting, flatulence, bloating, abdominal discomfort, constipation, fecal impaction, anorexia, steatorrhea, urticaria	<ul style="list-style-type: none"> • Poor taste may affect adherence • May interfere with the absorption of some medications (warfarin, diuretics, thyroid hormone, beta-blockers, digoxin) and fat-soluble vitamins; medications should be taken 1-hour before or > 4-hours after bile acid sequestrant administration
Colestipol (Colestid®)	5-gram packet 1 to 6 times/day Tablet form also available	Same as above	<ul style="list-style-type: none"> • Same as above
Colesevelam (WelChol®)	1.25 to 3.75 g/day	Constipation, dyspepsia, nausea, nasopharyngitis, headache, asthenia, influenza-type symptoms, rhinitis, hypoglycemia in diabetic patients, myalgias, hypertension	<ul style="list-style-type: none"> • Does not decrease the absorption of co-administered medications

has been poorly understood. A number of mechanisms have been proposed including mutations in ileal bile acid transporters and rapid small bowel transit causing diminished ileal epithelial contact time.⁴⁸⁻⁵³ Neither of these mechanisms, however, have strong supporting data nor have the findings not been consistently demonstrated.

Most recently, a role of altered feedback inhibition of bile acid synthesis has been proposed and its support is gaining momentum.⁵⁴ This altered feedback regulation

is thought to be mediated by FGF19 (fibroblast growth factor 19).⁵⁵⁻⁵⁷ Walters and colleagues recently found that patients with PBAD had a marked decrease in plasma levels of FGF19, about 50% that of controls, and this level correlated inversely with bile acid synthesis as measured by the serum level of the bile acid precursor 7- α -hydroxy-4-cholesten-3-one (aka "C4", see Figure 1).⁵⁸ As a consequence of this deficiency, the hepatocytes are unable to downregulate bile acid synthesis. It was speculated that this disrupted feedback

Table 3. Tips to Making Bile Acid Sequestrants More Palatable

- Add powder to a half cup of applesauce or other fruit sauce, strained baby fruits or crushed pineapple and mix thoroughly
- Add powder to a half cup of fruit drink, juice, or other non-caffeinated drink and mix thoroughly
- Add powder to a half cup of milk or broth
- Refrigerate the mixture
- Stir well
- Mix it with half water to dissolve it first, then finish it off with a thick type juice/nectar or smoothie
- Try mixing with pudding or custard

control by FGF19 may result in a large bile acid pool with incomplete ileal absorption and increased bile acid delivery to the colon causing diarrhea. The exact nature of the defect that leads to altered FGF19 production or release requires further investigation.

Treatment of Bile Acid Diarrhea

Treatment of patients with bile acid diarrhea secondary to another cause (e.g., active Crohn's ileitis, microscopic colitis, small intestinal bacterial overgrowth) should target the underlying disease. Unfortunately, for most patients with bile acid diarrhea, no such cause is found or is effectively treatable. Therefore, for over 40 years, the treatment of bile acid diarrhea has relied on the use of oral administration of bile acid sequestrants.⁵⁹ These agents are positively charged indigestible resins that bind the bile acids in the intestine to form an insoluble complex that is excreted in the stool preventing their secretomotor actions on the colon. There are currently three bile acid sequestrants commercially available, albeit for a non-United States Food and Drug Administration (FDA)-labeled indication (i.e., off label use): cholestyramine, colestipol, and colesevelam (Table 2).

Cholestyramine and colestipol are FDA-approved for the treatment of hypercholesterolemia (both agents) and pruritus related to partial biliary obstruction (cholestyramine only). Most patients with abnormal SeHCAT retention have been found to respond to treatment with cholestyramine: 96% response in patients with SeHCAT retention <5%, 80% response when <10% retention, and 70% response when <15% retention.²⁴ However, as a powdered resin, their use has historically

been limited by their unpleasant taste, which can lead to poor adherence with long-term use. Indeed, 40% to 70% of patients given bile acid sequestrants discontinue them.^{60,61} Furthermore, gastrointestinal side effects are common and include nausea, borborygmi, flatulence, bloating, and abdominal discomfort which can be present in as high as 30% of patients.⁶² Constipation may also occur, making titration of the dose important. For cholestyramine, the most commonly used bile acid sequestrant, starting with one 4 gram packet a day (5 grams for colestipol) and titrating upward as needed (maximum 6 times/day for both agents) seems to be an effective strategy. Colestipol also comes in tablet form; a form worth considering if the powder form is poorly tolerated. Other tips for improving the palatability of bile acid sequestrants are mentioned in Table 3.

Colesevelam is a newer bile acid sequestrant that binds bile acids with a higher affinity than either cholestyramine or colestipol. Importantly, a tablet form is available, improving its patient acceptability.⁶³ Colesevelam is FDA-approved to treat hypercholesterolemia and, interestingly, as an adjunct treatment for type 2 diabetes mellitus. In a retrospective chart review and patient questionnaire, colesevelam at doses between 1.25 and 3.75 g/day was found to be well tolerated and effective in patients with BAM after cancer treatment, including some who had failed prior cholestyramine therapy.⁶⁴ As previously mentioned, colesevelam was found to be more effective than placebo in a small, randomized controlled trial in patients with D-IBS with regards to symptom control and colon transit.⁶⁵ Furthermore, single nucleotide

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polymorphisms of FGFR4 and β -klotho have been found that appear to identify a subset of D-IBS patients who may benefit from colestevlam.⁶⁶

Importantly, cholestyramine and colestipol interfere with the absorption of some medications (e.g., warfarin, diuretics, thyroid hormone, beta-blockers, digoxin) and fat-soluble vitamins. Therefore, these other medications should be taken 1-hour before or at least 4-hours after bile acid sequestrant administration. Apparently, colestevlam does not decrease the absorption of co-administered medications,⁶² presumably because of differences in chemical structure compared to cholestyramine and colestipol. Because bile acid sequestrants are not absorbed, they have no systemic side effects.

CONCLUSION

BAM appears to be a common cause of watery diarrhea; however, its role seems to be poorly appreciated among clinicians. As a consequence, bile acid diarrhea remains an underrecognized cause of chronic diarrhea and results in many patients receiving an incorrect diagnosis, thereby delaying proper treatment. Given the limitations in the availability of diagnostic testing and difficulties in completing an adequate empiric trial of a bile acid sequestrant, bile acid diarrhea is likely to remain a problematic diagnosis, at least for the near future. The development and validation of a relatively simple and inexpensive laboratory-based diagnostic test, such as the plasma measurement of C4, will hopefully change this scenario. Although the current treatment of BAM remains the use of bile acid sequestrants, the availability of colestevlam has improved patient tolerability to this form of therapy. Perhaps a more specific therapy, such as a FGF19 or FXR agonist, will become available for clinical use in the future. ■

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