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Systematic review: the management of chronic diarrhoea due to bile acid malabsorption

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SUMMARY

Background
Bile acid malabsorption (BAM) is a common, yet under-recognised, cause of chronic diarrhoea, with limited guidance available on the appropriate management of patients with BAM.

Aim
To summarise the evidence supporting different treatments available for patients with bile acid malabsorption, noting their impact on clinical outcomes, tolerability and associated side effects.

Methods
A literature search was conducted through PubMed, the Cochrane Database of Systematic Reviews and Scopus. Relevant articles studied patients who had been diagnosed with BAM and were clinically assessed before and after therapy.

Results
A total of 30 relevant publications (1241 adult patients) were identified, which investigated the clinical response to drugs, including colestyramine, colestipol, colesevelam, aluminium hydroxide and obeticholic acid. The most commonly used diagnostic test of bile acid malabsorption was the SeHCAT test (24 studies). Colestyramine treatment was by far the most studied of these agents, and was successful in 70% of 801 patients (range: 63–100%).

Conclusions
Colestyramine and colestipol are generally effective treatments of gastrointestinal symptoms from BAM, but may be poorly tolerated and reduce the bioavailability of co-administered agents. Alternative therapies (including colesevelam and aluminium hydroxide) as well as dietary intervention may also have a role, and the promising results of the first proof-of-concept study of obeticholic acid suggest that its novel approach may have an exciting future in the treatment of this condition. Future trials should employ accurate diagnostic testing and be conducted over longer periods so that the long-term benefits and tolerability of these different approaches can be evaluated.

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INTRODUCTION

Bile acids are synthesised in the liver from cholesterol and play a key role in the absorption of dietary fats from the small intestine. Bile acid synthesis occurs by either the classical pathway via microsomal cholesterol 7α-hydroxylase (CYP7A1) or the alternative pathway via mitochondrial sterol 27-hydroxylase (CYP27A1).[1] The classical pathway is responsible for 90–95% of bile acid synthesis and gives rise to two primary bile acids: cholate and chenodeoxycholate. These are then conjugated with glycine or taurine and secreted into the biliary tree.[2] Following their involvement in micelle formation in the small intestine, about 95% of bile acids are actively reabsorbed in the terminal ileum and returned to the liver via the portal venous system in a process known as the enterohepatic circulation.[3] Only 3–5% of bile acids reach the colon to be excreted in the faeces (about 0.3–0.5 g/day).

Bile acid malabsorption (BAM) is a defect in this enterohepatic circulation of bile acids, whereby increased proportions of the secreted bile acids are not reabsorbed in the ileum and instead reach the colon. Here, they undergo deconjugation and dehydroxylation to produce the secondary bile acids: deoxycholate and lithocholate.[4] Bile acids in the colon (particularly the dihydroxylated chenodeoxycholate and deoxycholate) activate increased fluid secretion by the triggering of intracellular secretory processes, raising mucosal permeability, increasing mucus secretion and inhibiting Cl/OH^- exchange.[5] Furthermore, an increase in motility is provoked as the bile acids stimulate colonic contractions and thereby decrease colonic transit time. Overall, this secremotor effect will manifest clinically as the classical symptoms of BAM, which include watery diarrhoea and other gastrointestinal symptoms, such as bloating, faecal urgency and faecal incontinence.

Three types of BAM are classically recognised.[6] Type 1 BAM results from ileal resection, bypass or conditions such as Crohn's disease. Type 2 (primary or idiopathic) BAM is associated with no definitive aetiology or obvious histological changes in the ileum. Some argue that the use of the term 'idiopathic' may be inaccurate and have proposed a new mechanism for type 2 BAM based on recent findings.[7] The authors showed that plasma levels of the ileal hormone fibroblast growth factor 19 (FGF19), which reduces hepatic bile acid synthesis via farnesoid X receptor (FXR), were decreased in this condition by roughly half in relation to controls. This results in impaired negative feedback by FGF19 and therefore excessive bile acid production leading to BAM. Type 3 BAM can occur secondary to various other causes, such as upper gastrointestinal surgery (e.g. post-cholecystectomy), chronic pancreatitis, coeliac disease, small intestinal bacterial overgrowth and radiation enteritis.

Diagnosis of BAM is difficult as a 24-h measurement of faecal bile acids, the definitive method, is unpleasant and only available in a few research laboratories.[8] Another test of BAM is the ^{14}C glycocholate breath test,[9] which has fallen from favour and is more of historical interest due to its limited clinical utility.[10] The 7-day ^{75}Selenium homocholic acid taurine (^{75}SeHCAT) test is an alternative that is more appropriate for clinical practice. This nuclear medicine test measures the whole body retention of a radiolabelled taurine-conjugated bile acid analogue (^{75}Se) after 7 days, and a retention value less than 10–15% is usually considered diagnostic of BAM.[11] This test has a sensitivity for diagnosing BAM of 80–90%, a specificity of 70–100% and delivers a low radiation dose to the patient.[12] Access to SeHCAT scanning remains limited, however, and it has never been approved for use in some countries, including the US, where the diagnosis of BAM is commonly made by performing a 'therapeutic trial' with a bile acid sequestrant.[13] This strategy has the advantage of not requiring specialist intervention, but, as treatment is often poorly tolerated and response variable, it should not be considered to be a definitive diagnostic marker.[8] The measurement of the serum bile acid precursor 7α-OH-4-cholesten-3-one (7αC4) has been proposed as an alternative indicator of BAM.[14] The plasma C4 levels increase when bile acid synthesis increases, and C4 levels are markedly increased in patients with BAM with a sensitivity and specificity of 90% and 77%, respectively, for type 1 BAM, and 97% and 74%, respectively, for type 2 BAM. Furthermore, C4 levels have been shown to correlate well with SeHCAT retention.[14–16] This assay is currently limited to a few specialist centres, but is a simple, sensitive and inexpensive alternative to other tests for BAM.[17] It is predicted that with the growing availability of mass spectrometers in diagnostic laboratories, this test will become more widely available.[18] Finally, the recent data highlighting the involvement of FGF19 and FXR in the development of type 2 BAM suggest that measuring serum levels of FGF19 could be developed as a simple blood test to aid the diagnosis of BAM and predict response to therapy.[19] Serum FGF19 has been shown to have a significant positive correlation with SeHCAT values. The negative and positive predictive values of

Aliment Pharmacol Ther 2014; 39: 923-939

FGF19 ≤145 pg/mL for a SeCHAT value <10% were shown to be 82% and 61% respectively.[19] Serum FGF19 has also been shown to have a significant inverse correlation with plasma C4 levels. The sensitivity and specificity of FGF19 at 145 pg/mL for detecting a C4 level >28 ng/mL were 58% and 79% respectively.[20]

Evidence suggests that BAM is a very common cause of chronic diarrhoea, present in up to 50% of patients suffering from chronic watery diarrhoea.[21, 22] Nevertheless, BAM (particularly type 2) is poorly appreciated by clinicians, and a large number of these patients will be incorrectly diagnosed as having functional disease.[23] Improved access to definitive diagnostic investigations and a greater awareness amongst clinicians of the likelihood of BAM may result in the condition being more readily diagnosed, and subsequently treated.

Where an underlying aetiology of BAM is identified (e.g. Crohn's disease), therapies should be targeted towards the specific condition. For many patients, however, no such cause is established or treatable. Therefore, while some patients may find that a reduced fat diet (<30 g/day) or conventional anti-diarrhoeals improve their symptoms, treatment has historically relied upon oral bile acid sequestrants (BAS).[24] BAS are positively charged nondigestible resins that bind to bile acids in the intestine with high affinity to form an insoluble complex that is excreted in the faeces. Before the advent of statins, these agents were commonly used to reduce serum cholesterol, as sequestering bile in the intestine leads to increased conversion of cholesterol into bile acids in the liver. Their use in diarrhoea, however, has been to prevent the secremotor actions of free bile acids on the colon. There are three BAS commercially available: colestyramine, colestipol and, most recently, colesevelam. Colestyramine and colestipol are most commonly used and come in powders or granules to be dissolved in water to make a paste. Colesevelam is a newer BAS, which is available in tablet form and forms a polymeric gel in the gastrointestinal tract. It therefore has a more gelatinous consistency compared with other BAS in the enteric environment, and is believed to have improved tolerability as a result.[25] Colesevelam is currently unlicensed in the UK for this indication and very few gastroenterologists would consider it for primary treatment of BAM.[23] The detailed molecular mechanisms behind BAS modulation of the bile acid pool are only beginning to be understood. Conventional BAS are thought to markedly alter the composition of bile by preferentially binding the more hydrophobic bile acids chenodeoxycholic acid and deoxycholic acid. Colesevelam differs in that it more efficiently binds the more hydrophillic cholic acid, thus the bile composition produced by colesevelam may differ from the conventional BAS.

Other non-BAS therapy includes aluminium hydroxide, which is thought to possess bile acid-binding properties comparable with colestyramine and may provide relief of diarrhoeal symptoms in BAM. [26] Aluminium hydroxide is most commonly prescribed for dyspepsia and gastro-oesophageal reflux disease and is rarely prescribed for BAM in clinical practice.[23] The recent discovery of the involvement of FGF19 and FXR in the development of type 2 BAM appears to be a major advance in our understanding of the condition and is a potential therapeutic target.[27] The FXR agonist Obeticholic acid (OCA), a semi-synthetic derivative of chenodeoxycholic acid (CDCA), has undergone its first proof-of-concept clinical trial in the context of BAM and may prove to be an exciting alternative to conventional therapies.[28]

Recent research recommendations from the National Institute of Health and Care Excellence (NICE) stress that a programme of research is needed to evaluate the efficacy and tolerability of treatment for BAM.[29] There is currently a paucity of national guidance available on the appropriate management of patients with BAM from sources, including NICE, BSG and AGA; yet, an estimated six million and four million adults diagnosed with irritable bowel disease (IBD) in Europe and North America, respectively, could benefit from targeted therapeutic intervention for BAM in the UK.[30] The aim of this review is to summarise the evidence supporting different treatments for patients with BAM, noting their impact on clinical outcomes, tolerability and associated side effects.

METHODS

A literature search was conducted through PubMed, the Cochrane Database of Systematic Reviews and Scopus (January 1980–June 2013). A search was performed of all articles published in the English language and linked to the keywords: 'bile acid malabsorption', 'bile acid diarrhoea', 'bile acid malabsorption AND treatment', 'bile acid malabsorption AND colestyramine', 'bile acid malabsorption AND colestipol', 'bile acid malabsorption AND colesevelam', 'bile acid malabsorption AND anti-diarrhoeals', 'bile acid malabsorption AND aluminium hydroxide' and 'bile acid malabsorption AND diet.'

A total of 1573 publications were initially identified. Our inclusion criteria included randomised controlled trials or case series comprising at least 4 patients in whom the diagnosis of BAM had been made, and

containing details of the clinical response to therapy. The titles of all articles identified by the search criteria were scanned and the abstracts of all potentially relevant papers were manually reviewed. The full text was obtained of any articles that appeared to be eligible and the reference lists of each included article were examined to identify any further appropriate articles.

RESULTS

Study characteristics

Thirty relevant publications were identified in the literature search, comprising 1241 adult patients who had been diagnosed with BAM and were clinically assessed before and after therapy.[28, 31, 32] The articles included one randomised controlled trial, 16 prospective case series, 12 retrospective case series and one article that compared treatment results between two centres, α and β, using retrospective and prospective data respectively. Chronic diarrhoea symptoms were the predominant complaint in all patients. The lack of randomised controlled trials is likely to be the result of poor funding and commercial interest into what is a majorly under-recognised condition. In addition, treatment has relied on conventional BAS for years and colesevelam, the only new treatment available, is not yet licensed for BAM.

The most commonly used diagnostic test of BAM was the SeHCAT test (24 studies). These studies reported the whole body retention values used to assess the presence and/or severity of BAM; however, the cut-off value defined as 'abnormal' varied between studies (range: <8% to <15%). Other methods of diagnosis included a therapeutic trial of colestyramine,[32] measurement of faecal bile acids[33, 34] and the measurement of serum 7αC4.[35] In one study, a diagnosis of BAM was confirmed, but the method of diagnosis was not stated.[31]

A detailed analysis of all studies, including design, number of participants, method of diagnosis, type of therapy, details of clinical outcomes and reasons for treatment failure and side effects, is displayed in Table 1.

Clinical response to colestyramine therapy

Twenty-three studies investigated the clinical response to colestyramine alone in 801 patients diagnosed with BAM. In all studies, colestyramine was given as a first-line treatment. A clinical response was most commonly defined as a reduction in the frequency of bowel movements either alone (eight studies) or combined with a firmer stool consistency (five studies), improvement in quality of life (one study) or abdominal symptoms (one study). The remaining eight studies reported a symptomatic improvement or cessation of diarrhoea. Treatment was successful in 559 (70%) patients (range 63–100%) who were all able to tolerate colestyramine and maintained a good clinical response at follow-up. Reasons for treatment failure are outlined below.

Of the 23 studies investigating colestyramine in this paper, 242 (30%) patients reported treatment failure with first-line colestyramine therapy and did not continue with treatment. Of these patients, 132 (16%) found therapy ineffective; 86 (11%) found colestyramine intolerable due to unpalatability or side effects; 1 (0.12%) was non-compliant with the treatment regime; 7 (0.87%) were unavailable for follow-up; and for 16 (2%) the reasons were unclear. Reported side effects included abdominal bloating and pain, dyspepsia, nausea and vomiting, flatulence, borborygmi, abdominal distension, constipation and diarrhoea increasing in severity.

Twenty-one studies made a diagnosis of BAM using the 7-day SeHCAT scan and upon analysis of these studies, it was noted that treatment success occurred in 103 of 153 (67%) patients with <5% retention, 467 of 644 (73%) of patients with <8–11.7% retention and 210 of 358 (59%) of patients with <15% retention. These results suggest that there may not be an association between the severity of BAM and response to colestyramine. It should be noted, however, that one study[36] makes a large contribution to this analysis, providing 84%, 24% and 48% of the total number of patients in the <5%, <8–11.7% and <15% SeHCAT bands respectively.

Clinical response to colestipol

The clinical response to colestipol alone has been investigated in only one study[37] in which 12 patients received first-line treatment with colestyramine and, due to its poor taste, one patient switched to colestipol treatment. This patient had an improvement in his/her diarrhoea symptoms (less than or equal to two stools per day) within 1 week that was maintained after 2 months of follow-up.

Clinical response to colesevelam therapy

The clinical response to colesevelam was investigated in 90 patients with BAM across five studies (one randomised control trial and four case series). Colesevelam was investigated as a first-line therapy in a randomised controlled trial of 24 patients,[35] which found that colesevelam moderately increased 24-h colonic transport time, was associated with firmer stool consistency and had a significant benefit the authors described as a 'greater ease of stool passage.'

Table 1 | Studies investigating the clinical response to colestyramine, colestipol, colesevelam and aluminium hydroxide therapy for chronic diarrhoeal symptoms in patients with bile acid malabsorption

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Merrick 1985[44]	P (33)	7d SeHCAT < 8%	Group 1: COL/AH Group 2: COL Group 3: COL	Group 1 (type 1 BAM): 19/23 (82%) had symptomatic relief with COL or AH. Group 2 (type 3 BAM): 4/5 (80%) had symptomatic relief with COL Group 3 (type 2 BAM): 4/5 (80%) had symptomatic relief with COL	Group 1: treatment not tolerated in 2 (9%) and COL refused in 2 (9%) Group 2: treatment not tolerated in 1 (20%) Failure in group 3: 1 (20%) lost for follow-up
Sciarretta 1986[49]	P (6)	7d SeHCAT <10%	COL	Disappearance of diarrhoea in 6 (100%)	None
Arlow 1987[33]	R (8)	Faecal bile acids (two to three times above normal)	COL	8 (100%) had a significant improvement in their symptoms, reporting fewer and firmer bowel movements per day.	No side effects or poor tolerance reported
Sciarretta 1987[45]	P (20)	7d SeHCAT <8%	COL (At least 10 days)	19 (95%) showed response (Showed a reduction in stool frequency within 1 week)	No improvement in 1 (5%)
Williams 1991[50]	P (43)	7d SeHCAT <5/10/15%	COL/AH	Overall, 27 (63%) had a therapeutic response (≤2 bowel actions/day and increase in stool consistency within 48 h) Lower SeHCAT score associated with better response: SeHCAT <5%: 21/22 (95%) responded to COL >5% and <10%: 3/13 (23%) responded to COL and 3/13 (23%) responded to AH, but 7/13 (54%) did not respond to these agents >10% and <15%: 0/8 (0%) responded to COL	1/16 (SeHCAT <5%) responded initially, but could not tolerate COL 15/16 found therapy ineffective
Galatola 1992[51]	P (42)	7d SeHCAT <11.7%	COL	39 (93%) reported an improvement in abdominal symptoms at follow-up (range: 1–24 months, median: 12 months). Mean bowel frequency decreased from 4.1 ± 0.2 to 1.5 ± 0.1 ($P < 0.0001$)	Treatment not tolerated in 2 (5%) No improvement in 1 (2%)
Sciarretta 1992[52]	P (25)	7d SeHCAT <8%	COL	23 (92%) reported a reduction in bowel movement frequency after a follow-up period of 1–6 months (mean: 4.3)	Treatment not tolerated in 1 (4%) No improvement in 1 (4%)

Table 1 | (Continued)

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Ford 1992[42]	R (84)	7d SeHCAT <5/10/15%	COL 1st line AH 2nd line	Overall, 36 (43%) had complete resolution of diarrhoea and could tolerate COL; 53 (63%) had some improvement and tolerated COL. 49 (58%) had complete resolution of diarrhoea, and 66 (79%) had either a full or partial response, but 13/49 with full response found it unpalatable and did not continue treatment; and AH (2nd) was effective in 10/2113 (77%) Lower SeHCAT score associated with better response to COL: SeHCAT <5%: 37/40 (93%) had full response >5% and <10%: 12/29 (41%) full response, 10 (34%) partial >10% and <15%: 0% full, 7/15 (47%) had partial response	COL therapy failure in 31 (37%): No improvement in 18 (14%) Unpalatable in 13(26%) AH (2nd) had no improvement in 3/13 (23%)
Eusufzai 1993[53]	P (8)	7d SeHCAT <10%	COL	5 (63%) responded to treatment (positive change in diarrhoea)	No improvement in 2 (25%) Diarrhoea became more severe in 1 (13%)
Nyhlin 1994[54]	R (21)	7d SeHCAT <10%	COL	18 (86%) had a good systematic response	Therapy ineffective in 2 (10%) Failure in 1 (5%) due to noncompliance No adverse effects stated
Rudberg 1996[55]	P (9)	7d SeHCAT <15%	COL (6 months)	8 (89%) responded (improvement in stool frequency and consistency SeHCAT <5%: 1/1 (100%) responded >5% and <10%: 2/3 (67%) responded >10% and <15%: 5/5 (100%) responded	1 (11%) showed no improvement
Cramp 1996[56]	P (13)	7d SeHCAT <15%	COL	11 (85%) reported reductions in stool frequency. 5 were available for follow-up (range: 1–18 months) and a benefit was maintained in 3 (23%)	2 (15%) were unresponsive 2 (15%) were intolerant (worsening nausea) 2 (15%) were lost to follow-up 4 (30%) since died

Table 1 | (Continued)

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Niaz 1997[57]	R (16)	7d SeHCAT <15%	COL (assessed over 2 weeks)	15 (94%) responded, with a mean stool frequency reduction from 7.2/day to 2.1/day ($P < 0.001$)	Failure in 1 due to no improvement
Sinha 1998[58]	P (9)	7d SeHCAT <5/10/15%	COL	6 (67%) had an immediate response (<24 h) to therapy and a marked reduction in stool frequency (median: 5/day to 2/day, $P = 0.03$) post-treatment Lower SeHCAT score associated with better response SeHCAT <5%: 1/1 (100%) responded >5% and <10%: 4/4 (100%) responded >10% and <15%: 1/4 (50%) responded	Treatment not tolerated in 2 (22%) No reduction in stool frequency in 1 (11%)
Rössel 1999[59]	R (13)	7d SeHCAT <15%	COL	13 (100%) initially responded, but 7 (54%) continued treatment	6 (46%) discontinued due to side effects including nausea and constipation
Smith 2000[41]	P (96)	7d SeHCAT <10%	Conventional (1st) BAS (2nd)	Conventional: 27/96 (28%) had an improvement in symptoms[Either prednisolone, codeine or loperamide] BAS: 58/69 (84%) responded to either COL or COS 11/96 (11%) failed both treatments	COS was given instead of COL later in the study due to its more acceptable taste
Ung 2000[37]	P (12)	7d SeHCAT <10%	COL (1st) COS (2nd) (2 months)	COL (1st): 10 (83%) tolerated COL and had a good response (an improvement in diarrhoea (≤2 stools/day) within 1 week that was maintained after 2 months); 1(8%) had partial improvement over 1–2 months COS (2nd) 1/1 (100%) had a rapid response	COL taste not tolerated in 1 (8%) who switched to COS
Fernandez-Banares 2001[60]	P (46)	7d SeHCAT <11%	COL	43 (93%) had clinical remission (<2 formed or semiformed stools per day) BAM with MC: 19/22 (86%) had clinical remission BAM with IBS-D: 24 (100%) had clinical remission	No improvement in 3/22 (7%) Adverse side effects: none

Table 1 | (Continued)

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Wildt 2003[61]	R (54)	7d SeHCAT <10%	COL	38 (70%) responded to treatment (>25% reduction in bowel movements) No significant association between response and SeHCAT value or type of BAM	Reasons for failure were unclear 2 (4%) had worsening of diarrhoea, and side effects included constipation, nausea, borborygmi, meteorism, flatulence and abdominal pain
Knox 2004[31]	R (61)	Not stated	COL 1st line: 61 COV 2nd line: 16	COL (1st): 45 (74%) were tolerant, 16 (26%) were intolerant. Further details of clinical response not reported. COV (2nd): 9/16 (56%) remained on for >6 months For 8 COV patients with long-term follow-up: mean (±SE) number of daily bowel movements decreased from 5.8 ± 1.3 to 2.0 ± 0.7 ($P < 0.03$); and mean health-related quality of life score increased from 45 ± 5.4 to 51 ± 4.5 as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)	COL: intolerance mostly due to unpalatability and abdominal bloating COV failure: 2 (13%) had lack of improvement; 3(19%) had bloating/constipation; and 2 (13%) sought alternative anti-diarrhoeals.
Puleston 2005[32]	R (5)	Therapeutic trial of COL	COV 2nd line after failed COL therapy	COV (2nd): 5 (100%) diarrhoea resolved without side effects Length of time until follow-up ranged from 2 to 7 months	COL failure: 2 (40%) unpalatability and bloating; 1 (20%) had dyspepsia, 1 (20%) had intractable vomiting; and 1 (20%) had intractable nausea
Fernandez-Banares 2007[22]	P (37)	7d SeHCAT <11%	COL (12-month follow-up period)	28 (76%) had a good response, which was maintained at follow-up (diarrhoea cessation). Median time to achieve clinical remission was 6 days.	Treatment ineffective in 9 (24%)

Table 1 | (Continued)

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Wedlake 2009[40]	R and Q (45)	7d SeHCAT <10% or by clinical criteria	COV 1st line: 15 COV 2nd line after failed COL therapy: 30	Whole cohort: 39 (87%) reported symptom improvement and 30 (67%) have continued long-term COV (1st): 13 (87%) continued long-term; 11 up to last follow-up (median 34 months, range: 4–44 months) and 2 until their deaths (After 6 and 13 months) COV (2nd): 17 (57%) continued long-term; 14 up to last follow-up (median 22, range 4–41) and 3 until death (After 3, 11 and 27)	Of 15 who discontinued: 5 due to intolerance (had ≥1 of flatulence, bloating and constipation) 5 considered COV ineffective 3 felt the regime was too difficult (2 had resolved symptoms)
Menon 2011[62]	R (25)	7d SeHCAT <10%	COL	18 (72%) had diarrhoea symptoms resolved and continued treatment until last follow-up (median 1.58 years, range 1–5)	7 (28%) stopped treatment: Constipation in 1 (4%) No improvement in 6 (24%)
Odunsi-Shiyanbade 2010[35]	RCT (24)	Serum 7αC4	COV: 12 Placebo: 12 (12–14 days)	COV: Moderately increased 24 h colonic transit time (mean 4 h, $P = 0.22$) and associated with greater ease of stool passage ($P = 0.048$) and firmer stool consistency ($P = 0.12$). Treatment effect significantly associated with baseline serum 7αC4 ($P = 0.0025$).	No serious adverse effects or early termination of therapy Headache, nausea, flatulence and green coloured stools occurred at similar rates in both groups (10–45%)
Borghede 2011[36]	R (171)	7d SeHCAT<15%	COL	108 (71%) reported a positive effect on bowel habits (lower frequency of stools per day and/or a firmer consistency) No association between BAM severity and treatment response SeHCAT <5%: 80/129 (72%) responded >5% and <10%: 20/28 (80%) responded >10% and <15%: 8/14 (57%) responded	Intolerance in 21 (12%) No improvement: 42 (25%)

Table 1 | (Continued)

First author and Year	Design (*N*)	Test for detecting BAM	Therapy (Duration if stated)	Clinical response	Adverse effects/ reasons for therapy failure
Orekoya 2012[63]	R (68)	7d SeHCAT ≤8%	COL 1st line: 68 COV 2nd line: 12	COL (1st): 41 (60%) had symptom improvement COV (2nd): 5 (42%) had a positive response M:F response to BAS was 76%:60%	COL failure: 18 (26%) reported poor tolerance, 9 (13%) found COL ineffective COV: None reported poor tolerance
Dhaliwal 2013[43]	R (α)/P (β) (129/99)	7d SeHCAT<10%	BAS (1st: COL/ COS; 2nd: COV) [α: 2001–2006] [β: 2008–2012]	Response to treatment (rated as good, partial or poor) with BAS recorded across two centres: α & β Centre α: 60 (47%) good; 30 (23%) partial; 15 (12%) poor Centre β: 40 (40%) good; 23 (23%) partial; 10 (10%) poor	Centre α: 24 had no treatment response Centre β: 17 has no treatment response
Johnston 2013	P (10)	7d SeHCAT<10%	OCA/LOP Resc (2 weeks)	Clinical improvement in all patients including stool frequency (23 to 14 per week, $P = 0.02$), stool type according to the Bristol Stool-form Scale (5.15 to 4.34, $P = 0.05$) and a diarrhoea index [(stool frequency * mean BSFS) + loperamide use (weekly mg*3)] (113 to 76, $P = 0.005$) Reduced symptoms of abdominal pain, urgency and bloating in most patients. Fasting FGF19 increase (133–237 pg/mL; $P = 0.007$) & most patients had a large OCA first dose/postprandial response; reduction in fasting BA (1.5–0.9 μmol/L; $P = 0.13$) & postprandial BA (4.9–3.0 μmol/L, $P = 0.02$). Reduction in postprandial BA & increase in fasting FGF19 both correlated with reduction in stool frequency.	OCA was well tolerated and no adverse events were reported of clinical concern.

N, number of patients; P, prospective case series; R, retrospective case series; RCT, randomised controlled trial; Q, questionnaire; COL, colestyramine; COS, colestipol; COV, colesevelam; AH, aluminium hydroxide; OCA, obeticholic acid; LOP Resc, loperamide rescue therapy; BAS, bile acid sequestrants; BA, bile acids; 7d SeHCAT, 7-day ^{75}Selenium homocholic acid taurine test; α, centre α; β, centre β.

In the four case series, a clinical response was defined as a symptomatic improvement in two studies, diarrhoea cessation in one study and a reduction in stool frequency with improvement in quality of life as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) in one study. The SIBDQ has been shown to be a valid and reliable tool that can successfully detect meaningful clinical changes in health-related quality of life in inflammatory bowel disease (IBD);[38, 39] however, it is yet to be validated in the context of BAM. Wedlake *et al.* investigated colesevelam as both a first- and second-line therapy whilst the remaining three studies investigated second-line colesevelam use only.[40]

As a first-line treatment, Wedlake *et al.* demonstrated that 13 of 15 (87%) patients found therapy successful, reporting an improvement in symptoms and continuing long-term treatment.[40] As a second-line treatment (63 patients across 4 studies), the response to colesevelam was investigated after failure of colestyramine therapy. Treatment was successful in 36 (57%) patients (range: 42–100%) who were able to tolerate colesevelam and maintained a clinical response at follow-up (range: 2–44 months). To date, there have been too few studies investigating colesevelam in BAM to reliably assess whether a significant relationship exists between treatment success and the severity of bile acid malabsorption. Odunsi-Shiyanbade *et al.* did report, however, that colesevelam treatment effect was significantly associated with the severity of BAM as measured by baseline serum 7αC4 ($P = 0.0025$), a bile acid precursor.[35]

Overall, 29 (32%) of the 90 patients across the five studies found colesevelam therapy unsuccessful. Two of these patients reported a resolution of symptoms; however, 17 (19%) patients found therapy ineffective; 8 (9%) found therapy intolerable due to unpalatability or side effects; and 3 (3%) felt the treatment regime was too difficult to follow. Side effects included abdominal bloating, constipation, flatulence, nausea and vomiting. Patients in Odunsi-Shiyanbade's randomised controlled trial reported no serious adverse effects or early termination of therapy.[35] Minor side effects, including headache, nausea and green coloured stools, occurred at similar rates in both the treatment and control groups.

Clinical response to conventional anti-diarrhoeals

Smith *et al.* investigated the clinical response to conventional anti-diarrhoeal therapies in 96 patients with BAM diagnosed by a SeHCAT score <10%.[41] This study did not, however, specify response to individual drugs, stating only that patients received first-line treatment with codeine, loperamide or prednisolone (not considered a conventional anti-diarrhoeal agent). An improvement in symptoms was reported in 27 (28%) of these patients.

Clinical response to aluminium hydroxide

Ford *et al.* investigated the clinical response to aluminium hydroxide as a second-line therapy in 13 patients with BAM as diagnosed by a SeHCAT score less than 10%.[42] These patients all had a full response (complete resolution of diarrhoea) to colestyramine initially, but found it unpalatable and could not continue with treatment. Aluminium hydroxide improved symptoms in 77% of these patients who had previously failed colestyramine therapy.

Clinical response to treatment with more than one drug

Five studies investigated the clinical response to more than one drug used separately, but did not report how many patients received treatment from either drug. One study investigated the use of obeticholic acid therapy, but allowed the use of loperamide as a rescue therapy and did not state the number of patients who required this rescue therapy.

Two studies investigated the use of BAS therapy. Dhaliwal *et al.* compared the treatment response with BAS (first-line colestyramine or colestipol; second-line colesevelam) between two centres, α and β, comprising 129 and 99 patients with BAM and a SeHCAT score less than 10% respectively.[43] Clinical response was graded good, partial or poor. Response in centre α was reported as good in 60 patients (47%), partial in 30 patients (23%) and poor in 15 patients (12%). No response was reported in 24 patients (19%) and overall, of the 129 patients, 70% had a response that was either good or partial. Response in Centre β was reported as good in 40 patients (40%), partial in 23 patients (23%) and poor in 10 patients (10%). No response was reported in 17 patients (17%) and overall, of the 99 patients, 64% had a response that was either good or partial. Across the two centres therefore, 67% of the 228 patients reported a response that was either good or partial. Smith *et al.* studied second-line BAS therapy (either colestipol or colestyramine) in 69 patients with BAM who had previously failed conventional anti-diarrhoeal therapy.[41] All patients had a 7-day SeHCAT score less than 10%, and 84% of these patients reported an improvement in symptoms and quality of life.

Two studies investigated the use of colestyramine and aluminium hydroxide. Merrick *et al.* studied 23 patients

with type 1 BAM and a 7-day SeHCAT score less than 8%.[44] These patients received treatment with either colestyramine or aluminium hydroxide and 82% were found to have symptomatic relief. Williams *et al.* studied 13 patients with a 7-day SeHCAT score between 5% and 10% who received treatment with either colestyramine or aluminium hydroxide; 23% responded to colestyramine and 23% responded to aluminium hydroxide, while 54% found that therapy did not improve their symptoms.[45]

Johnston *et al.* investigated the use of obeticholic acid (OCA) with loperamide rescue therapy over 2 weeks, in a proof-of-concept study, on 10 patients with type 2 BAM diagnosed by a 7-day SeHCAT score less than 10%.[28] Patients recorded stool frequency and type [according to the Bristol Stool-form Scale (BSFS)]. A diarrhoea index [(stool frequency × mean BSFS) + loperamide use (weekly mg)] was also calculated. Clinical improvements were found in all patients, including stool frequency (23 to 14 per week, $P = 0.02$), stool type (5.15 to 4.34, $P = 0.05$) and the diarrhoea index (113 to 76, $P = 0.005$). Patients also tended to report reduced symptoms of abdominal pain, urgency and bloating. OCA was well tolerated and no adverse events were reported of clinical concern. Laboratory outcomes included an increased fasting FGF19 from 133 to 237 pg/mL ($P = 0.007$) and a reduction in fasting and postprandial bile acids from 1.5 to 0.9 μmol/L ($P = 0.13$). A reduction in postprandial bile acids & increase in fasting FGF19 both correlated with reduction in stool frequency.

Response to a low- and high-fat diet

One study by Koga *et al.* studied the effects of dietary fat on faecal bile acid excretion in nine Crohn's disease patients with BAM on an elemental diet.[34] Whilst the results of this study are of interest, as this study only reported laboratory responses to dietary change, it was decided to not include this study in the clinical results table. A diagnosis of BAM was made in patients shown to have a significantly higher rate of faecal bile acid excretion than controls. Patients were initially fed with a fat-restricted elemental diet containing approximately 1.5 g/day of fat. With the additional of 50 g/day of butterfat, the faecal bile acid excretion rate was significantly increased in all patients, and the authors suggest that the amount of dietary fat should be an important consideration in the evaluation of BAM in Crohn's disease.

Summary of the current treatment options available

A summary of the current treatment options available is displayed in Table 2. OCA is not included in this table as it is not yet available in clinical practice. Details of their advantages; disadvantages; treatment dose and schedule; and cost are presented in this table, and these points will be considered in the following discussion.

DISCUSSION

This review of the treatment of BAM is the largest to date and covers 33 years of evidence supporting different treatments for a common, yet under-diagnosed, cause of chronic diarrhoea.

Bile acid sequestrant therapy

The vast majority of studies have investigated the use of BAS therapies for BAM, with colestyramine being by far the most studied of these agents. This review suggests that colestyramine is an effective intervention in a relatively high proportion of patients with BAM, but treatment success may not be associated with the severity of BAM in contrast to the findings of a previous review of idiopathic BAM.[11] Smith *et al.* suggest that colestipol may also be effective, and may be better tolerated than colestyramine due to its more acceptable taste; however, this study did not describe the response to colestipol alone.[41] Only one patient in a study by Ung *et al.*[37] reported treatment from colestipol alone and hence limited conclusions can be drawn from these data.

Colesevelam is currently rarely prescribed in clinical practice[23] and in the absence of large-scale studies remains unlicensed for use in BAM. Emerging evidence[35, 40] suggests that it may be an effective alternative to traditional BAS therapy. Furthermore, many of the patients who had failed colestyramine therapy were successfully treated with colesevelam and the majority (57%) continued long-term treatment. Larger studies are clearly warranted to establish whether colesevelam might have better efficacy than colestyramine and colestipol as first-line therapy for BAM. One downside of colesevelam is its cost as, when administered at a low dose, it is more expensive compared with other bile acid sequestrants. However, the pricing of these BAS is similar when administered at higher doses.

Colesevelam has the advantage of availability in tablet form, as a major drawback of traditional BAS is that they can be poorly tolerated due to unpalatability (only available in granules and powders).[4] Colesevelam forms a polymeric gel in the gastrointestinal tract and thereby has a more gelatinous consistency compared with other BAS in the enteric environment, and is believed to have improved tolerability as a result.[25] A downside is that

Table 2 | A summary of the treatment options available for the chronic diarrhoeal symptoms of bile acid malabsorption

Treatment	Advantages	Disadvantages	Dosage range and schedule
Colestyramine	Most studied and established treatment Appears to be effective in high proportion of patients	Can be poorly tolerated due to unpalatability and abdominal side effects (come in powders) May reduce the bioavailability of co-administered agents and fat-soluble vitamins (levels therefore need to be monitored and supplemented where necessary)	4 g daily initially, increased by 4 g at weekly intervals (in 1–4 divided doses) to max. 36 g daily. Other drugs should be taken 1 h before or 4–6 h after
Colestipol	May be an effective alternative in those who cannot tolerate taste of colestyramine	Not traditionally indicated and no large-scale studies to date Can be poorly tolerated due to unpalatability (come in granules) and abdominal side effects May reduce the bioavailability of co-administered agents and fat-soluble vitamins (levels therefore need to be monitored and supplemented where necessary)	5 g daily initially, increased in 5 g increments every 1 month to max. 30 g daily Other drugs should be taken 1 h before or 4–6 h after
Colesevelam	Available in tablet form May have improved tolerability Apparent lack of effect on the bioavailability of co-administered agents	Not licensed for BAM No large-scale studies to date Tablets are large in size Rather expensive compared with other bile acid sequestrants if administered at a low dose	3.75 g daily in 1–2 divided doses; max. 4.375 g daily
Conventional anti-diarrhoeals	Better tolerated than bile acid sequestrants No effect on bioavailability of co-administered agents Available in tablet form Relatively inexpensive	No large-scale studies to date Not a targeted treatment	Loperamide: initially 4–8 mg daily in divided doses; max of 16 mg daily. (*Loperamide or Imodium®*) Codeine: 30–60 mg every 4 h; max of 240 mg daily (*codeine phosphate)* Co-phenotrope: initially four tablets, followed by two tablets every 6 h until diarrhoea controlled (max of 10 tablets/day)
Aluminium hydroxide	Better tolerated than BAS No effect on bioavailability of co-administered agents Available in tablet form	Not licensed for BAM No large-scale studies to date	*Alu-Cap®* (Aluminium-only preparation) one capsule four times daily. *Maalox® or Mucogel®* (Co-magaldrox – Mixture with magnesium hydroxide) suspension; 10–20 mL three times daily; 20–60 min after meals and when required
Dietary intervention	No need for drug treatment and has direct effect on the faecal bile acid excretion rate	No large-scale studies to date Compliance can be low due to poor taste Requires formal dietetic assessment	–

the colesevelam tablets are large, and taking multiple tablets daily might present a challenge for some patients.[40]

Another drawback of BAS therapy is that, while BAS are not absorbed and therefore have no systemic side effects, they are capable of binding other compounds. As

a result, they may reduce the intestinal absorption of many drugs (including warfarin, digoxin, diuretics and beta blockers) and fat-soluble vitamins (vitamins A, D, E and K), thus significantly reducing their oral bioavailability.[46] As a precaution, it is advised that other drugs are taken 1 h before or at least 4–6 h after BAS administration, and increased monitoring of digoxin levels, or prothrombin time for patients receiving warfarin, may be necessary if these agents are used in combination with BAS.[4] Periodic checking for deficiencies of fat-soluble vitamins is also recommended, especially in women who are pregnant or breast-feeding, and vitamin supplementation may be warranted, with appropriate intervals between dosing of the vitamins and bile acid sequestrants.[4] A benefit of colesevelam is its apparent lack of effect on the bioavailability of co-administered agents.[47] This has been attributed to its unique 'open' polymer chemical structure compared with traditional BAS, that maximises interactions with bile acids and reduces potential interactions with other drugs.[25] This may increase compliance, particularly in those patients who require the use of multiple medications.

Other drug therapies

Non-BAS drug therapy for BAM is not traditionally associated with the same issues of tolerability and drug interaction. Conventional anti-diarrhoeals are prescribed for the treatment of BAM by an estimated 26% of British gastroenterologists,[23] yet these agents have not yet been extensively studied for their role in the treatment of BAM. The one study of such agents in this review did not specify response to individual drugs and found that a relatively low proportion of patients had symptomatic improvement on first-line treatment with codeine, loperamide or prednisolone (not normally considered a conventional anti-diarrhoeal agent).[41] Co-phenotrope is an anti-diarrhoeal treatment that is commonly used in clinical practice and therefore has been listed in Table 2, but it has yet to be studied in the context of BAM. Racecadotril is another treatment licensed for acute diarrhoea that was launched very recently; however, no publications exist to date studying its utility in BAM.

Aluminium hydroxide is rarely prescribed for BAM in clinical practice.[23] It has been infrequently studied in the context of BAM, with no large-scale or randomised studies to date. It has been suggested, however, that it possesses bile acid binding properties comparable with colestyramine.[26] Furthermore, evidence in this review suggests that it could be an effective alternative to BAS therapy,[44, 45] and may effectively be used to treat patients who have been intolerant of colestyramine.[42] As with colesevelam, larger studies are warranted to establish its efficacy.

The first proof-of-concept study of the FXR agonist OCA was promising and showed that therapy with OCA in type 2 BAM may be well tolerated and effective, resulting in clinical improvements in stool frequency and type.[28] This novel drug may be the first of many following the discovery of the involvement of FGF19 and FXR in the development of type 2 BAM, and this therapy has the advantage of affecting a more specific therapeutic target than conventional treatment. OCA also does not appear have the same issues of unpalatability and interaction with other agents that affect colestyramine and colestipol. Whilst OCA is not yet available for clinical use, larger randomised controlled trials of OCA are clearly needed to establish its efficacy.

Diet

A low-fat diet may be considered an appropriate therapy in patients with mild symptoms of BAM, with or without the addition of medium-chain triglycerides (MCTs) added as a calorific supplement, which do not require bile acids for solubilisation.[13] Koga *et al.* demonstrated that fat intake was associated with faecal bile acid excretion rate and, although future studies are needed to clarify the benefits of such interventions, this would suggest that the amount of dietary fat should be an important consideration in the evaluation of BAM.[34] It may be beneficial to refer patients to an experienced dietician, as he/she will provide individual dietary advice based upon a patient's BMI, weight history and symptoms, and will potentially increase compliance as this diet can have a poor taste.

Limitations of this review

Comparing data from these studies is made more challenging as uniform diagnostic testing was not used to identify patients with BAM. The majority of authors used the 7-day SeHCAT test (22 studies); however, the cut-off retention value defined as 'abnormal' varied between these studies, and four other studies described the use of other diagnostic tests. Caution also needs to be taken when interpreting the results of one study[31] in which the method of diagnosis was not stated. Puleston *et al.*[32] employed a therapeutic trial of colestyramine to make a diagnosis of BAM (despite subsequently commencing their patients on colesevelam due to poor tolerance of cholestyramine) and such an approach is often used as a diagnostic tool;[8] however, it should not be regarded as a definitive diagnostic marker.[35]

Another pitfall of combining data from these studies is that there is variation in the author's definition of a 'response' to treatment. Some authors described specific outcome measures such as stool frequency and consistency, while others used more general measures such as 'symptomatic improvement'. Furthermore, the dosage and timing of drug administration would have varied between studies.

Finally, many of these studies do not state the duration of time for which patients were clinically assessed or followed up while on treatment. This issue is significant as while a large proportion may show an improvement in symptoms initially, many of them may have been unable to continue long-term treatment. The discontinuation rates of BAS prescribed for cholesterol lowering are known to be high, and one study found that discontinuation rates with traditional BAS were 59% and 83% at 1 and 4 years respectively.[48] It is essential that future studies of treatment for BAM are carried out over similarly long periods, and contain clear details of those patients who were able to continue long-term treatment, as well as those who reported improvement initially.

CONCLUSIONS

The relationship between BAM and patient outcomes in response to treatment remains complex and uncertain. Colestyramine and colestipol therapy may be effective in some patients, but their usage is often limited in clinical practice because of their palatability and ability to bind to other medications. Early studies of alternative therapies (including colesevelam and aluminium hydroxide) as well as dietary intervention are encouraging and the clinical benefits of these need to be further explored. The results of the first trial of OCA are certainly promising and this novel drug may have an exciting future in the treatment of this condition. NICE research recommendations[29] stress that a programme of research is needed to evaluate the efficacy and tolerability of treatment for BAM, and it is vital that future trials employ accurate diagnostic testing and are conducted over longer periods so that the long-term benefits and tolerability of these different approaches can be evaluated.

AUTHORSHIP

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