Bile acid malabsorption in chronic diarrhea: Pathophysiology and treatment

Alan Barkun MD, Jonathan Love MD, Michael Gould MD, Henryk Pluta MD, A Hillary Steinhart MD


BACKGROUND: Bile acid malabsorption (BAM) is a common but frequently under-recognized cause of chronic diarrhea, with an estimated prevalence of 4% to 5%.

METHODS: The published literature for the period 1965 to 2012 was examined for articles regarding the pathophysiology and treatment of BAM to provide an overview of the management of BAM in gastroenterology practice.

RESULTS: BAM is classified as type 1 (secondary to ileal dysfunction), type 2 (idiopathic) or type 3 (secondary to gastrointestinal disorders not associated with ileal dysfunction). The estimated prevalence of BAM is >90% in patients with resected Crohn disease (CD) and 11% to 52% of un-resected CD patients (type 1); 33% in diarrhea-predominant irritable bowel syndrome (type 2); and is a frequent finding post-cholecystectomy or postvagotomy (type 3). Investigations include BAM fecal bile acid assay, 23-seleno-25-homo-tauro-cholic acid (SeHCAT) testing and high-performance liquid chromatography of serum 7-α-OH-4-cholesten-3-one (C4), to determine the level of bile acid synthesis. A less time-consuming and expensive alternative in practice is an empirical trial of the bile acid sequestering agent cholestyramine. An estimated 70% to 96% of chronic diarrhea patients with BAM respond to short-course cholestyramine. Adverse effects include constipation, nausea, bloating, abdominal pain. Other bile acid sequestering agents, such as colestipol and colesveleam, are currently being investigated for the treatment of BAM-associated diarrhea.

CONCLUSIONS: BAM is a common cause of chronic diarrhea presenting in gastroenterology practice. In accordance with current guidelines, an empirical trial of a bile acid sequestering agent is warranted as part of the clinical workup to rule out BAM.

Key Words: Bile acid malabsorption; Cholestyramine; Chronic diarrhea; Enterohepatic circulation; FGF19; SeHCAT

Chronic diarrhea is one of the most common presentations in gastroenterology and general practice (1). While prevalence rates in Canada are difficult to determine, an estimated 4% to 5% of the overall population and 7% to 14% of elderly individuals in the community experience chronic diarrhea (2-4). In the period 2003 to 2008, annual sales of over-the-counter antidiarrheal medications in Canada reportedly doubled to $50 million (5).

Diarrhea is defined as the abnormal passage of loose or liquid stools more than three times per day, and/or stool volume >200 g/day (1). Chronic diarrhea is defined as an increase in stool frequency and/or volume that persists for longer than three to four weeks. Chronic symptoms generally do not suggest an infectious etiology, although patients may report that symptoms are preceded by gastrointestinal infection or food poisoning. The most common causes in clinical practice are inflammatory syndromes of the small bowel or colon (eg, Crohn disease [CD], celiac disease); functional bowel disorders (eg, irritable bowel syndrome [IBS];) neoplasia; pancreatic insufficiency resulting in malabsorption; intestinal dysmotility; and small bowel malabsorption (eg, postgastrointestinal surgery) (Table 1).

A common but frequently underinvestigated cause of chronic diarrhea is bile acid malabsorption (BAM) resulting from dysregulation of the enterohepatic recycling of bile acids and of bile acid production. The present review summarizes recent developments in the pathophysiology, investigation and treatment of BAM, and addresses its relevance to the clinical management of chronic diarrhea.

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TABLE 1
Potential causes of chronic diarrhea in clinical practice

<table>
<thead>
<tr>
<th>Colon</th>
<th>Small bowel</th>
<th>Pancreas</th>
<th>Endocrine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic neoplasia</td>
<td>Celiac disease</td>
<td>Chronic pancreatitis</td>
<td>Hyperthyroidism</td>
<td>Factitious diarrhea</td>
</tr>
<tr>
<td>Inflammatory bowel disease (ulcerative colitis, Crohn's colitis)</td>
<td>Crohn disease</td>
<td>Pancreatic carcinoma</td>
<td>Diabetes</td>
<td>Surgery (eg, small bowel resection, internal fistulas)</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>Other small bowel enteropathies</td>
<td></td>
<td>Hypoparathyroidism</td>
<td>Drugs (eg, nonsteroidal anti-inflammatory drugs, antihypertensives, antibiotics, antiarrhythmics, antineoplastics, drugs containing magnesium)</td>
</tr>
<tr>
<td></td>
<td>Bile acid malabsorption</td>
<td></td>
<td>Addison disease</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td></td>
<td>Disaccharidase deficiency</td>
<td></td>
<td>Hormone-secreting tumours (eg, VIPoma, carcinoid, gastrinoma)</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td></td>
<td>Small bowel bacterial overgrowth</td>
<td></td>
<td>Other</td>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td></td>
<td>Mesenteric ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiation enteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Chronic infection (eg, giardiasis)</td>
<td></td>
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</tr>
</tbody>
</table>

Bile acid production and the enterohepatic circulation

The enterohepatic circulation of bile acids was first described by Small et al (6) four decades ago (Figure 1). Primary bile acids, principally cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized from cholesterol in the liver, conjugated with glycine or taurine to increase their water solubility and secreted to bile. Secondary bile acids, primarily deoxycholic acid (DCA) and lithocholic acid, are derived from primary bile acids as a result of modifications (eg, deconjugation, 7-dehydroxylation) by intestinal bacteria. These modifications increase passive absorption of secondary bile acids in the colon.

The main pathway for cholesterol conversion to CA and CDCA is the neutral pathway, in which the rate-limiting enzyme is the cytochrome P450 enzyme cholesterol 7α-hydroxylase (CYP7A1) (7). In the alternative (acidic) pathway, 27-hydroxylation of bile acid intermediates of the CYP7A1 pathway primarily results in CDCA synthesis; this pathway accounts for <20% of total bile acid production (8). Other minor pathways involve cholesterol 25-hydroxylation, which is not part of the CYP450 system; and cholesterol 24-hydroxylation (CYP46), which converts 24S-cholesterol in the brain to bile acids (7).

METHODS

For the present narrative review, the PubMed database was searched using a combination of controlled vocabulary and text words to identify reports related to bile acid diarrhea for the period October 1965 to October 2012. The search terms “bile acid malabsorption” filtered for “Humans” obtained 923 results, which were manually searched for relevance to providing an overview of the pathophysiology, investigation and treatment of BAM. Supplemental information was obtained through secondary searches using the terms “chronic diarrhea”, “inflammatory bowel disease” or “IBD”, “irritable bowel syndrome” or “IBS”, “enterohepatic circulation”, “cholestyramine”, “colestipol” and “colesevelam”.

Approximately 95% of primary bile acids are reabsorbed by the distal ileum through active uptake by the apical sodium-dependent bile acid transporter (ASBT), returned to the liver via the portal circulation and taken up by hepatocytes. A small percentage of bile acids entering the colon can be passively absorbed, resulting in an overall net loss of 1% to 3% (9). The conservation of the bile acid pool is altered by more rapid intestinal transit and changes in gut flora due to diet, medications or other factors.

Cholesterol and bile acid levels are tightly regulated. Of particular interest are the liver X receptor and the farnesoid X receptor (FXR), both of which act as transcription factors regulating enzyme expression. The dimerized liver X receptor/retinoid X receptor (RXR) binds to oxidized cholesterol metabolites and induces the expression of CYP7A1, resulting in increased bile acid synthesis (7,10).

Bile acid production is regulated by FXR, which is expressed primarily in ileal enterocytes and hepatocytes (Figure 2). Bile acids activate FXR, which forms a dimerized FXR/RXR complex. In the liver, FXR/RXR downregulates CYP7A1 expression, resulting in decreased bile acid synthesis and increased expression of the bile salt export pump, and downregulates CYP8B1, which is necessary for CA synthesis (11,12). The result is a decrease in bile acid synthesis and uptake, and increased export to bile (10). In enterocytes, FXR/RXR acts on ASBT to reduce ileal uptake of bile acids (13). High intracellular bile acid levels in enterocytes also stimulate the release of fibroblast growth factor 19 (FGF19), which feeds back to the FGF receptor-4 (FGFR4) and its coreceptor Klotho on hepatocytes to downregulate CYP7A1 and reduce bile acid production (14,15). This decreases intestinal bile acid absorption and prevents the intracellular accumulation of bile acids. Thus, bile acid production is regulated through negative feedback mechanisms in the liver and remotely in the ileum.

The composition of the bile acid pool is influenced by various factors. The principal constituents are the primary bile acids (CA, CDCA) and the secondary bile acid DCA; DCA accumulates in the bile pool because 7-dehydroxylation cannot be reversed (10). DCA formation from CA is increased by diet (eg, high fat) and other factors that slow colonic transit times (10), as well as increased Gram-positive anaerobes and 7-alpha-dehydroxylase activity (16). Absorption and bioavailability of DCA are influenced by colonic transit time and pH in the distal colon (16).

Diets high in taurine (eg, seafood), or high in fat or low in fibre will increase the amount of taurine-conjugated bile acids (17,18). The ASBT is also more effective at transporting dihydroxy bile acids (ie, DCA, CDCA) (13), which influence the bile acid pool.
Medications also play a role. Glucocorticoids upregulate ASBT (19), suggesting an alternative mechanism of symptom control in patients with inflammatory bowel disease. Cholesteramine has been shown to preferentially reduce dihydroxy (CDCA, DCA) bile acids (19), suggesting an alternative mechanism of symptom control in patients with terminal ileal disease (eg, celiac disease, cholecystectomy, bacterial overgrowth) that alter intestinal motility or bile acid absorption (Table 2) (26).

BAM is often regarded as a rare phenomenon, reflected in a survey of gastroenterologists in the United Kingdom (28). One-third of new patients presented with chronic diarrhea. BAM was considered in the diagnostic workup in 22% of chronic diarrhea cases. Overall, 1% of all new cases and 3% of chronic diarrhea cases were diagnosed with BAM; among BAM cases, 61% were type 1, 22% were type 2 and 15% were type 3. Thirty-nine per cent of clinicians investigated only a selected group of patients, and 22% reported they investigated BAM rarely or not at all.

Often under-recognized in practice is type 2 BAM (idiopathic BAM), which potentially affects a wide range of patients with chronic diarrhea. While the etiology of idiopathic BAM is unclear, several underlying pathophysiological mechanisms have been proposed. Some (29-31), but not all (32), studies have suggested that idiopathic BAM is associated with more rapid small-bowel and colonic transit times. Genetic variants in the FGF19-FGFR4-Klotho pathway, which affects colonic transit times, have been reported in diarrhea-predominant IBS (IBS-D) (33). However, these variants may play a more important role in dysregulation of the bile acid pool. A recent study reported that 38% of IBS-D patients exhibited increased bile acid synthesis, as measured by serum levels of 7α-hydroxy-4-cholesten-3-one (C4), and higher body mass index (34).

Similar results were found in a study comparing idiopathic BAM patients with diarrhea versus healthy controls (35). Fasting C4 levels were significantly higher in patients with idiopathic BAM compared with controls (51 ng/mL versus 18 ng/mL), suggesting dysregulation of bile acid synthesis. Moreover, median FGF19 levels were significantly lower in idiopathic BAM versus controls (120 pg/mL versus 231 pg/mL), indicating that a deficiency in FGF19 feedback inhibition of bile acid synthesis may contribute to an overproduction of bile acids that cannot be accommodated by ileal reabsorption. FGF19 levels were also found to be low in patients postcholecystectomy (type 3 BAM).

BAM investigations

Traditional investigations of BAM, such as direct testing of bile acid content in fecal samples (36,37) or 14C cholyglycine testing of 14C in expired air and stool, are difficult and unpleasant to perform (38). Another method to assess BAM is SHeCAT testing (sensitivity >80%, specificity >98%) (39,40), in which 23-selena-25-homo-
Barkun et al

**Table 3**

<table>
<thead>
<tr>
<th>Author (reference), year</th>
<th>Patient group</th>
<th>n</th>
<th>SeHCAT at 7 days, %</th>
<th>BAM prevalence, %</th>
<th>Response to cholestyramine, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford et al (53), 1992</td>
<td>Idiopathic chronic diarrhea</td>
<td>74</td>
<td>&lt;15</td>
<td>27.0</td>
<td>92.5 (SeHCAT &lt;5)</td>
</tr>
<tr>
<td>Sinha et al (54), 1998</td>
<td>Idiopathic BAM</td>
<td>9</td>
<td>&lt;15</td>
<td>n/a</td>
<td>66.7</td>
</tr>
<tr>
<td>Sciarretta et al (32), 1987</td>
<td>IBS-D, postcholecystectomy</td>
<td>46</td>
<td>&lt;8</td>
<td>39*</td>
<td>43.4</td>
</tr>
<tr>
<td>Cramp et al (56), 1996</td>
<td>Chronic diarrhea secondary to HIV infection</td>
<td>19</td>
<td>&lt;15</td>
<td>84.2*</td>
<td>84.6</td>
</tr>
<tr>
<td>Ung et al (57), 2000</td>
<td>Idiopathic chronic diarrhea</td>
<td>94</td>
<td>&lt;10</td>
<td>44.7</td>
<td>n/a</td>
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<tr>
<td>Smith et al (58), 2000</td>
<td>IBS-D</td>
<td>197</td>
<td>&lt;10</td>
<td>33.5</td>
<td>70.0</td>
</tr>
<tr>
<td>Wildt et al (59), 2003</td>
<td>Idiopathic chronic diarrhea</td>
<td>133</td>
<td>&lt;15</td>
<td>56*</td>
<td>n/a</td>
</tr>
<tr>
<td>Fernández-Bañares et al (61), 2007</td>
<td>Chronic watery diarrhea</td>
<td>62</td>
<td>&lt;11</td>
<td>59.7</td>
<td>45.2 (all)</td>
</tr>
<tr>
<td>Wedlake et al (62), 2009</td>
<td>IBS-D</td>
<td>1223</td>
<td>&lt;5</td>
<td>10</td>
<td>96 (SeHCAT &lt;5)</td>
</tr>
<tr>
<td>Borghede et al (49), 2011</td>
<td>Idiopathic chronic diarrhea</td>
<td>114</td>
<td>&lt;15</td>
<td>59.6</td>
<td>74.3 (SeHCAT &lt;5)</td>
</tr>
<tr>
<td>Kurien et al (63), 2011</td>
<td>IBS-D</td>
<td>273</td>
<td>&lt;10</td>
<td>39.2</td>
<td>n/a</td>
</tr>
<tr>
<td>Gracie et al (64), 2012</td>
<td>Idiopathic chronic diarrhea</td>
<td>373</td>
<td>&lt;15</td>
<td>50.9*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27.3 (IBS-D)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Included patients with type 1 and/or type 3 BAM. †Systematic review of 18 studies. n/a Not applicable; SeHCAT 23-seleno-25-homo-tauro-cholic acid

**Prevalence of type 1 BAM**

BAM secondary to ileal dysfunction is common. A retrospective review of 298 patients with chronic watery diarrhea found seven-day SeHCAT retention to be <10% in 15 of 29 patients (51.7%) with unresected CD, 40 of 43 patients (93.0%) with resected CD, 12 of 12 patients (100%) following small bowel resection and two of three patients (66.7%) following radiation injury (49). Lenicek et al (50) reported that BAM severity was associated with the extent of ileal resection in CD patients. Elevated C4 levels were detected in 61.7% of resected CD patients, and less commonly in unresected ileitis or colitis patients (14% and 11%, respectively) (50,51). In an analysis of CD patients referred for SeHCAT testing for chronic diarrhea refractory to antidiarrheal medications or steroids, SeHCAT retention <5% was found in 90% of resected and 28% of unresected CD patients (52).

**Prevalence of type 2 BAM in idiopathic chronic diarrhea**

SeHCAT testing has proven to be a useful research tool to detect BAM in patients with unexplained chronic diarrhea (49,53-74). The estimated prevalence of idiopathic BAM in chronic diarrhea ranges from 37.5% to 59.6% (Table 3).

Approximately one-third of patients with a diagnosis of IBS-D have underlying BAM (Table 3). A systematic review of 18 studies (n=1223) reported that 10% of patients had BAM using a cut-off value of SeHCAT <5% of baseline (severe BAM) (62). Approximately 32% had BAM using a cut-off of SeHCAT <10% (severe and moderate BAM), and 26% had some degree of BAM (SeHCAT <15%; severe, moderate and mild BAM).

Idiopathic BAM associated with postinfective diarrhea is another interesting area of study. A case review found 16 of 29 patients (55%) with a positive SeHCAT test had a history of acute gastroenteritis before the onset of chronic diarrhea (65). Similarly, a retrospective analysis of 135 patients with SeHCAT <10% identified 25 cases of postinfective BAM responsive to cholestyramine (66). The precise mechanisms leading to postinfective BAM require further elucidation.
Prevalence of type 3 BAM

Type 3 BAM is common in patients with a variety of gastrointestinal disorders not associated with ileal dysfunction. BAM appears to be related to impaired biliary secretion in patients with chronic pancreatitis (67). In celiac disease, BAM has been attributed to atrophy of the small intestinal mucosa, and impairments in gall bladder and small bowel motor function (68).

BAM is a frequent complication following gall bladder surgery, with one case series reporting a marked degree of BAM in 25 of 26 patients with postcholecystectomy diarrhea (69). While fecal bile acid loss has been documented in this setting, one study found that rising C4 levels did not appear to be related to a change in bowel habits (70). Animal studies have reported a significant increase in bile acid production and an increased proportion of short-chain bile acids following cholestyramine and ileal resection (71), suggesting that severe disruption of the enterohepatic circulation postsurgery results in chronic diarrhea. BAM may also be a contributing factor in patients with postvagotomy diarrhea (72), although the mechanisms are poorly understood.

Response to bile acid sequestering agents

A large proportion of patients with severe BAM (SeHCAT <5%) will respond to an empirical trial of cholestyramine (Colestid; Pfizer, Kingwood, New Jersey). In the case series reported by Nyhlin et al (52), response rates were 88% in resected CD and 28% in unresected CD. A total of 37 of 40 patients with severe BAM (all types) responded to cholestyramine 1 g/day to 8 g/day in the series by Ford et al (53). A large series demonstrated a response in 71% of patients taking cholestyramine; treatment with a bile acid sequestering agent was effective regardless of BAM type (49).

In addition, a substantial proportion of patients with IBS-D will respond to cholestyramine. In their systematic review of 15 treatment studies, Wedlake et al (62) found that clinical response was correlated with BAM severity. The overall response to empirical therapy with cholestyramine was 96% for severe BAM (SeHCAT <5% of baseline), 80% for moderate or severe BAM (SeHCAT <10%), and 70% for any degree of BAM (SeHCAT <15%). Because one-quarter of IBS-D patients have some degree of BAM, it would be expected that a large proportion of patients would respond to empirical use of cholestyramine. Wedlake et al (62) concluded that BAM is not a rare finding in IBS-D patients and speculated that as many as 500,000 adults in the United Kingdom could benefit from therapeutic intervention for bile acid malabsorption. A similar number of Canadians would be expected to benefit from treatment due to the higher prevalence of IBS-D in Canada (73).

A long-term follow-up (mean 99 months) of 14 patients with chronic diarrhea (74) found that seven of 14 experienced resolution of symptoms and no longer required cholestyramine. Of the remaining seven symptomatic patients, diarrhea was well controlled in five using cholestyramine and in two using antidiarrheal medications.

Cholestyramine is the only bile acid sequestering agent approved by Health Canada for the symptomatic control of bile acid-induced diarrhea due to short bowel syndrome to help reduce fecal bile acid loss (75). Cholestyramine powder is usually administered at a starting dose of 4 g/day, increased as needed to 4 g one to six times/day; in clinical practice, less frequent dosing (eg, 4 g twice/day) is often effective in relieving BAM-associated diarrhea. Lower doses (eg, 4 g twice/day) are generally used in patients with short-bowel syndrome. Adverse effects may include constipation, nausea, bloating, and abdominal pain.

The bile acid sequestering agents colestipol (Colestid; Pfizer, Canada) and colesevelam (Lodalis, Welchol; Daiichi Sankyo, Japan) would also be expected to be clinically useful based on their mode of action; however, neither is indicated for the treatment of BAM-associated diarrhea in Canada (76,77). There are no published reports of colestipol in BAM. Dosing for hyperlipidemia is 2 g/day to 16 g/day administered either once-daily or in divided doses, or one to six packets (5 g/packet or 7.5 g/packet) of colestipol given once-daily or in divided doses. The most common adverse effects are constipation, abdominal pain/cramping, bloating, flatulence, and nausea/vomiting.

Colestevam, a water-insoluble polymer, has been shown to have modest effects on intestinal transit time. A study randomly assigned 24 patients with IBS-D to colestevam 1.875 g twice/day or placebo for 12 to 14 days. Colestevam eased stool passage and had a nonsignificant effect on 24 h colonic transit time (P=0.22). There was no effect on the number of bowel movements per day; however, there was a tendency to improved stool consistency (78). A retrospective study in cancer patients with BAM symptoms receiving colestevam reported improvements in diarrhea (83%), urgency of defecation (74%), frequency of defecation (72%), steatorrhea (71%), abdominal pain (68%) and fecal incontinence (62%) (79). The optimal dosing of colestevam for BAM has not been established. The dosing for hyperlipidemia is six 625 mg tablets/day (or three tablets twice per day), or one 3.75 g packet/day (or 1.875 g packet twice/day). The most common adverse effects are constipation, dyspepsia and nausea.

All bile acid sequestering agents have the potential to bind other drugs. Interactions may occur with drugs such as glyburide, glimepiride, glipizide, tetracycline, penicillin G, levofloxacin, cyclosporine, olmesartan, phenobarbital, warfarin, digitalis, and oral contraceptives containing ethinyl estradiol and norethindrone (75-77). Patients should generally be advised to take medications either 1 h before or 4 h to 6 h after the bile acid sequestering agent (80).

In addition, bile sequestering agents may interfere with the absorption of fat-soluble vitamins (81,82). During long-term use, periodic monitoring of serum vitamin A and E levels and prothrombin time are generally be advised.

CONCLUSIONS

BAM is a frequently overlooked condition in patients with chronic diarrhea. BAM may be suspected in patients with persistent symptoms of watery diarrhea, notably in patients with ileal disease or following gastrointestinal surgery. Idiopathic BAM is a contributing factor in approximately one-third of patients presenting with IBS-D. While the etiology is not fully understood, alterations in the enterohepatic circulation, accelerated intestinal transit, an increase in the bile acid pool, and insufficient FGF19 levels appear to contribute to the onset and persistence of chronic diarrhea symptoms.

Because objective testing with SeHCAT or C4 is not widely available in gastroenterology practice, an empirical trial of a bile acid sequestering agent, such as cholestyramine, should be used to rule out underlying BAM as part of the clinical work-up of patients with chronic diarrhea, as currently recommended by American Gastroenterological Association and British Society of Gastroenterology guidelines.

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