Carol Rees Parrish, MS, RDN, Series Editor

Does Your Patient Have Bile Acid Malabsorption?

John K. DiBaise

Bile acid malabsorption is a common but underrecognized cause of chronic watery diarrhea, resulting in an incorrect diagnosis in many patients and interfering and delaying proper treatment. In this review, the synthesis, enterohepatic circulation, and function of bile acids are briefly reviewed followed by a discussion of bile acid malabsorption. Diagnostic and treatment options are also provided.

INTRODUCTION

In 1967, diarrhea caused by bile acids was first recognized and described as cholerhetic ('promoting bile secretion by the liver') enteropathy.[1] Despite more than 50 years since the initial report, bile acid diarrhea remains an underrecognized and underappreciated cause of chronic diarrhea. One 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 (IBS) or functional diarrhea by exclusion, thereby interfering with and delaying proper treatment. A key objective of this review is to raise awareness of this clinical condition so that it may be considered in the differential diagnosis of chronic diarrhea.

John K. DiBaise, MD Professor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ

We will first describe bile acid synthesis and enterohepatic circulation, followed by a discussion of disorders causing bile acid malabsorption (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 microsomal cholesterol 7α-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 7α-hydroxylation of cholesterol catalyzed by CYP7A1, the rate-limiting step.[3] This pathway occurs exclusively in the liver and gives rise to two primary bile acids: cholate and chenodeoxycholate. Importantly, as will be discussed further in the diagnosis of BAM section, 7-α-hydroxy-4-cholesten-3-one (aka, C4) is a metabolic intermediate in the rate limiting step for the synthesis of bile acids and correlates well with fecal

bile acid loss. 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, and 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 (Figure 1).[6,7]

Enterohepatic circulation requires carrier-mediated transport.[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-ß, 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 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
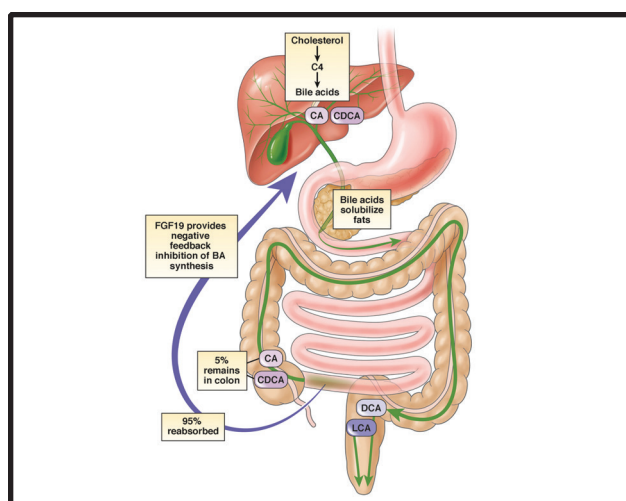

Figure 1. Enterohepatic circulation of bile acids. See text for details.
BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; FGF, fibroblast growth fact 19; C4, 7-α-hydroxy-4-cholesten-3-one.
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inducing 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 ß-klotho, it activates the FGF receptor 4 (FGFR4) on the hepatocyte leading to a phosphorylation cascade that downregulates bile acid synthesis (Figure 2).[13]

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, dispersing the droplets 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. Of note, some degree of passive absorption of bile acids occurs throughout the length of the small bowel. The presence of bile acids 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 including:

- Contribute to cholesterol metabolism by promoting the excretion of cholesterol.[1]

- Denature dietary proteins, thereby accelerating their breakdown by pancreatic proteases.[15]

- 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]

- Act as signaling molecules outside of the gastrointestinal tract.[18]

Clinical Presentation and Role of Bile Acids in Bile Acid Malabsorption

Nonbloody diarrhea is the hallmark symptom of BAM. In an online survey of 100 patients with BAM out of 1300 members of a BAM support group, 85% reported fecal urgency, 54% abdominal pain, 88% occasional fecal incontinence, and 52% felt the need to be close to the bathroom.[19] Among those with abdominal discomfort, 40% reported fatigue and at least 60% 'brain fog', which prevented work efficiency. After treatment with bile acid sequestrants, gastrointestinal and systemic
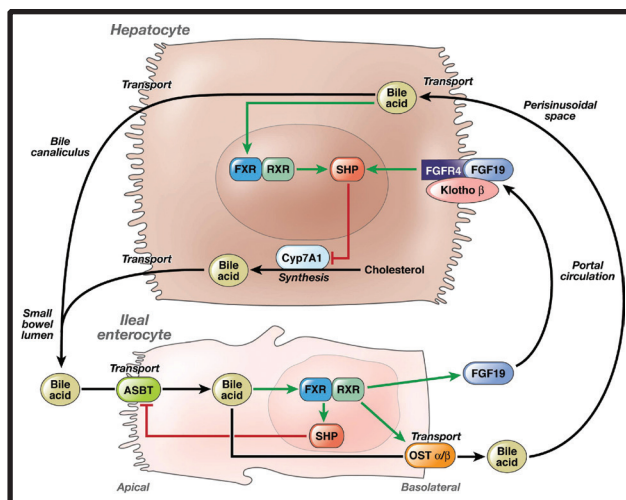

Figure 2. Molecular mechanisms responsible for the control of bile acid synthesis. See text for details.
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symptoms improved or resolved by at least 50%, and there was a significant improvement in work absences and altered work hours.

Excess bile acids entering the colon contribute to the classical symptoms associated with BAM. Bile acids stimulate secretion in the colon by activating intracellular secretory mechanisms, increasing mucosal permeability, inhibiting Cl^-/OH^- exchange and enhancing mucus secretion.[20] Colonic water secretion depends on the concentration of bile acids, with concentrations typically > 3 mmol/L leading to secretion.2[1] Bile acids also stimulate colonic motility by inducing propulsive contractions thereby shortening colon transit time, potentially worsening urgency and diarrhea.[22,23] Interestingly, low concentrations of bile acids downregulate colon secretion and promote fluid and electrolyte absorption.[24] 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 Malabsorption

Due to the limited availability of diagnostic tests for BAM, its prevalence remains unclear. The availability of the [75]Selenium-homocholic acid

Table 1. Causes of Bile Acid Malabsorption

Etiology of BAM	Consider BAM if Symptomatic
Type 1	• Terminal ileal resection or bypass • Terminal ileal disease (e.g., Crohn's disease)
Type 2	• No definitive etiology • No demonstrative ileal disease
Type 3	• Small intestinal bacterial overgrowth • Postcholecystectomy • Postvagotomy • Celiac disease • Radiation enteritis • Chronic pancreatitis

taurine (SeHCAT) retention test (see below) in Europe has, nevertheless, allowed an estimate of its prevalence, at least in the Western world. Two systematic reviews of studies that estimated the prevalence of primary bile acid diarrhea using the SeHCAT test in patients with chronic unexplained diarrhea and/or diarrhea-predominant irritable bowel syndrome (D-IBS)] suggest that, at the best confidence interval (<10%) for SeHCAT retention percentage, 16.9% to 35.3% of patients had an abnormal result suggesting BAM.[25,26] A recent prospective study analyzed data from 118 consecutive patients meeting Rome III criteria for D-IBS who underwent SeHCAT testing. Twenty-eight (24%) were found to have BAM (8 mild, 8 moderate and 12 severe).[27]

It is estimated that 5% of the population in developed countries has chronic diarrhea at any point in time, incurring direct and indirect costs of about $660 million per year.[28] Given the 25%-30% prevalence of BAM in patients with chronic diarrhea, the prevalence in the general population would be about 1%.

Types of Bile Acid Malabsorption

In a retrospective analysis of 373 patients undergoing SeHCAT testing, 190 were found to have BAM. Multivariate analysis showed that prior cholecystectomy, terminal ileal resection or right hemicolectomy for Crohn's disease or other reasons were associated with BAM.[29] Nearly 65% of those with BAM had either no risk factors for BAM or met criteria for D-IBS.

The cause of BAM may be divided into three main types (Table 1).[30]:

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. 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.[31] When more than 100 cm of distal ileum in adults is resected, 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).[32]

Type 2 BAM, often referred to as primary bile acid diarrhea (PBAD), is the most common cause of bile acid malabsorption 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 has been poorly understood. Recently, a role of altered feedback inhibition of bile acid synthesis has been proposed.[33] This altered feedback regulation is thought to be mediated by FGF19 (fibroblast growth factor 19).[34-36] Walters and colleagues 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 C4.[37] As a consequence of this deficiency, the hepatocytes are unable to downregulate bile acid synthesis. It was speculated that this disrupted feedback control by FGF19 may result in a large bile acid pool with incomplete ileal absorption and increased bile acid delivery to the colon causing

Table 2. Principal Diagnostic Tests for Bile Acid Malabsorption

Test	Advantages	Disadvantages
[75]SeHCAT	• Well-defined diagnostic cutoffs • Level of retention predicts response to bile acid binders	• Radiation exposure • Not widely available
Fecal Bile Acids	• Gold standard • Measures total and individual bile acids • Direct measure	• Variable daily bile acid excretion • Requires 48-hr sample • Requires 96-hr 100 g/d fat diet • Unknown response to bile acid binders • Requires sophisticated testing methods • Not widely available
C4	• Blood test • Single visit • No diet limitations	• Requires fasting sample • Suboptimal specificity • Diagnostic accuracy still uncertain • Unknown response to bile acid binders • Requires sophisticated testing methods

diarrhea. The exact nature of the defect that leads to altered FGF19 production or release requires further investigation.

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 (Table 1).

Diagnosis of Bile Acid Malabsorption

There are 3 main types of diagnostic tests for BAM (Table 2): the direct measurement of fecal bile acids, the measurement of serum biomarkers of bile acid synthesis, and the evaluation of terminal ileal reabsorption of bile acids with the SeHCAT retention test. Another test of BAM that has fallen from favor and is more of historical interest is the ^{14}C-glycocholate breath test.[38] All of these tests have limitations that to date have hindered the recognition of BAM in patients with chronic diarrhea.

The measurement of total and individual fecal bile acids is a direct measure of excess bile acids exiting the colon. The diagnosis of BAM by measurement of fecal bile acids in a 48-hour stool collection while on a 100 g/d fat diet for 2 days prior to starting and during the collection, the definitive method, is unpleasant and requires high performance liquid chromatography (HPLC) with mass spectrometry (MS) and, as such, until

recently was available only in research laboratories. Unlike with the SeHCAT test, there are currently no randomized clinical trials that have evaluated the response of bile acid binders to those with elevated fecal bile acids. There are ongoing investigations into whether measurement of bile acids in a single, random stool sample may be able to replace the need for a 48-hour stool collection.

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.[39] Diagnostic cut-offs and response to bile acid sequestrant therapy are as follows: < 5% (severe) with 96% response, < 10% (moderate) with 80% response, and < 15% (mild) with 70% response.[25] 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.[40] While the SeHCAT test is currently the clinical gold standard, it has never been approved for use in the United States and is not widely available in the rest of the world.

More recently, the measurement of serum biomarkers of bile acid synthesis has been proposed as a potential test of BAM.[41] Serum 7-α-hydroxy-4-cholesten-3-one (C4) is a direct measure of bile acid synthesis, and C4 levels are substantially elevated in BAM patients with a sensitivity and specificity of 90% and 77%, respectively for type 1 BAM (see

Table 3. 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	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 at least 4-hours after bile acid sequestrant administration
Colestipol (Colestid®)	5-gram packet, 1 to 6 times/day Tablet form also available	Same as above	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	Does not decrease the absorption of co-administered medications

below) and 97% and 74%, respectively for type 2 BAM (see below).[42,43] Furthermore, C4 levels have been shown to correlate well with SeHCAT retention.[44] Despite its obvious advantages in the diagnosis of BAM, this test also requires HPLC-MS.[45] and, until recently, was available for research use only. Alternatively, FGF19 represents an indirect measure of bile acid reabsorption as it provides feedback inhibition on hepatic bile acid synthesis. FGF19 is measured by enzyme-linked immunosorbent assay. Sensitivity and specificity of FGF19 are lower than with C4.[43] Both C4 and FGF19 have diurnal variations necessitating fasting samples. Ultimately, while convenient, these fasting biomarkers lack sufficient diagnostic accuracy on their own and while the C4 test may be considered as a screening tool, the FGF19 test cannot. Recently, a report described the use of chenodeoxycholate-stimulated FGF19 response as a provocative test of BAM.[46] Further study is needed before this test can be accepted into clinical practice.

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. Importantly, in the recent Canadian Association of Gastroenterology clinical practice guideline on the management of bile acid diarrhea, testing rather than a therapeutic trial with bile acid binder, using SeHCAT (where available) or fasting plasma C4, was recommended.[47]

Treatment of Bile Acid Malabsorption

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 BAM, no such cause is found or is effectively treatable. Therefore, for over 50 years, the treatment of BAM has relied on the use of oral administration of bile acid sequestrants.[41] 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 3). Dietary intervention (i.e., low fat diet with or without medium chain triglyceride supplementation) and aluminum hydroxide may also have a role; however, data regarding their use is limited.[48]

Cholestyramine and colestipol are FDA-approved for the treatment of hypercholesterolemia (both agents) and pruritus related to partial biliary obstruction (cholestyramine only). In one report, most patients with abnormal SeHCAT retention were found to respond to treatment with cholestyramine in a dose-response manner: 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.[49] Indeed, 40% to 70% of patients given bile acid sequestrants discontinue them.[50,51] A recent systematic review on the management of chronic diarrhea related to BAM identified 30 relevant publications (1241 patients) and found that cholestyramine was the most studied treatment, and was successful in 70% (of 801) patients.[49] In a retrospective survey of 377 patients diagnosed with BAM by SeHCAT, at follow-up, 50% of the patients reported improvement in the diarrhea; however, 74% reported continued diarrhea and 62% regularly used anti-diarrheal medications.[52] Sixty-four percent considered their quality of life to be reduced because of the diarrhea while 50% reported that the diarrhea was unaltered or worse than before the diagnosis of BAM was established. Thus, it is clear that many patients with BAM continue to have bothersome diarrhea despite proper diagnosis and treatment.

Gastrointestinal side effects are common with cholestyramine and colestipol and include nausea, borborygmi, flatulence, bloating, and abdominal discomfort.[53] 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 4. 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.

Colesevelam is a newer bile acid sequestrant that binds bile acids with a higher affinity than either cholestyramine or colestipol. It is available

Table 4. Tips to Making Bile Acid Sequestrants More Palatable

- Add powder to a half cup of applesauce or crushed pineapples 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 with half water to dissolve it first, then finish it off with a thick consistency juice/nectar or smoothie.
- Try mixing with pudding or custard.

in tablet form, improving its patient acceptability.[40] Colesevelam is FDA-approved to treat hypercholesterolemia and 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 many cancer patients who developed BAM, including some who had failed prior cholestyramine therapy.[54] Colesevelam was also 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.[55] Furthermore, single nucleotide polymorphisms of FGFR4 and ß-klotho have been found that appear to identify a subset of D-IBS patients who may benefit from colesevelam.[56] Colesevelam does not decrease the absorption of co-administered medications,[53] presumably because of differences in chemical structure compared to cholestyramine and colestipol.

A proof-of-concept open-label study indicated that obeticholic acid produces clinical benefit, increases FGF19 and reduces C4 in patients with primary and secondary forms of BAM.[57] Obeticholic acid, which is approved for the treatment of primary biliary cholangitis, stimulates the FXR of the terminal ileum, thereby increasing FGF19, which provides feedback inhibition on hepatic bile acid synthesis. Recently, a case report has suggested a possible benefit from the use of liraglutide[58] in BAM unresponsive to bile acid binders. Liraglutide, which is approved for the treatment of type 2 diabetes mellitus and obesity, also slows gastrointestinal transit. It is this mechanism that is speculated liraglutide exerts its effect on BAM by increasing passive absorption of bile acids throughout the small bowel and allowing enhanced active bile acid absorption in the terminal ileum. This may also lead to increased FXR activation and FGF19 secretion, which, in turn, will decrease hepatic bile acid synthesis.

Practice Guidelines

The Canadian Association of Gastroenterology recently published a clinical practice guideline on the management of BAM.[47] A systematic review was conducted and the quality of the evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. The quality of the evidence was generally rated as very low; as such, most of the recommendations are conditional. In patients with chronic diarrhea, consideration of risk factors (e.g., terminal ileal resection, cholecystectomy or abdominal radiotherapy), but not additional symptoms, was recommended for identification of patients with possible BAM. Testing, rather than a therapeutic trial with bile acid binder, using SeHCAT (where available) or fasting plasma C4, including patients with D-IBS, functional diarrhea and Crohn's disease without inflammation was recommended. Cholestyramine was suggested as initial therapy as was use of antidiarrheal agents if bile acid binders were not tolerated.

CONCLUSION

By recognizing that BAM is a relatively common cause of chronic diarrhea, it should follow that physicians will more readily recognize, evaluate, and treat patients with this condition. We recognize that given the limitations in the availability of diagnostic testing and difficulties in completing an adequate empiric trial of a bile acid sequestrant, BAM is likely to remain a problematic diagnosis, at least for the near future. The recent development and validation of a 48-hr fecal bile acid measurement and the convenient blood-based measurement of C4, will, hopefully, change this clinical practice. Treatment of BAM remains using bile acid sequestrants; the availability of colesevelam 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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