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# The Role of Bile Acid Sequestrant in Diarrhea Management: Too Good to Be True?

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## Abstract

**Background:** Chronic diarrhea can be caused by a wide range of conditions including malabsorption (e.g. Bile acid malabsorption (BAM)), infection (eg. *Clostridium difficile* (*C. difficile*)), other gastrointestinal diseases (e.g. ileal resection, bile acid overproduction, pancreatic insufficiency, bacterial overgrowth, cholecystectomy and malignancy), and even stress and anxiety. BAM is a condition associated with inability to effectively absorb bile in the small intestine which results in chronic diarrhea. Cholestyramine is a bile acid sequestrant (BAS) with the potential to control chronic diarrhea induced by BAM and *C. difficile* infection.

**Objective:** To explore the role of BAS in the management of chronic diarrhea and assess how the theoretical knowledge is supported by practical evidence.

**Methods:** Ovid (MEDLINE, PsychInfo, Embase) was searched for "Cholestyramine Resin" AND "Chronic Diarrhea" with limits on the years 1946 – present. 8 studies which were deemed to be relevant to the objective at hand were summarized. Additional sources from Grey literature search were added using the same research strategies.

**Results:** The results showed positive therapeutic impact of BAS, particularly cholestyramine in reducing stool frequency regardless of type and severity of BAM-induced diarrhea. However, low tolerability of BAS due to adverse effects can limit its use in some patients.

**Conclusion:** BAS was more likely to be a good option as a short-term medication to better control symptoms and prevent illness. Therapeutic effect of BAS in the management of chronic diarrhea can be considered in palliative care to benefit patients who can tolerate this medication although not without the existent controversies.

**Keywords:** Bile Acid Malabsorption (BAM); Bile acid sequestrant; Cholestyramine; Chronic diarrhea

## Introduction

Bile Acid Malabsorption (BAM) is an important cause of chronic diarrhea. Bile acids are synthesized by the liver and mainly function as a surfactant to emulsify fats and oils into micelles allowing for their proper digestion and absorption in the small intestine. The majority of bile acids secreted into duodenum are absorbed in the terminal ileum through the enterohepatic circulation recycling pathway, where they are taken up by the liver and re-secreted [1]. Bile acids are normally water soluble and can affect the osmotic gradient. In BAM, larger amounts of bile acids enter the large intestine, and excess concentrations of bile acids create a hypertonic environment which stimulates water/fluid secretion and intestinal motility leading to symptoms of diarrhea [2].

Chronic diarrhea can be induced by different types of BAM such as BAM secondary to ileal inflammation or resection, overproduction of bile acids (idiopathic BAM), and BAM induced by other conditions (e.g. gastrointestinal disease such as cholecystectomy, bacterial overgrowth in small intestine and pancreatic insufficiency). One of the most common causes of BAM in clinical practice is inflammatory bowel disease such as Crohn disease, also categorized as Type 1 BAM. During the inflammatory process of the distal ileum, enterocytes normally responsible for the reabsorption of bile acids lose their integrity and as well as the ability to co-transport sodium and bile acids across their luminal surface [3]. In all cases, excess bile acids pass through the small intestine into the large intestine which is problematic [4].

There are additional causes of diarrhea specific to malignancy including cancer (e.g. colon cancer, hepatic cancer and pancreatic cancer), cancer treatment (e.g. chemotherapy and radiotherapy), and infections (e.g. bacterial overgrowth) due to immunosuppression, stress and anxiety. Cancer treatments tend to indiscriminately kill normal fast growing epithelial cells in intestinal lining and cancer cells alike.

Removing tumors through surgery can also alter the ability to absorb certain substances, as some parts of the intestine are removed [5].

Bile acids secreted by the liver are effectively absorbed in the terminal ileum through specialized epithelial cells of the small intestine: damage to these cells, as well as removing the terminal part of the small intestine would allow excess amounts of bile acids to enter the large intestine resulting in chronic diarrhea. Furthermore, various malignancies may affect the levels of bile acids entering the large intestine: for example, colon cancer can alter the ability to absorb bile acids in the terminal ileum due to inflammation or obstruction [6]. Hepatic cancer can also lead to chronic diarrhea induced by intestinal lymphangiectasia, and paraneoplastic process, where increased levels of gastrin lead to stomach acid overproduction causing damage to the intestinal lining when entering the small intestine [7]. Similarly, in pancreatic cancer, gastrinomas can lead to increased secretion of stomach acids, damaging the intestinal lining and causing malabsorption [8].

Chronic diarrhea can also be caused by bacterial infections such as *Clostridium difficile* (*C. difficile*). This type of diarrhea is an antibiotic induced diarrhea which is developed when the normal flora of the intestine is altered. An antibiotic can kill the good bacterium which protect the body from infections and allows *C. difficile* bacteria to multiply and release toxins (toxin A and B) that damage the intestinal lining, causing colitis, and leading to abdominal pain and diarrhea [9].

## Objective

In this article, the role of BAS in the management of chronic diarrhea was explored to assess how the theoretical knowledge behind this potential method is supported by practical evidence.

## Literature Review

We searched Ovid (MEDLINE, PsychInfo, Embase) for "Cholestyramine Resin" AND "Chronic Diarrhea" with limits on the years from 1946 until present. We tried to follow closely the Cochrane Collaboration - Systematic Reviews of Health Promotion and Public Health Interventions Handbook guidelines although it is not a systematic review. We further limited our search to English language, human subjects and publication year (from 2007 until present): this yielded 243 results. 33 of them included op-ed pieces, qualitative studies, randomized clinical trials (RCT) (There were only 4), prospective cohort studies, as well as theoretical trial designs. Of these, only approximately 8 were deemed to be relevant to the objective at hand. 3 papers were review articles, 2 were retrospective case studies, 2 were cohort case studies, and 1 was a RCT reviewed by 2 independent reviewers. These articles were then read and the relevant points and themes were summarized with the focus on the outcome of BAS application and its role in chronic diarrhea. Corroborative themes were also identified and the responsible authors were cited as they came up. Additional sources were added to the literature search using the same

research strategies by way of being referenced in the article. It included a Grey literature search, such as Internet searches of Google, Care Search, and the Grey Literature Report.

## Case Scenario 1

Mrs. X is an 87-year-old female of Caucasian descent who presented with post aortic valve replacement complicated by cerebrovascular accident (CVA) and loose bowel movement (BM) up to 4 times daily. She was admitted to Day Treatment Centre of the geriatric healthcare system facility with deconditioning. There was no abdominal pain, nausea, vomiting or constipation. She denied any burning sensation with urination, but she became incontinent of bowel and urine post CVA. In addition, she was experiencing dizziness with change in position which was further induced by diarrhea. She felt extremely fatigued as a result of diarrhea. She was found to be negative for *C. difficile* infection. She was afebrile with stable vital signs and her abdominal exam was benign.

Her past medical history was remarkable for congestive heart failure; hypertension; hyperlipidemia; sleep apnea; macular degeneration; bilateral cataract extraction; hiatus hernia; depression; mild cognitive impairment; osteoarthritis; osteoporosis; compression fracture of the second lumbar vertebra and spinal stenosis. Family history was significant for CVA on her father's side and dementia on her mother's side. She is an ex-smoker who quit 50 years ago and she was not consuming any alcohol or utilizing recreational drugs during her life time. She had no allergies. Her medications included Lipitor, Bisoprolol, Plavix, Duloxetine, Ferrous fumarate, Multivitamins, Potassium chloride and Ramipril. Her computed tomography of the brain at the time of the CVA was consistent with acute ischemia. Her magnetic resonance imaging of the brain revealed subacute ischemic changes of the left thalamus. Her lipids profile identified mild elevation of low-density lipoprotein and hemoglobin A1c was within normal limits. Her hemoglobin, liver function tests, albumin and creatine kinase were within normal limits.

Echocardiogram revealed hyperdynamic left ventricular bioprosthetic aortic valve. Her polysomnography was consistent with moderate obstructive sleep apnea. Chest x-ray revealed mild left pleural effusion. Her urinary and bowel incontinence probably was secondary to spinal stenosis; however, the impact of stroke could not be ruled out as well. Resins (cholestyramine) 4 g once a day (od) orally (po) was trialed, and she responded well to it. She stabilized from diarrhea within 4 weeks, and soon afterwards her fatigue and dizziness resolved. She was able to discontinue use of the resin 2 months later upon discharge from the program.

## Case Scenario 2

Mrs. Y is a 71-year old woman of Jewish descent with a long-standing history of irritable bowel syndrome. She was a resident of long-term care (LTC) and was bed bound. She presented with a daily frequency of 6-8 loose bowel movements (BM), as well as severe abdominal pain. In addition, she had multiple other comorbidities, including

bipolar disorder, dermatitis, osteoarthritis, B12 deficiency anemia and cognitive impairment. Her medications included valproic acid, gabapentin, vitamin B12, and quetiapine. She was utilizing loperamide for a long time prior to admission to LTC with some response. Cholestyramines were attempted 4 g orally three times a day which provided relief to her symptoms, reducing her daily frequency of BM to 1-2, but a large volume of fluid intake was required with every package of cholestyramine and increased bloating was limiting her ability to use cholestyramine in the dose which was needed to fully control her loose bowel.

As a result, her BM was only partially controlled with a daily intake of 1 package of 4 g of cholestyramine. The frequency of her BM decreased to 3 to 4 times daily with this regiment. Abdominal pain and discomfort associated with diarrhea had drastically subsided. She stabilized and was able to be redirected from her issues. Her mood lifted and quality of life significantly improved (she continued on BAS for 7 years). Unfortunately, she developed aspiration pneumonia and was transferred to acute care for further management. At that time ceftriaxone treatment 1 g daily intramuscular was initiated for 5 days. Despite continued 1 g of cholestyramine orally once a day, her symptoms returned.

When she was readmitted back to LTC following recovery from aspiration pneumonia and a course of antibiotics, she was in psychological distress suffering from severe diarrhea (with a frequency of 8-10 loose BM daily). Her quality of life became extremely poor; she was depressed and lost any interest in her remaining life. Cholestyramine was resumed at 1 g orally 3 times a day and she stabilized a few days later. Luckily, she was found to be negative for *C. difficile* infection at that time. Her mood improved soon after her BM pattern stabilized.

## BAS mechanism of action

BAS such as cholestyramine are strong ion exchange resins that bind to bile acids and form water insoluble complexes. This causes excess of bile acids to become osmotically inactive and no longer able to stimulate fluid secretion in the large intestine, which can improve the symptoms of diarrhea secondary to BAM [10]. Cholestyramine can also bind to toxin A and B released by *C. difficile* bacterium and reduce diarrhea associated with *C. difficile* infection and other symptoms these toxins cause [11].

## Results

As reported in a study at Sheffield Teaching Hospitals on 107 patients who were diagnosed with chronic diarrhea induced by BAM, BAS such as cholestyramine were found to be effective in treating diarrhea: all the patients were commenced on BAS (cholestyramine) and 54% (58/107) were followed up with a median time since diagnosis of 6 years. The median stool frequency decreased from seven stools per day to three ( $p=0.0008$  indicating statistically significant results) among those using BAS, while patients with no treatment did not show any changes in their daily bowel frequency [12]. The

positive impact of cholestyramine in reducing stool frequency was similarly observed in the cases of Mrs. X and Mrs. Y. In the same study, the main reason for discontinuing the treatment was low tolerability of the BAS due to side effects such as deterioration of bloating and pain in the abdomen [12].

This was similar to Mrs. Y's case in which the dose of medication was reduced as a result of low tolerability of the drug. In another study on 26 diagnosed patients, cholestyramine was likewise found to be effective as short-term treatment of chronic watery diarrhea: patients provided with cholestyramine sachets (4 g twice daily) showed significant decrease in number of watery stool in 8 weeks of treatment compared to patients provided with hydroxypropyl cellulose placebo sachets [13]. The case of Mrs. X was similar in the sense that positive response was observed in a short-term treatment (4 weeks). Furthermore, in a study on 46 patients, the potential use of cholestyramine was tested for reducing the risk of developing *C. difficile* associated diarrhea. All the 46 patients were on ceftriaxone treatment (for Lyme borreliosis; 2 g per day), as well as cholestyramine treatment (4 g per day). It was found that only three out of the 46 (6.5%) patients developed *C. difficile* diarrhea compared to six out of 26 (23.1%) patients following 1-3 days' treatment with 1 g of intravenous ceftriaxone, but without oral cholestyramine ( $p=0.06$  indicating statistically insignificant results) [14]. The positive impact of cholestyramine in this study was similar to Mrs. Y's case where cholestyramine probably helped to prevent development of *C. difficile* diarrhea while she was on ceftriaxone.

In a retrospective study of 201 patients with chronic bile acid diarrhea, where BAM ileal dysfunction (Type I) was observed in 77 patients, Idiopathic BAM (Type II) was observed in 68 patients and BAM introduced by other conditions (Type III) was observed in 56 patients, cholestyramine treatment was found to be effective in treating diarrhea regardless of type and severity of BAM. The results showed that 71% of the patients who were able to take cholestyramine (150/201) reported a positive effect on their bowel habits (CI: 63% to 78%) [15]. In a similar retrospective study involving 25 patients diagnosed with post-infective BAM, the long-term aspect of cholestyramine treatment was investigated as well; cholestyramine treatment was found to be effective in treating diarrhea by decreasing the mean frequency of diarrhea from 7.8 to 1.9 stool per day ( $p=0.001$  indicating statistically significant results) which was similar to Mrs. Y's case (where BM frequency reduced from 6-8 times daily to 1-2 times). 18 of the 25 (72%) patients had a successful resolution of their diarrhea by cholestyramine from which 15 patients followed up with the treatment (median of 6 years with the range of 1-15 years) [16]. Likewise, in the case of Mrs. Y cholestyramine was continued for 7 years.

According to a literature review, an estimate of 70%-90% of patients with chronic diarrhea induced by BAM via either of the previously indicated origins showed positive response to cholestyramine treatment in a short-term period [3]. A similar presentation was observed in Mrs. X where she was able to discontinue BAS after 2 months with complete resolution of

diarrhea. Although cholestyramine treatment was found to be effective in treating diarrhea regardless of type and severity of BAM, a systematic review revealed a dose-response relationship based on the severity of BAM and response to cholestyramine: positive response to cholestyramine occurred in 96% of patients with severe BAM (Se-homocholeic acid taurine (SeHCAT) retention <5%), 80% of patients with moderate BAM (SeHCAT retention <10%) and 70% of patients with mild BAM (SeHCAT retention <15%).<sup>17</sup> Similarly, in the case of Mrs. Y, the response to BAS was positive regardless of the type and the severity of BAM which could not be accurately established.

## Discussion

As suggested by the studies reviewed above, BAS and particularly cholestyramine have shown to be effective in treating chronic diarrhea secondary to BAM by improving diarrhea symptoms and impacting bowel habits. In all types of BAM, excess amounts of bile acids entering the large intestine stimulates fluid secretion and intestinal motility leading to symptoms of diarrhea. Cholestyramine is able to reduce fluid secretion in the large intestine and improve symptoms of diarrhea through binding to bile acids and making them osmotically inactive [2,9]. As mentioned earlier, BAM could be induced by various conditions such as malignancy, ileal inflammation or resection, overproduction of bile acids and etc.; however, as shown in the retrospective study performed by Borghede et al. [14] and as seen in the case of Mrs. Y, bile acid diarrhea could be effectively managed with cholestyramine regardless of type and severity of BAM. This is based on the mechanism of action of cholestyramine and its ability to bind to bile acids. The resulting conjugation of BAs by cholestyramine prevents passive absorption, thus allowing the BAs to remain in the intestinal lumen where they act as a detergent for transport of insoluble lipids. Although cholestyramine treatment is not guaranteed to work in every case, there is around 70% chance of positive response among patients who are able to take this drug [3,15]. As seen in the case of Mrs. X, the patient was able to tolerate cholestyramine well and also responded positively to it. Moreover, according to Wedlake et al. positive response to cholestyramine was observed in 96% of patients with severe BAM, 80% of patients with moderate BAM and 70% of patients with mild BAM which suggests that cholestyramine treatment can be successful regarding severity of BAM, although it is more likely to be effective in severe cases of BAM compared to less severe cases [16].

Cholestyramine is also a toxin binding agent. The pilot case study performed by Puri et al. revealed the positive impact of cholestyramine in reducing frequency of *C. difficile* diarrhea in patients with *C. difficile* infection by binding to toxins released by the bacteria [13]. Similarly, it can be speculated that in the case of Mrs. Y, cholestyramine was found to be effective in preventing the development of *C. difficile* diarrhea while the patient was on antibiotics.

It should also be noted that diarrhea can be multifactorial and frequently occurs without clearly diagnosed underlying

conditions, especially in palliative care patients and individuals with multiple comorbidities. Often, a patient fails to respond to other attempted interventions, and in such a case, BAS can be trialed. If a positive response is observed, then BAM may be suspected. This was the situation in Case 1 in the patient with a history of hyperlipidemia which can indirectly lead to diarrhea associated with underlying conditions such as pancreatitis NYD (not yet diagnosed). Interestingly, the patient was on Lipitor and Bisoprolol prior to a cardiac surgery complicated by a cerebrovascular accident (CVA), but was not experiencing diarrhea. It should also be noted that some studies have found a possible link between open heart surgeries and GI problems such as diarrhea. For example, one study found that 68 out of 4401 patients who underwent open heart surgery were diagnosed with mild GI problems such as distention, decreased bowel sounds, and diarrhea after surgery [17]. The fact that the patient responded to BAS leads us to suspect that her source of diarrhea was possibly related to BAM. Case 2 focuses on a patient with irritable bowel syndrome (IBS). BAM has been reported as a possible cause of diarrhea in patients with IBS.<sup>19</sup> Moreover, it is recommended that consideration be given for BAM in patients with D-IBS type symptoms [18]. Since the side effects of BAS are minimal, it is usually a less invasive treatment compared to other medications such as loperamide which can lead to abdominal pain, drowsiness, blurred vision, megacolon, and paralytic ileus, just to name a few [19]. Outside of BAM, BAS is also used for treating primary hypercholesterolemia and hypercholesterolemia associated with mild hypertriglyceridemia in patients who are not responding to dietary treatment [20]. BAS is also used as a second line-treatment for pruritus associated with cholestatic disease in patients with incomplete biliary obstruction [20].

## Cholestyramine side effects

Beside the benefits of cholestyramine, there are some side effects associated with this drug such as worsening of abdominal pain, nausea, bloating and flatulence which often make this drug difficult to tolerate [21].

## BAS limitation

Low tolerability of BAS by patients due to adverse effects of this drug was the main reason for discontinuation of treatment and as a result, a full response to BAS was difficult to assess in the selected studies [11,22]. In addition, the available retrospective case studies were small in size and the proportion of patients suffering from BAM who trialed cholestyramine was low [14,15].

There was only one RCT among the reviewed literature and despite that there was no statistical difference in response between receiving cholestyramine and hydroxypropyl cellulose with intention-to-treat (53.8% vs. 38.4%;  $p=0.43$ ), or per-protocol (63.6% vs. 38.4%;  $p=0.22$ ) analyses, the mean percent of decrease in frequency of watery stool was statistically significantly higher with cholestyramine than with hydroxypropyl cellulose (-92.4+/-3.5% vs. -75.8+/-7.1%;  $p=0.048$ ). The lack of statistical significance between both

groups could be attributed to having a small sample size in the available study and a deficiency in existent RCTs [12]. As a result, the adequate response to BAS could be difficult to assess, which may contribute to the bias in the reported outcome.

In addition, the degree and intensity of chronic diarrhea, and the inclusion criteria were different in the reviewed studies which may further lead to bias in the reported outcome. Moreover, limitations in diagnostic tests to accurately identify the severity of diarrhea while assessing the response to BAS can also be an obstacle to accurately report the outcome.

### Limitations with diagnosing BAM

There are four primary methods to diagnosis BAM: <sup>14</sup>C-glycocholate breath and stool test, <sup>75</sup>Selenium HomotauroCholic Acid Test (SeHCAT), 7  $\alpha$ -hydroxy-4-cholesten-3-one (C4), and fecal BAs [23]. The <sup>14</sup>C-glycocholate breath and stool test is a laboratory test which is no longer widely used [24]. The <sup>75</sup>Selenium HomotauroCholic Acid Test (SeHCAT) is a valid test, but it is not widely available in countries such as the United States [25]. The study by Wedlake et al. reviewed earlier used a SeHCAT [17]. 7  $\alpha$ -hydroxy-4-cholesten-3-one (C4) is a simple and accurate method which is

applicable to patients who do not have liver disease or take statins and have a normal circadian rhythm [17]. Unfortunately, this method has been studied in a limited number of studies with small groups of patients, and thus further research is required to determine whether this method is appropriate [17]. Fecal BAs are not widely available and this is not a desired method of testing, but recent data suggests that there is an advantage to studying the fecal excretion of individual BAs and their role in BAM, but again more research is needed to confirm this [17]. BAs are the downstream products of cholesterol catabolism that eventually become conjugated primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA) [24]. Fecal BA analysis provides a direct method of quantifying total and specific components within the BA, mainly cholic acid (CA) [24]. Recently studies have shown that smaller peaks in postprandial CA are associated with ileal resections while smaller increases in CDCA are associated with ileal resections with hemicolectomy [25]. The various diagnostic methods are outlined in **Table 1**. It should also be noted that fecal BAs can also represent conditions such as pancreatitis. Therefore, it seems that as of now, trials of the various methods for individuals suspected of having BAM, is the only option [16]. A greater availability of these four tests and more research will allow physicians to have a better understanding of which methods are appropriate.

**Table 1** Tools used for diagnosis of BAM [24-31].

Diagnostic Tool	Mechanism	Advantages	Disadvantages	Studies
<sup>14</sup> C-Glycocholate Breath and Stool Test	Detects BA deconjugation within gut due to bacterial growth	Rapid, simple, outpatient procedure	Requires stool test with breath test to differentiate BAM from bacterial overgrowth	Vijayvargiya et al. [24]; Fromm H, Hoffman A [26]; Scarpello JHB, Sladen GE [27]
<sup>75</sup> SeHCAT	<sup>75</sup> Selenium homotaurocholic BA is resistant to bacterial degradation and passive diffusion. Greater levels of <sup>75</sup> Selenium in stool suggests BAM	Less radiation exposure, simple, better patient compliance	Unavailable in many countries, conflicting studies	Vijayvargiya et al. [24]; Sciarretta et al. [28]
Serum 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4)	Measures the downstream product of a rate-limiting enzyme (CYP7A1) in BA synthesis	One blood test, no radiation exposure	Requires special equipment and training to quantify C4	Vijayvargiya et al. [24]; Camilleri et al. [29]
Fecal BA	Directly measures BA levels in stool	No radiation, total and specific BAs	Variations in daily BA excretion	Vijayvargiya et al. [24]; Griffiths WJ, Sjoval J [30]; Tiraterra et al. [31]

### Conclusion

Overall, BAS such as cholestyramine was found to be effective in reducing chronic diarrhea secondary to BAM and *C. difficile* infection in patients who were able to tolerate this drug. However, due to the associated side effects, patients suffering from BAM found this drug difficult to tolerate and this was considered to be the main reason for discontinuation of treatment. Consequently, cholestyramine was more likely to be a good option as a short-term medication rather than long term. Overall, BAS treatment resulted in illness prevention and better control of symptoms; thus, this method of treatment could be considered as an option in palliative care settings to improve the quality of life in this frail population.

### Future Research

The use of BAS such as cholestyramine and other similar therapeutic agents currently available to treat chronic diarrhea need to be more extensively tested in properly conducted RCT and in multiple clinical settings. Utilizing larger sample sizes with longer follow up and standardizing the inclusion criteria are necessary to minimize bias in reporting the results. Information on medication dose response of BAS is needed to move forward towards being widely used in clinical applications. Diagnostic tests such as the SeHCAT test need to be widely available to ensure a clear diagnosis. The role of BAS in *C. difficile* infection prevention should be further explored to eliminate the bias in the reported outcome. In addition, development of drugs that provide the advantages of

cholestyramine but have fewer and less severe adverse effects could be key for the next generation of BAS. Drugs with lower adverse effects would be easier for patients to tolerate and higher tolerability would improve adherence and benefit a wider range of high-risk populations.

## Conflict of Interest

The authors declare that there are not conflicts of interest.

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