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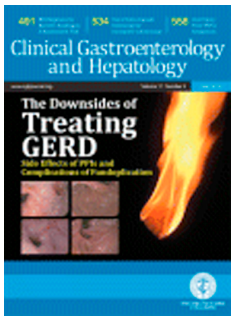


CANADIAN ASSOCIATION OF GASTROENTEROLOGY CLINICAL PRACTICE GUIDELINE ON THE MANAGEMENT OF BILE ACID DIARRHEA

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PII: S1542-3565(19)31002-X
DOI: https://doi.org/10.1016/j.cgh.2019.08.062
Reference: YJCGH 56748

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 28 August 2019

Please cite this article as: Sadowski DC, Camilleri M, Chey WD, Leontiadis GI, Marshall JK, Shaffer EA, Tse F, Walters JRF, CANADIAN ASSOCIATION OF GASTROENTEROLOGY CLINICAL PRACTICE GUIDELINE ON THE MANAGEMENT OF BILE ACID DIARRHEA, *Clinical Gastroenterology and Hepatology* (2019), doi: https://doi.org/10.1016/j.cgh.2019.08.062.

# CANADIAN ASSOCIATION OF GASTROENTEROLOGY CLINICAL PRACTICE GUIDELINE ON THE MANAGEMENT OF BILE ACID DIARRHEA

**Running title**: Management of Bile Acid Diarrhea

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**Financial support**
This guideline was supported through unrestricted grants to the Canadian Association of Gastroenterology by Pendopharm and GE Healthcare Canada, neither of which had any involvement in the development of this guideline.

**Abbreviations used in this paper:**
5-ASA: 5-aminosalicylate; AGA, American Gastroenterological Association; BAD, bile acid diarrhea; BAST, bile acid sequestrant therapy; BMs, bowel movements; BSG, British Society of Gastroenterology; CAG: Canadian Association of Gastroenterology; CI: confidence interval; CoE: certainty of evidence; CPG: clinical practice guideline; DTA, diagnostic test accuracy; FGF19, fibroblast growth factor; GRADE: Grading of Recommendation Assessment, Development and Evaluation; HTA, Health Technology Assessment; HPC, hydroxypropyl cellulose; IBS, irritable bowel syndrome; IBS-D, diarrhea predominant IBS; NPV, negative-predictive value; OR, odds ratio; PICO, patient population, intervention, comparator, outcome; PPV, positive-predictive value; RCT: randomized controlled trial; SeHCAT,[75]selenium homocholic acid taurine or tauroselcholic acid; SIBO, small intestinal bacterial overgrowth; SR, systematic review

**Disclosures**

NO, I do not have any industry or government relationships to report: (DS, FT, GL)

ADVISORY BOARD: Abbvie (JM), Allergan (JM, MC), American College of Gastroenterology (WC), American Neurogastroenterology and Motility Society (WC), AstraZeneca (JM), BioKier (MC), Boehringer-Ingelheim (JM), Celgene (JM), Celltrion (JM), Ferring (JM), Hospira (JM), Janssen (JM), Merck (JM), Pfizer (JM), Pharmascience (JM), Rome Foundation (WC), Shire (JM), Takeda (JM)

CONSULTING: Allergan (WC), AstraZeneca (MC), Biomerican (WC), Dignify Therapeutics (MC), Elobix AB (MC), Enterin (MC), ENYO Pharma (JW), GE Healthcare (JW), IM Health (WC), Intercept Pharma (JW), Ironwood (MC, WC), Lupin (JM), Merck (JM), Metacrine Inc. (JW), Nestle (WC), Novartis Pharma (JW), Pharmascience (JM, JW), Prometheus Diagnostics (JW, WC), QOL Medical (WC), Ritter (WC), Salix (WC), Shire (MC, WC), Takeda (MC), Theravance (MC), Zealand Pharma (JW)

EDUCATION/RESEARCH GRANT: Allergan (MC), AstraZeneca (MC), Elira (MC), ENYO Pharma (JW), GE Healthcare (JW), Intercept Pharma (JW), NGM Biopharma (MC), Novartis Pharma (JW, MC), Novo Nordisk (MC), Prometheus Diagnostics (JW), Rhythm (MC)

SPEAKER'S BUREAU: Abbvie (JM), Allergan (JM), Ferring (JM), GE Healthcare (JW), Janssen (JM), Pendopharm (ES), Shire (JM), Takeda (JM)

**Writing assistance**
The consensus group would like to thank Pauline Lavigne and Steven Portelance (unaffiliated) who provided medical writing services on their behalf, supported by funds from the Canadian Association of Gastroenterology.

**Author contributions**
The Clinical Practice Guideline group (DS, MC, WC, ES, JW), GL, and FT reviewed the literature and drafted the statements. GL and FT assessed the evidence and provided GRADE (Grading of Recommendation Assessment, Development and Evaluation) evaluations. All members of the Consensus Group voted on the recommendations. The manuscript was initially drafted by the chair (DS) and the methodologists (GL, FT), after which it was revised based on input from all members of the Consensus Group, as well as the moderator (JKM). As per CAG policy for all clinical practice guidelines, the manuscript was made available to all CAG members for commenting before submission for publication. Members were notified that the manuscript was available on the members-only section of the CAG website and open for comment for a 2-week period.

## ABSTRACT

**Background & Aims:** Chronic diarrhea affects about 5% of the population overall. Altered bile acid metabolism is a common but frequently undiagnosed cause.

**Methods:** We performed a systematic search of publication databases for studies of assessment and management of bile acid diarrhea (BAD). The certainty (quality) of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation approach. Patient population, intervention, comparator, and outcome questions were developed through an iterative process and were voted on by a group of specialists.

**Results:** The certainty of evidence was generally rated as very low. Therefore, 16 of 17 recommendations are conditional. In patients with chronic diarrhea, consideration of risk factors (terminal ileal resection, cholecystectomy or abdominal radiotherapy), but not additional symptoms, was recommended for identification of patients with possible BAD. The group suggested testing using $^{75}$selenium homocholic acid taurine (where available) or 7α-hydroxy-4-cholesten-3-one, including patients with irritable bowel syndrome with diarrhea, functional diarrhea, and Crohn's disease without inflammation. Testing was suggested over empiric bile acid sequestrant therapy (BAST).

Once remediable causes are managed, the group suggested cholestyramine as initial therapy, with alternate BAST when tolerability is an issue. The group suggested against BAST for patients with extensive ileal Crohn's disease or resection and suggested alternative anti-diarrheal agents if BAST is not tolerated. Maintenance BAST should be given at the lowest effective dose, with a trial of intermittent, on-demand administration, concurrent medication review, and reinvestigation for patients whose symptoms persist despite BAST.

**Conclusions:** Based on a systematic review, BAD should be considered for patients with chronic diarrhea. For patients with positive results from tests for BAD, a trial of BAST, initially with cholestyramine, is suggested.

**KEY WORDS:** SeHCAT; C4; fibroblast growth factor 19; FGF19; IBS

## INTRODUCTION

Diarrhea is a common symptom in the general population of developed countries. Among community dwelling persons the 1-month rate of diarrhea was 7.6% in Canada and the United States, 6.4% in Australia, and 3.4% in Ireland; about 20% of subjects sought medical care for this symptom.[1] The prevalence of chronic diarrhea has been estimated to affect about 5% of this population overall,[2] and may be higher among older individuals.[3]

The most common causes of chronic diarrhea in clinical practice are functional disorders (eg, irritable bowel syndrome [IBS]), and inflammatory diseases (eg, Crohn's disease, celiac disease).[3] However, a common but frequently, underdiagnosed cause of chronic diarrhea is dysregulated bile acid recycling within the enterohepatic circulation: either excessive biosynthesis/secretion of bile acids, or malabsorption of bile acids by the ileum. Unabsorbed bile acids in the colon appears to cause diarrhea by stimulating fluid, mucus, or sodium secretion; increasing gastrointestinal motility; damaging the mucosa; or stimulating defecation.[3,4]

Three subtypes of bile acid diarrhea (BAD) have been described: Type 1, patients with terminal ileal disease (eg, Crohn's disease, resection) or radiation injury resulting in impaired reabsorption of bile acids; type 2, idiopathic or primary; and type 3, other conditions (eg, celiac disease, cholecystectomy) that alter intestinal motility or bile acid absorption.[3,5] BAD has been reported in about 25-35% of patients with chronic diarrhea or diarrhea-predominant IBS (IBS-D).[6] Rates are even higher in patients with underlying terminal ileal disease, or other conditions such as cholecystectomy.

The diagnosis of BAD continues to be a challenge, although this may be improved in future with the general availability of screening serological test and other diagnostic tests discussed below. While a treatment trial with a bile acid sequestrant therapy (BAST) is often used, this approach has not been adequately studied, and is likely imprecise, and may lead to both under-treatment and overtreatment. Specific diagnostic tests are under investigation, particularly radiodiagnostic measurement of bile acid pool loss with $^{75}$selenium homocholic acid taurine (SeHCAT, GE Healthcare Canada Inc., Ontario, Canada), or measurement of serum levels of biomarkers of bile acid synthesis including 7α-hydroxy-4-cholesten-3-one (C4) or the ileal regulatory hormone, fibroblast growth factor 19 (FGF19). SeHCAT testing is unavailable in some countries (including the USA).

BAD is generally not cured, and as is the case with many chronic gastrointestinal diseases or disorders, many patients will require lifelong treatment.[7,8] Treatment is generally with BAST, but is also dependent on the underlying causes of BAD, severity of symptoms, or the presence of other comorbid illnesses (eg, Crohn's disease, celiac disease).

BAD is an understudied, often underappreciated condition, and questions remain regarding its diagnosis and treatment. There have been guidelines on the management of chronic diarrhea from the American Gastroenterological Association (AGA),[9] and the British Society of Gastroenterology (BSG),[10] but diagnosis and management of BAD was not extensively assessed in these publications. The BSG updated guidelines on the investigation of chronic diarrhea in adults,[11] published after the consensus meeting, addressed some issues related to BAD.

The purpose of this guideline is to critically review the literature relating to diagnostic testing, and the induction and maintenance treatment of BAD, with the aim of developing specific consensus recommendations for patients with BAD.

## METHODS

*Scope and purpose*

These consensus statements focused on specific issues pertaining to the medical management of BAD, which the participants and GRADE experts (FT, GL) identified *a priori*.

*Sources, literature searches, and systematic reviews (SRs)*

The Editorial Office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University performed a systematic search of MEDLINE, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) for literature published between 1990 and September 2017. Key search terms were bile acid, cholecystectomy, cholestyramine, colestipol, colesevelam, diarrhea, loperamide, malabsorption, resection, SeHCAT, and sequestrants. An additional search of the databases for SeHCAT trials published prior to 1990 (database inception as start date) was also performed. Only human studies published in English were considered. Further details of the search strategies are provided in Appendix 1.

*Assessment of the certainty (quality) of evidence (CoE)*

Prior to the face-to-face meeting, the statements were converted to specific PICO (patient population, intervention, comparator, and outcome) questions by the 2 non-voting methodologists (FT, GL). The overall certainty of evidence (CoE) was determined using the GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach[12] to assess risk of bias (of individual studies and overall across studies), indirectness, inconsistency, imprecision, as well as other considerations (including publication bias). As described in GRADE[12,13] and used in previous consensus guidelines from the CAG,[14-18] CoE was graded as very low, low, moderate, or high. GRADE evaluations for each statement were provided prior to, and discussed at, the consensus meeting.

The consensus group agreed that four statements (Statements 11, 13, 14, and 17) met GRADE criteria for "good practice statements", that these recommendations were clinically obvious, and that collection and GRADE assessment of evidence for these statements was not a good use of resources.[19] Although formal GRADE evaluations were not performed, details of these statements are provided in the text.

Approved product labeling from government regulatory agencies varies from country to country, and though not ignored, recommendations are based on evidence from the literature and consensus discussion and may not fully reflect the product labeling for a given country.

*Consensus process*

A face-to-face consensus meeting was held in Toronto, Ontario, Canada, in February 2018. The international consensus group was comprised of 5 voting gastroenterologists (including the chair [DS]), from Canada, the US, and the UK. Other participants included a nonvoting moderator (JM), the 2 GRADE experts (FT, GL), and a nonvoting observer.

The consensus process was facilitated by the CAG via a web-based consensus platform (ECD solutions, Atlanta, Georgia, USA). The platform allowed consensus participants to review results of the initial literature searches and "tag" (select and link) the references to specific statements. Copies of the "tagged" references were available to all members of the consensus group. The full consensus group voted anonymously on their level of agreement with the individual statements using a modified Delphi process.[20,21] Participants suggested revisions and commented on the statements, after which, the specific statements were revised through 2 iterations.

At the 1-day consensus meeting, evidence for each of the PICO questions was presented, after which an Evidence-to-Decision framework was completed.[22] Each PICO question was discussed and revised, and voting members anonymously indicated their level of agreement on a scale of 1 to 5. In favour of a specific strategy was defined as ≥75% of votes being 5 (strongly yes) or 4 (yes). A vote against the strategy was defined as ≥75% of votes being 1 (strongly no) or 2 (no). A vote of 3 indicated neutral. Once reaching agreement on the PICO question, the "strength" of the recommendation (strong vs. conditional) was determined based on 4 components: (a) CoE, (b) benefit/harm balance, (c) patients' values/preferences, and (d) resource requirements.[23] When the CoE was low or very-low, unless at least 1 of the other 3 factors was overwhelmingly strong, the strength of the recommendation would typically default (without a vote) to "conditional", using the phrasing "we suggest". If the statement warranted a vote, and ≥75% of participants voted "strong, then the recommendation would be designated as "strong" and the phrasing was "we recommend".

During the meeting, consensus was not reached on 4 of the PICO questions, therefore no statement was developed and no recommendation made. Evidence and subsequent discussion pertaining to these 4 questions is summarized briefly in the text.

The manuscript was initially drafted by the meeting chair (DS), then reviewed and revised by the remaining members of the consensus group. The manuscript was then made available to all CAG members for comment over a 2-week period prior to submission for publication.

In accordance with CAG policy, written disclosures of any potential conflicts of interest for the 24 months prior to the consensus meeting were provided by all participants, reviewed by the CAG ethics committee, and made available to all group members.

*Role of the funding sources*

Funding for the consensus meeting was provided by unrestricted, arms-length grants to the CAG by Pendopharm and GE Healthcare Canada. The CAG administered all aspects of the meeting, and the funding sources had no involvement in the process at any point, nor were they made aware of any part of the process from the development of search strings and the statements, to drafting and approval of these guidelines.

## RECOMMENDATION STATEMENTS

The individual recommendation statements are provided and include the strength of recommendation and certainty of supporting evidence (according to the GRADE approach), and the voting result. This is followed by a discussion of the evidence considered for the specific statement. A summary of the recommendation statements is provided in Table 1. See Appendix 2 for detailed CoE assessments (including description of study limitations, inconsistency, indirectness, imprecision, publication bias) and the Evidence-to-Decision frameworks.

### Diagnosis of BAD

***Statement 1: In patients with chronic non-bloody diarrhea, we recommend using risk factors (history of terminal ileal resection, cholecystectomy, or abdominal radiotherapy) as the initial assessment to identify patients with possible BAD.***
GRADE: Strong recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%.

***Statement 2: In patients with chronic non-bloody diarrhea, we suggest against using symptom presentation as the initial assessment to identify patients with possible BAD.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: no, 100%.

**Key evidence**: No published randomized controlled trials (RCTs) were available comparing the clinical impact of using vs not using risk factors or symptom presentation for the diagnosis of BAD, therefore evidence from observational, diagnostic test accuracy (DTA) studies was evaluated. Overall, studies show that history of terminal ileal resection, cholecystectomy, or radiotherapy, are the risk factors most commonly associated with having a positive SeHCAT test suggestive of a BAD diagnosis (Table 2).[24-30]

No symptoms have consistently been predictive of a greater likelihood of having SeHCAT-diagnosed BAD among patients with chronic diarrhea. Rates of abdominal pain or discomfort, distension, bloating, flatulence, urgency, were similar or less frequent among patients with BAD and those with diarrhea due to other causes.[24,31-33] Some studies have reported an association between stool weight, consistency, or frequency and a higher risk of BAD among patients with chronic diarrhea, but no diagnostic accuracy data, or definitions are available.[7,31-35]

All studies had either high or unclear risk of bias, inconsistency (with respect to the specific symptoms and clinical characteristics as risk factors for BAD) and imprecision.

**Discussion**: In patients presenting with non-bloody, chronic diarrhea or IBS-D, rates of SeHCAT retention suggestive of BAD are much higher in those with risk factors compared to those in whom other possible causes have been excluded. Rates of BAD were lower in patients without compared to those with risk factors, specifically rates of severe BAD (SeHCAT retention <5%) were about 10%[6,36] compared to 24-48%,[24,26,29] rates of at least moderate BAD (SeHCAT retention <10%) were 19-39%[6,25,34,36] compared to 38-58%,[24,26,29] and rates of at least mild BAD (SeHCAT retention <15%) were 24-27%[6,24,36] compared to 46-68%.[24,26,29] The risk factors most commonly identified are shown in table 2. In patients with ileal resection, BAD appeared to be independent of resection length; resections of <10 cm were sufficient to cause BAD.[26]

The potential harms of using clinical risk factors as a triage test for BAD could include overdiagnoses leading to unnecessary diagnostic tests and/or treatments, or underdiagnoses leading to ongoing patient suffering. In patients with ileal resection, there is an extremely high risk of BAD, and diagnostic testing may not be necessary before treatment, whereas patients with chronic diarrhea post-cholecystectomy or post-radiotherapy may warrant diagnostic tests. No consistent correlation has been found between the length of resection and SeHCAT retention; therefore, all patients should be considered at high risk post-resection.[25,26,37]

Other conditions such as diabetes, pancreatitis, small intestinal bacterial overgrowth (SIBO), microscopic colitis, vagotomy, and celiac disease have been occasionally, but not consistently, associated with an elevated risk of BAD.[26,38]

No symptoms have been identified that will reliably predict a diagnosis of BAD. In fact, data suggest that reliance on symptoms can lead to underdiagnosis in clinical practice; one survey found that 44% of patients reported they had experienced symptoms for more than 5 years before diagnosis.[39] While symptom presentation is inaccurate for BAD, it continues to play a role in the differential diagnosis to rule out other conditions.

Based on the available data, the consensus group recommends that in patients with chronic non-bloody diarrhea, a history of terminal ileal resection, cholecystectomy, or radiotherapy, but not symptom presentation, be used during initial assessment to help identify patients with BAD.

***Statement 3: In patients with chronic diarrhea including IBS-D and functional diarrhea, we suggest SeHCAT testing to identify patients with BAD.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%.

**Key evidence**: Data on the diagnostic accuracy of SeHCAT retention test (as initial test for diagnosis) were derived from 2 prospective DTA studies, both conducted by Sciarretta et al in Italy.[37,40] These were designed as case-control studies to assess the ability of SeHCAT retention to discriminate between cases and controls. However, using other secondary results, a 2013 Health Technology Assessment (HTA) calculated the diagnostic accuracy of SeHCAT retention for predicting response to BAST.[41] In the first study, the sensitivity and specificity of SeHCAT retention (cut-off value <5%) were 85.7% (95% CI, 42.1–99.6) and 100% (95% CI, 54.1–100), respectively, in a subgroup of patients (n=13) with diarrhea without evidence of intestinal or extraintestinal pathology.[37,41] The second study, which included 46 patients with IBS-D or cholecystectomy, found the sensitivity and specificity of SeHCAT retention (cut-off value <8%) were 95.0% (95% CI, 75.1–99.9) and 96.2% (95% CI, 80.4–99.9), respectively.[40,41] In both studies, response to BAST was defined as disappearance of diarrhea. No studies were found that measured the diagnostic accuracy of SeHCAT in patients with chronic diarrhea, which avoided a case-control design and used a proven reference standard (because there is currently no such reference standard, apart from the surrogate response to BAST).

Both DTA studies were found to be at serious risk of bias with respect to the index tests and reference standards used, serious indirectness of the study populations and index tests, and very serious imprecision as a result of the very small sample sizes, and the lower limit of the confidence interval crossing the threshold for a clinically useful diagnostic test. This suggests that the data are insufficient to support or refute the clinical utility of SeHCAT in patients with IBS-D. Therefore, other factors and indirect supportive evidence were considered.

**Discussion**: Overall, the CoE for the diagnostic accuracy of SeHCAT was determined to be very low. As discussed in statement 1, prevalence data suggest that up to 40% of patients with functional diarrhea or IBS-D may have at least moderate BAD as assessed by a SeHCAT cut-off value <10%.[6,25,34,36]

In addition, a systematic review (SR) including 15 observational studies showed a correlation between the severity of SeHCAT loss and response to treatment with BAST:

response to cholestyramine was 96% in patients with <5% retention, 80% at <10% retention and 70% at <15% retention.[6] This was not confirmed by newer SR of 21 studies, that found response rates with BAST of 67% at <5% retention, 73% at <8–11.7% retention and 59% at <15% retention.[42] However, one study[26] published after the earlier SR, which included a large number of patients with secondary BAD, made a disproportionately large contribution to the <5% retention group in this second analysis. Response rates were much lower in patients with negative SeHCAT tests; only 15% of patients had a good or partial response, compared to 65.6% of patients with a SeHCAT retention <15%.[29] A study has been proposed to evaluate the diagnostic accuracy of SeHCAT retention in which the test result will be concealed from clinicians and patients, and all patients will receive BAST.[43]

Cost-effectiveness and feasibility were also considered. The HTA assessed the cost-effectiveness of SeHCAT testing compared to response to BAST based on data from 3 small trials and rather limited assumptions.[41] They concluded that for the short term (first 6 months), the optimal choice between SeHCAT testing and no SeHCAT testing depended on willingness to pay, but that a trial of BAST would be more cost-effective. From the long-term perspective, the optimal choice was a trial of BAST, no SeHCAT testing, or SeHCAT testing with cut-off retention value <15% depending on the scenario. Feasibility can be an issue in some areas, because nuclear medicine facilities or the isotope may not be available.

BAST has poor tolerance and a high dropout rate; a positive SeHCAT test may have the additional benefit of providing the clinician with a stronger argument to encourage patients to stay on therapy when a definite diagnosis of BAD has been made.[44] Other factors to consider are the potential harms of SeHCAT use, such as: radiation risks, patient inconvenience and anxiety, and loss of opportunity to use BAST in cases of false-negative results. Cut-off values to initiate treatment are sometimes inconsistent,[45] and the role of “borderline” SeHCAT retention in therapeutic decisions is ill defined.

Taking all these issues together, the consensus group concluded that SeHCAT retention is a relatively safe test, BAST is a relatively safe treatment (although poorly tolerated), and the anticipated benefit of SeHCAT retention testing likely outweighs the uncertainty of the evidence. While other tests show promise for the future, SeHCAT retention has been the most widely tested, with consistent results.

***Statement 4: In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, we suggest SeHCAT testing.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%.

**Key evidence**: An observational cohort study, included a subgroup of 44 patients with unoperated Crohn's disease in clinical remission (other than diarrhea) who had normal hematology and C-reactive protein.[28] SeHCAT retention was abnormal (<10%) in 54% of patients. Of the 24 patients with abnormal SeHCAT retention, 20 received initial conventional treatment (prednisolone ± 5-aminosalicylate [5-ASA]), followed by BAST when conventional treatment failed. Response rates were 55% with conventional treatment, and 40% with BAST, with 5% failing both treatments. The treatment duration, and outcome assessments, as well as the use of BAST in patients with normal SeHCAT retention were not clearly described. Diagnostic accuracy and the effects of using test results to inform management choices could not be calculated because of the lack of a control group.

The CoE was downgraded to very low due to very serious risk of bias (with regard to the reference standard, patient flow, and timing) and very serious imprecision (very small sample size).

**Discussion**: Although there is very low certainty evidence supporting use of SeHCAT testing to guide management decisions in patients with Crohn's disease, testing may play a role in patients with ileal Crohn's disease in complete remission, who have ongoing chronic diarrhea.

Observational studies suggest that almost half of the patients with ileal Crohn's disease who have not undergone resection will have a positive SeHCAT suggestive of a diagnosis of at least moderate BAD (Table 3).[25,26,28,29] These patients may have a 2-4 times greater likelihood of having a positive SeHCAT compared to having a negative test.[25,29]

Given the association between positive SeHCAT testing and response to BAST in patients with Crohn's disease who continue to have persistent diarrhea despite conventional treatments, the consensus group made a conditional recommendation in favour of SeHCAT testing in patients with Crohn's disease who have no objective evidence of active inflammation.

***Statement 5: In patients with chronic diarrhea including IBS-D and functional diarrhea, we suggest using a C4 assay to identify possible BAD.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 60%; neutral, 20%

*No recommendation A: In patients with chronic diarrhea including IBS-D and functional diarrhea, the consensus group could not make a recommendation for or against the use FGF19 assay to identify possible BAD.*
GRADE: NO recommendation, very-low-certainty evidence; Vote on PICO question: strongly yes, 20%; neutral, 80%.

**Key evidence:** The majority of published DTAs compared 7 α-hydroxy-4-cholesten-3-one (C4)[46-48] and fibroblast growth factor 19 (FGF19)[32,49,50] assays to SeHCAT testing. These showed good inverse correlation between C4 and SeHCAT testing, and between FGF19 and SeHCAT testing, however, the overall CoE for the diagnostic accuracy of SeHCAT was assessed for statement 3 and determined to be very low. Therefore, the true diagnostic accuracy of these tests cannot be estimated from these studies.

One study assessing C4 and FGF19 assays used direct measurement of 48-hour fecal bile acid as a reference standard.[51] This prospective DTA study included 30 patients with IBS-D who had replicate C4 and FGF19 samples 5 years apart, which could be compared to fecal bile acid levels. When patients with prior cholecystectomy were excluded, the sensitivity and specificity of serum C4 were 40% and 85%, respectively, with a 40% positive-predictive value (PPV) and an 85% negative-predictive value (NPV) for the diagnosis of BAD. For FGF19, the sensitivity and specificity were 20% and 75%, respectively, with a 17% PPV and 79% NPV for the diagnosis of BAD.

The CoE was downgraded to very low due to moderately serious risk of bias and very serious imprecision (confidence interval lower limits crossing threshold for clinically useful diagnostic tests, small sample sizes) in the DTA that used fecal bile acid levels as reference standard.[51] Similarly, there was very serious risk of bias and serious indirectness in the studies that used SeHCAT retention as reference standard.

**Discussion**: Although there appears to be a good correlation (inverse) between C4 and SeHCAT results, and between FGF19 and SeHCAT results, SeHCAT retention has not been adequately validated as reference standard. Theoretically, C4 and FGF19 should be good markers of bile acid loss. C4 is a metabolic intermediate in the rate limiting step for the synthesis of bile acids from hepatic cholesterol. FGF19 is a hormone released by ileal enterocytes after

stimulation of nuclear farnesoid X receptors typically by absorbed bile acids. Both markers have been correlated with fecal loss of bile acids (Figure 1).[51-53] In addition, FGF19 levels have been shown to correlate with C4 levels.[54]

Currently, there are no well-defined cut-off values for the diagnosis of BAD. In one prospective study, C4 ≥52.5 ng/mL and FGF19 ≤61.7 pg/mL were diagnostic for BAD.[51] Other observational studies have used cut-offs of 30-48 ng/mL for C4.[46,55] One study found a wide range of normal values for C4 (corrected for cholesterol) from 0.76 to 8.0 mg/mol and for FGF19 from 48 to 343 pg/mL.[33]

Insufficient evidence is available with C4, and even less with FGF19. In addition, the FGF19 assay was not available as a commercial clinical test at the time of the meeting, which impacts the feasibility of implementing that test. Therefore, the consensus group made a conditional recommendation in favour of C4, but was unable to make a recommendation for or against the use of the FGF19 assay to identify BAD.

***Statement 6: In patients with suspected BAD, we suggest against initiating empiric BAST over performing SeHCAT to establish a diagnosis of BAD.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question (*In patients with suspected BAD, should we initiate empiric BAST over performing SeHCAT to establish a diagnosis of BAD?):* yes, 20%; no, 40%; strongly no, 40%

**Key evidence**: No direct comparative or DTA studies were found to inform this statement. As described in statement 3, 2 studies on the diagnostic accuracy of SeHCAT testing for predicting response to BAST yielded very low certainty evidence in favour of using SeHCAT testing.[37,40] The cost-effectiveness analysis included in the HTA conducted by Riemsma et al. found that in the short term, a trial of BAST may be the optimal choice. However, over the long term, the optimal choice (trial of BAST, no SeHCAT testing, or SeHCAT at cut-off retention value 15%) varied depending on the scenario.[41] The analysis provided very low CoE regarding the optimal strategy.

**Discussion**: There is very little evidence to determine the relative role of testing with SeHCAT testing versus using an empiric trial of BAST to make a diagnosis of BAD. Other factors were considered when making a conditional recommendation against empiric treatment.

A poor response to a therapeutic trial of BAST could be related to non-compliance and early discontinuation, which could result in a falsely negative diagnosis with patients being denied other effective alternative BAST that may be better tolerated.[38,56] As discussed in statement 3, a definitive diagnosis of BAD, may help educate and motivate patients to adhere to treatment.[38,44]

Conversely, in patients in whom there is a very high index of suspicion (where a positive SeHCAT test is found in >90%), such as terminal ileum resection or right hemicolectomy, early initiation of therapy may be preferred. In addition, while a test and treat strategy was preferred for most patients, it was recognized that SeHCAT testing or other diagnostic tests are not available in some areas. In these cases, a trial of BAST may be the only option.

## Induction therapy for BAD

***Statement 7: In patients with Type 1 or Type 3 BAD, we suggest the use of treatments for remediable causes (eg, Crohn's disease, microscopic colitis, SIBO) in addition to treatment for BAD for induction of clinical response.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 80%; yes, 20%.

**Key evidence**: No RCTs or directly applicable cohort studies were identified in which treatment for remediable causes was compared to BAST in patients with Type 1 or Type 3 BAD. A cohort study (described in statement 4), included subgroups of patients with IBS-D (n=65, n=40 treated) and unoperated Crohn's disease in clinical remission (other than diarrhea, n= 24, n=20 treated) who were diagnosed with BAD (SeHCAT retention <10%).[28] The rates of response to initial conventional treatment (prednisone ± 5-ASA for Crohn's disease patients, or anti-diarrheal agents for non-Crohn's disease patients) were 55% among treated Crohn's disease patients, and 15% among treated IBS-D patients. Conventional therapy followed by BAST was successful in 40% of treated Crohn's disease patients and 70% of treated IBS-D patients.

This study lacked a control group and blinding, and had a subjective outcome measure. No evidence was found for other conditions (eg, microscopic colitis, SIBO). The CoE was downgraded to very low due to serious risk of bias, indirectness, and imprecision.

**Discussion**: Little data was available to define the role of other non-BAST treatments in patients with BAST and comorbid conditions. Specific treatments for comorbid conditions that

may cause diarrhea (eg, Crohn's, microscopic colitis, SIBO) may achieve control of diarrhea and other symptoms, but conversely this may delay BAST for BAD. In addition, depending on the condition, the treatment (eg, corticosteroids, immunosuppressive agents, biologics, or antibiotics) may be associated with more risks or side effects than BAST treatment, and the investigations may be more invasive and costly (eg, colonoscopy).

As mentioned in statement 4, patients with Crohn's disease with continuing diarrhea have a high rate of BAD. These patients were still more likely to benefit from conventional treatment, although some did benefit from BAST.[28]

Some studies suggest that BAD and collagenous colitis are associated but are likely independent diseases.[57-59] In case series of collagenous colitis, BAST improved symptoms, but had no effect on histopathology.[57] In another case series, 86% of patients with microscopic colitis who had BAD benefited from BAST, whereas no patients with collagenous colitis without BAD improved.[59] The etiology of microscopic colitis is not well defined, and may include infectious agents, medications, or other causes in some patients, which may require other specific treatments. Other treatments that may be beneficial include corticosteroids, antibiotics, anti-diarrheal agents, or immunosuppressive therapies.[59,60]

In a large case series, 36% of patients with SIBO who were tested, had SeHCAT retention <10%.[26] These patients may benefit from BAST, but antibiotic therapy is the current standard for SIBO.[61] The etiology of SIBO is very complex and may involve disorders of protective antibacterial mechanisms, anatomical abnormalities or motility disorders. Patients with SIBO require treatment of the underlying disease, as well as nutritional support.[62]

Although there is little evidence to guide therapeutic decisions, in patients with comorbid conditions, BAD may not be the sole cause of symptoms. Although some patients will respond to BAST for BAD, others might not, or may have other symptoms in addition to diarrhea that will not benefit from BAST. Therefore, the consensus group agreed that it was prudent to individualize therapy and address other remedial causes of gastrointestinal symptoms, with the order of therapy guided by severity of each condition.

***Statement 8: In patients with BAD, we suggest using cholestyramine over no treatment for induction of clinical response.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%.

***Statement 9: In patients with BAD, we suggest using cholestyramine over other BASTs as initial therapy for induction of clinical response.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%.

**Key evidence**: One RCT compared cholestyramine to hydroxypropyl cellulose (HPC).[63] Although HPC was chosen as a placebo, it may be pharmacologically active, and a small case series suggested it may be effective in BAD.[63,64] The RCT was an 8 week study in 26 patients with chronic functional watery diarrhea or IBS-D, of which 77% of the cholestyramine- and 54% of HPC-treated patients had a SeHCAT retention rate ≤10%.[63] There was no significant difference in clinical remission rates (defined as <3 bowel movements /day over 1 week, with <1 watery stool/day) between treatments (53.8% vs. 38.4%; P = 0.43). However, there was a significant improvement in the decrease in watery stools/day (-92.4±3.5% vs. -75.8±7.1%; P=0.048). Since HPC binds bile acids and may have a bulking effect, it may have some efficacy for BAD;[63-66] this makes it difficult to interpret the lack of significant differences in clinical remission rates with HPC compared to cholestyramine.

A SR of 23 cohort studies including 801 patients with BAD found that first-line cholestyramine was successful in 69.8% of patients overall, 67% of those with SeHCAT retention <5%, 73% of those with SeHCAT retention <8-11.7%, and 59% of those with SeHCAT retention <15%.[42] Study designs, patient populations, inclusion and exclusion criteria, diagnostic tests and cut-off values for BAD, cholestyramine dosing and timing of administration, and definitions of clinical response varied widely among the studies. An additional cohort study published after the SR reported a response rate of 56% with first-line cholestyramine in 87 patients with BAD (defined as SeHCAT <15%).[67]

Although the RCT found that the rate of drug-related adverse events did not differ between cholestyramine and hydroxypropyl cellulose,[63] the SR of cohort studies reported that 11% of patients found cholestyramine intolerable due to unpalatability or side effects (range 0 to 46%).[42] The most common side effects included abdominal bloating and pain, dyspepsia, nausea/vomiting, flatulence, borborygmi, abdominal distension, constipation and increased

severity of diarrhea. In the additional cohort study, almost half (45%) of treatment failures were related to medication intolerance.[67] However, both studies had no control group for comparisons, and relationships to study drug were not assessed.

RCTs assessing the efficacy of cholestyramine compared with other BAST in patients with BAD were not found. Evidence for using cholestyramine over other BASTs as initial therapy considered other factors such as adverse events, clinical experience, and cost. There is no direct evidence that cholestyramine is associated with more side effects than other BAST. However, a RCT of BAST for cardiovascular disease prevention reported higher rates of gastrointestinal side effects (55% vs. 16%), and lower rates of compliance (53% vs. 77%) with adjunctive cholestyramine compared to monotherapy with a statin.[68] In contrast, a SR of 6 RCTs in patients with diabetes found that adverse rates with adjunctive colesevelam were similar to placebo (relative risk, 1.06; 95% CI, 0.97–1.15), with the most common events with colesevelam being GI-related (eg, constipation, dyspepsia, and nausea) and minor in nature.[69] The majority of clinical experience with BASTs in BAD has been with cholestyramine, with few data on the other agents; in addition, colesevelam and colestipol tend to be more costly compared to cholestyramine.

The overall CoE was very low. Very serious indirectness and serious imprecision were found in the RCT,[63] and serious risk of bias, indirectness, and imprecision in the cohort studies.[42,67]

**Discussion**: Clear RCT evidence demonstrating the benefits of BAST was not available, but, case series, and SRs of observational studies support a dramatic and rapid response for many patients. Although no patient preference data was found, the high dropout rates in all of these studies suggest that some patients may place a greater value on being free of the side effects or unpalatability of cholestyramine compared to reduction in their diarrhea frequency or severity. However, because BAST targets the problem, the potential higher response rates in patients with more severe BAD (as measured by SeHCAT retention),[6] and the lack of response in patients who test negative for BAD[29] (see statement 3), the consensus group suggested that patients with BAD receive treatment with BAST over no treatment. This was a conditional recommendation because of the very low CoE, and poor tolerability profile, making it important to discuss the benefits and side effects with patients.

Although the consensus group suggested that cholestyramine be used initially over the other BAST agents (colesevelam or colestipol), there are few comparative data. Compared with cholestyramine, colesevelam has a 4–6 times stronger binding affinity to bile acids. It may be better tolerated and have fewer clinical interactions.[67] The majority of clinical experience to date is with cholestyramine, with a limited number of cases using other BAST agents.[29,33,38,70] Response rates with first-line use of other BAST have been reported at 67% with colesevelam,[70] and 55% with colestipol.[33] Although cholestyramine appears to be less costly than colesevelam or colestipol, the lack of comparative data casts doubt on whether cholestyramine should be preferred; therefore, this was a conditional recommendation.

***Statement 10: In patients with BAD who are unable to tolerate cholestyramine, we suggest using an alternate BAST for induction of clinical response.***
GRADE: Conditional recommendation, low-certainty evidence. Vote on PICO question: strongly yes, 40%; yes, 60%.

**Key evidence:** No RCT data were available comparing alternate BASTs to either placebo or other treatments as 2nd-line therapy in patients with BAD who are unable to tolerate cholestyramine. One RCT compared first-line colesevelam and placebo for BAD-associated diarrhea in 26 patients with Crohn's disease in remission.[70] There was a statistically non-significant improvement in the primary endpoint (proportion of patients with >30% reduction of liquid stools/day) with colesevelam (66.7%) vs. placebo (27.3%) based on intention-to-treat analysis (risk difference, 0.394; 95% CI, −0.012 to 0.706; p=0.0566). Colesevelam significantly improved the secondary endpoints of reduction in number of liquid stools/day and improvement in stool consistency compared to placebo. This trial did not assess colesevelam as 2nd-line therapy, and had a very small sample size; therefore the CoE was downgraded to low for serious indirectness and imprecision.

Additional evidence comes from a SR of 4 observational cohort studies (n=63) that assessed the efficacy of 2nd-line colesevelam after failure of cholestyramine and reported a success rate of 57% (range 42 to 100%).[42] One other cohort study published after the SR included 15 patients who had not responded to cholestyramine and had received 2nd-line treatment with colesevelam.[67] Of these patients, 47% had a successful response. The CoE from the observational trials was downgraded to very low for serious risks of bias and imprecision.

There is no direct evidence that colesevelam is associated with a higher or lower frequency of adverse effects than cholestyramine or other BASTs. In the RCT, colesevelam was generally well tolerated; adverse events were mild (constipation, bloating, and nausea) and occurred in similar proportions of colesevelam and placebo groups (40.0% vs. 36.4%).[70] For safety, the SR included 1 RCT and 4 observational cohort studies, and found that 9% were unable to tolerate colesevelam due to unpalatability or side effects.[42] In the additional observational study, no patients reported treatment intolerance with colesevelam.[67] As discussed in statement 8, tolerability data for BASTs in non-GI conditions suggests high rates of gastrointestinal side effects with cholestyramine, while colesevelam has side effects rates similar to placebo.[68,69]

There have been limited reports describing the use of colestipol as 2nd-line therapy after failure of cholestyramine.[42,71]

**Discussion**: Case series data have suggested that patients who fail or are unable to tolerate cholestyramine may benefit from 2nd-line BAST.[29] In a large series of patients given one or more BAST, there were no significant differences in good/partial response rates between the cholestyramine (74%) and colesevelam (73%). However, whether alternate BAST was used as 1st- or 2nd-line therapy was not described.[29] Although, not regulatory approved for BAD, use of 2nd-line colesevelam in clinical practice appears to be quite common. In a survey of patients followed for up to 13 years, 38% of respondents continued with cholestyramine, while 32% had switched to colesevelam.[56] The consensus group agreed that compared to cholestyramine, colesevelam has a favourable benefit:risk profile and greater ease of administration (tablet vs. granules/powder). However, because of the limited clinical experience, and higher cost, suggested it be reserved for 2nd-line use.

***Statement 11: In patients with BAD receiving empiric BAST, gradual daily dose titration should be used to minimize side effects.***
Designated a good practice statement

**Key evidence:** Good practice statement, CoE not assessed.

**Discussion:** In general, most cohort studies reported gradual dose titration for cholestyramine to clinical response.[42,67] There was, however, no mention of dose titration of colesevelam or colestipol.

In BAD studies, cholestyramine was generally started at a low dose 2–4 g/d and titrated based on response (maximum 4–24g/d).[42,67] In an open-label study, the colestipol dose was initiated at 1 g twice daily, with an increase of 1 g/day every other day.[33] In BAD studies, colesevelam has been prescribed in a dose of 2 tablets (625 mg) 3 times/day.[70,72]

Product labelling for BAST agents recommends that cholestyramine be started at one 4-g dose daily and titrated to effect with a maximum of 24 g/day for all patients.[73] Initiation of colestipol granules (tablets) is recommended at 5 g (2 g) either once or twice daily, increasing by 5 g/day (2 g once or twice/day) but no more frequently than one/month, with a maximum of 30 g/day (16 g/day). No dose titration is recommended for colesevelam. Colesevelam is dosed at 3.75 g/day, as three 625-mg tablets twice daily, 6 tablets once daily, or one 3.75-g powder packet once daily. These colestipol and colesevelam doses are regulatory approved for cholesterol-lowering indications.

Generally, it is intuitive to gradually titrate medication to maximize symptom relief and minimize side effects. This is particularly relevant with BAST due to the high frequency of side effects and intolerance.[42] Gradual dose titration of BAST may reduce the risks of side effects, increase compliance, and potentially reduce costs.

***Statement 12: In patients with Crohn's disease with extensive ileal involvement or resection, we suggest AGAINST using BAST.***

GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question (*In patients with Crohn's disease with extensive ileal involvement or resection, should we use BAST vs. no BAST?*): yes, 20%; no, 80%.

**Key evidence:** There are no long-term studies assessing the safety of cholestyramine in patients with extensive ileal resection. It has been suggested that use of BAST in these patients can lead to an increased rate of steatorrhea.[74,75] A small series of 9 patients, in whom 3 had ileal

resection >100 cm and steatorrhea >20 g/day, found that the use of cholestyramine led to a small decrease in diarrhea, but an increase in steatorrhea with substantial caloric loss.[74,75]

**Discussion:** The degree of resection that constitutes "extensive" and may carry an increased risk of negative consequences with BAST, is unclear. In the case reports, the risk of steatorrhea was increased in patients with resections of >100 cm.[74,75]

Other data have shown no correlation between the length of resection, SeHCAT retention, and response to BAST. In case series of patients with ileal resection of up to 200 cm, the majority had severe BAD and responded to BAST.[26,76,77] In one case series, the mean length of resection was not significantly different in those who did or did not respond to BAST (35 cm vs. 46 cm).[78]

SeHCAT testing in patients with large ileal resection will almost universally indicate severe bile acid wasting and is unlikely to be of discriminatory clinical value. Although there are very few reports of adverse consequences of BAST use in patients with extensive resection, the consensus group concluded that the risk of steatorrhea makes it prudent to err on the side of caution and avoid BAST in this patient group. Furthermore, there is concern that these patients may have extensive inflammatory disease that should be identified and treated with antiinflammatory approaches rather than BAST. However, in some cases the benefits may outweigh the risks, and patients should be evaluated on a case by case basis.

## Maintenance therapy for BAD

***Statement 13: In patients with BAD who respond to BAST, we suggest that intermittent, on-demand dosing be tried.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%.

**Key evidence:** No studies were found that directly compared different dosing strategies in patients with BAD who had responded to BAST. Two small cohort studies suggested that for some patients, BAD symptoms could remain controlled with on-demand therapy or no therapy at all.[7,8] In a prospective cohort study of patients with post-cholecystectomy BAD, cholestyramine (2–12 g/day for 1–6 months) was effective in 23/26 patients, and 9/23 (39%) patients experienced recurrent diarrhea when treatment was withdrawn. Bowel habit remained regular in

14 patients (61%) who took the drug occasionally (on demand) in the event of sporadic episodes of slight diarrhea.[8] In the other cohort study in patients with BAD and IBS-D, recurrent diarrhea occurred in 33/35 (94%) of patients when cholestyramine (2–8 mg/day for 1 month) was withdrawn, and the drug was prescribed again at the dose that controlled the patient's symptoms.[7] Only 6% of patients were able to discontinue therapy without suffering recurrent diarrhea.

**Discussion:** Evidence suggests that some patients with BAD will require regular daily dosing, whereas others may be able to discontinue completely or use on-demand therapy for symptom control. The dose or frequency of BAST required to control symptoms may be dependent on severity of symptoms, underlying causes of BAD, or the presence of other comorbid illnesses (eg, gastroenteritis, *Clostridium difficile* infection). The need for BAST may also be affected by use of medications that cause constipation, which may reduce the need for BAST, or by medications that cause diarrhea, which may increase the need for BAST.

Long term use of BAST should balance the potentially high rate of relapse of diarrhea against the high rate of adverse events, poor palatability, and uncertainty around long-term harms (eg, malabsorption of fat and vitamins). Therefore, the consensus group suggested that during ongoing long-term therapy, intermittent, on-demand therapy should be attempted in order to minimize exposure to BAST, encourage compliance, and minimize costs.

***Statement 14: In patients with BAD who are unable to tolerate BAST, we suggest using alternative anti-diarrheal agents vs. no treatment for long-term symptomatic therapy.***
GRADE: Conditional recommendation, very-low-certainty evidence. Vote on PICO question: yes, 100%

**Key evidence:** No studies were found that systematically assessed the effectiveness of other anti-diarrheal agents in patients with BAD who are unable to tolerate BAST. As described in statement 8, 1 RCT that compared cholestyramine to HPC found no difference in clinical remission (53.8% vs. 38.4%) or adverse events.[63]

Three cohort studies assessed first-line loperamide in patients with BAD; however, the effectiveness was difficult to estimate due to differences in patient populations, study designs, and outcome measurements (mainly subjective improvement of symptoms).[28,79,80] A randomized double blind cross-over RCT in 18 patients with chronic diarrhea due to chronic radiation

enteritis compared loperamide (3 mg bid) and placebo for 14 days.[79] The study did not include dichotomized response rates, but did report significant improvements in stool frequency, stool weight, and SeHCAT retention with loperamide as compared to placebo. In a prospective cohort study of 19 patients with chronic diarrhea due to ileal irradiation and/or resection, 13 patients with resection 20–50 cm (n=7) or no resection (n=6), showed normalized or improved SeHCAT retention, with symptomatic improvement while on loperamide.[80] In 6 patients with resection > 80 cm, SeHCAT retention remained abnormal, and only 3 patients had "slight improvement" of diarrhea with loperamide. In another cohort study, 27/96 (28%) of patients reported improvement with conventional anti-diarrheal agents; however, this included codeine, loperamide, or prednisolone (not considered an anti-diarrheal agent), and did not specify response to individual medications.[28]

**Discussion:** Given the poor tolerability and high discontinuation rates with BAST, alternative treatments are often needed. HPC may improve diarrhea in patients with BAD through its bulking effects and its ability to bind bile acids.[63-66] In addition, some patients may benefit from loperamide; given its low cost and relatively good safety profile (although no cost-effectiveness data are available), a treatment trial may be warranted.

***Statement 15: In patients with BAD receiving empiric BAST, maintenance therapy should be used at the lowest dose needed to minimize symptoms.***
Designated a good practice statement

**Key evidence:** Good practice statement, CoE not assessed.

**Discussion:** The importance of minimizing exposure to BAST was discussed under statement 11 (dose titration during induction), and statement 13 (use of intermittent or discontinuing dosing during maintenance therapy).

Cohort studies have reported the use of cholestyramine for 6 to 44 months, which was titrated to response.[42] In one study, patients were allowed to titrate their own dose of cholestyramine (between 2 to 16 g/day) and sustained responses for over 1 year.[81] Colesevelam has been used for up to 44 months with some patients titrating the dose down.[72]

***Statement 16: In patients with BAD and recurrent or worsening symptoms despite stable BAST, diagnostic re-evaluation should be conducted.***
Designated a good practice statement

**Key evidence:** Good practice statement, CoE not assessed.

**Discussion:** Other diagnoses are common in patients with BAD, and a diagnosis of BAD is frequently seen in patients with other conditions (see statement 1). As discussed in statement 7, some patients may need specific treatments for other causes of chronic diarrhea.

BAD can have a variable course, and fat intake can cause fluctuations in SeHCAT retention, and severity of BAD. Low-fat dietary interventions can improve gastrointestinal symptoms for some patients.[82] However, sudden worsening of symptoms, not related to dietary changes, should prompt re-evaluation. The differential diagnosis should consider conditions such as microscopic colitis, Crohn's disease, celiac disease, SIBO, and functional bowel disease. Strategies in patients with worsening symptoms might include repeating SeHCAT testing with an escalation of therapy if needed, as well as other tests, such as stool tests for infectious etiologies, blood tests, colonoscopy, hydrogen breath tests as determined by the underlying cause of BAD, and the patient's history, risk factors, and symptoms.

***Statement 17: In patients being considered for BAST, a review of concurrent medications should be conducted to minimize the potential for drug interactions.***
Designated a good practice statement

**Key evidence:** Good practice statement, CoE not assessed.

**Discussion:** BAST agents may bind other drugs given concurrently, which necessitates separating administration to minimize the risk of reduced absorption of the concomitant medication. Health Canada recommends that when a drug interaction cannot be excluded, patients should take other drugs at least 1 hour before or 4-6 hours after the BAST.[73,83,84] Gastric emptying studies suggest that a window of 3 hours between administration of BAST and other medications is adequate to avoid potential interactions such as binding.[85]

Examples of some medications that may interact when coadministered with cholestyramine or colestipol include thyroid preparations, warfarin, hydrochlorothiazide, furosemide, phenylbutazone, phenobarbital, tetracycline, penicillin G, digoxin, mycophenolic

acid, and estrogen-containing drugs.[3,73,84] Colesevelam has a different structure, which maximizes interactions with bile salt and reduces the potential for interactions with other drugs.[86,87] Colesevelam does not appear to interact with some medications (eg. digoxin, fenofibrate, lovastatin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil), but has been found to reduce the absorption of others (eg, glyburide, levothyroxine, and oral contraceptives), and may interact with warfarin and phenytoin.[83]

*No recommendation B: In patients receiving long-term maintenance therapy with BAST, the consensus group could not make a recommendation for or against measuring fat-soluble vitamin levels at baseline and annually thereafter.*

GRADE: NO recommendation; very-low-certainty evidence. Vote on PICO question: yes, 20%; neutral, 80%

**Key evidence:** The literature search failed to identify any relevant article assessing fat-soluble vitamin levels before and after initiation of long-term maintenance therapy with BAST. Due to the action of BAST agents in sequestering bile acids, these agents may theoretically interfere with normal fat absorption, thus reducing absorption of folic acid and fat-soluble vitamins A, D and K.[73,83,84] Whether this interference can result in clinical consequences is based on rare case reports. Since 1970, there have been only a few reports of hypoprothrombinemia or hemorrhage in adults,[88,89] and of hypoprothrombinemia, hemorrhage, or folate deficiency in pediatric patients[90-92] taking cholestyramine.

**Discussion:** Cholestyramine has been associated with reduced vitamin and folate levels during long term use.[73] However, colestipol use for 1–2 years had no effect on vitamin A or folic acid levels, and only a small effect on vitamin D levels.[84] Colesevelam was not associated with significant reductions in the absorption of vitamins A, D, E or K during clinical studies of up to 1 year.[83] In general, the approved product labels recommend supplementation of vitamins A, D and K only if a deficiency occurs.[73,83,84]

The rare cases of vitamin K deficiency resulting in increased risk of coagulopathy have occurred within a few weeks to months or years after the start of therapy,[89] and generally can be corrected with oral vitamin K. Although, during long-term use periodic monitoring of vitamin levels and prothrombin time are sometimes advised,[3,93] the group did not reach consensus on the value of annual routine monitoring. Most of the consensus participants were neutral on this issue,

although it was suggested that performing an international normalized ratio (INR) at intervals during long-term treatment may be prudent.

## Future directions

The group recognised that specific, high-certainty evidence was lacking in many areas and recommended further studies that would improve the data available in future methodological evaluations.

In DTA studies, the diagnostic accuracy of an index test (a test under evaluation) is determined by comparing its results with that of a reference standard (best available method to determine the presence or absence of a target condition), by applying both in individuals who are suspected of having the target condition of interest. Yet, if the reference standard does not perfectly correspond to a true target condition, estimates of the accuracy of the index test can be biased. The main challenge in conducting DTA studies for BAD is the lack of a widely accepted or universally agreed-upon reference standard as the condition is defined and classified based on pathophysiologic mechanisms and its response to treatment (BAST). Also, the index tests (SeHCAT, C4, FGF19, fecal bile acid assay) provide a continuous measure of metabolic function. Hence, DTA studies are not the most appropriate study design.[41] In studies where all patients are tested with the index tests and all patients are treated with BAST, response to treatment can provide an imperfect, but the best available reference standard. This is because patients responding to BAST may be true positive patients with a true response, but may also be false positive patients with a "placebo" response. To date, only two small DTA studies reported information on the probability of response to treatment with BAST for people with a negative SeHCAT test, and no DTA studies have incorporated a blinded placebo arm.[37,40] Consequently, the lack of evidence of the accuracy of SeHACT test based on a reference standard and the variation in cut-off values of test results led to important uncertainties in the cost-effectiveness analyses in determining the optimal strategy in investigating BAD.[41] Therefore, one of the research priorities in BAD is for the scientific and clinical communities to agree upon a reference standard that best represents BAD (e.g. response to BAST), with full understanding that the reference standard is and will likely be imperfect.

Given the paucity of high certainty evidence on diagnostic tests, there is also a need for well-designed DTA studies comparing SeHCAT, C4 assay, FGF19, total and primary bile acid measurement in stool, with a reference standard for BAD (eg, response to BAST) by applying both the index tests and reference standard to all patients, [94,95] as well as RCTs comparing

SeHCAT testing vs empiric trial of BAST in patients with suspected BAD including assessment of objective clinical efficacy and safety outcome measures. A placebo-controlled RCT of BAST (colesevelam) in patients with evidence of BAD, based on fecal bile acid measurements, is ongoing (NCT03270085) and its results will help to inform the role of fecal bile acids as a diagnostic test for BAD.[96]

It is important to note that the diagnostic accuracy of total and primary bile acid excretion has not been formally assessed by GRADE for this guideline, because it was not a topic initially proposed for inclusion a priori. Nevertheless, there have been recent publications on assessing 48-hour total and primary bile acid fecal excretion (a test available in North America) as a diagnostic test for BAD. [95] Recent advances also assessed whether this test could be optimized by including assays of primary bile acids.[95] Most (if not all) are observational studies that have found significant correlation or association between elevated fecal bile acids and certain conditions that can cause diarrhea (i.e. IBS-D, chronic functional diarrhea).[95,97-99] While observational studies can provide evidence of significant association or correlation between predictor and outcome variables, they cannot prove causality because there are always residual confounding variables (unmeasured or imprecisely measured) that may have affected the results. Spurious associations can also arise with reverse causality. Future prospective studies are required to validate the diagnostic accuracy for BAD of primary bile acids at various cut-off concentrations in a single stool sample against a reference standard (ie, the ability of this test to accurately predict response to BAST).

RCTs are needed to compare cholestyramine to other BAST for the treatment of BAD. In addition, evidence is needed to guide dosing schedules. This includes assessment of whether there is any advantage to morning vs. evening dosing and once-daily vs. divided doses of BAST to maximize benefits and minimize interactions with other medications. Theoretically, there may be some efficacy benefits to targeting dosing to times of maximum gallbladder emptying, such as postprandially or in the morning, but more research is needed. In hypercholesterolemia there were no significant variations in the hypocholesterolemic effects when cholestyramine was timed with meals to optimize exposure to bile in the duodenum that followed gallbladder emptying.[100] However, the relevant mechanisms in BAD may be different, particularly as the therapeutic aim is to reduce the effects of free, secretory bile acid in the colon.

In conclusion, current evidence suggests that the accuracy of diagnostic tests (e.g. SeHCAT, C4) in predicting BAD or response to treatment are highly uncertain. Economic evaluation suggests that strategies of either empiric trial of BAST or performing SeHCAT testing may be cost-effective depending on the scenarios and the society's willingness-to-pay. Therefore, either strategy may be used to identify patients with possible BAD depending on cost, available resources, local expertise, and patient preferences.

**ACKNOWLEDGEMENTS**

The CAG would like to thank Pendopharm and GE Healthcare Canada, for their generous support of the guideline process. The consensus group would like to thank the following people for their contributions: Paul Sinclair, Cindy Roll, and Adria Cehovin (CAG representatives: administrative and technical support, and logistical assistance), Pauline Lavigne and Steven Portelance (unaffiliated, editorial assistance).

*Canadian Association of Gastroenterology Statement*

This clinical practice guideline (CPG) on the management of BAD was developed under the direction of Dr. Dan Sadowski, in accordance with the policies and procedures of the Canadian Association of Gastroenterology (CAG) and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Practice Affairs and Clinical Affairs Committees and the CAG Board of Directors. The CPG was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian, US, and UK panel comprised of experts on this topic. The CPG aims to provide a reasonable and practical approach to care for specialists and allied health professionals are charged with the duty of providing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The CPG is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available, and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

## TABLES

*Table 1: Summary of consensus recommendations for the management of BAD**

| **Diagnosis of BAD** |
|---|
| Statement 1: In patients with chronic non-bloody diarrhea, we recommend using risk factors (history of terminal ileal resection, cholecystectomy, or radiotherapy) as the initial assessment to identify patients with possible BAD.<br>GRADE: Strong recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%. |
| Statement 2: In patients with chronic non-bloody diarrhea, we suggest against using symptom presentation as the initial assessment to identify patients with possible BAD.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: no, 100%. |
| Statement 3: In patients with chronic diarrhea including IBS-D and functional diarrhea, we suggest SeHCAT testing to identify patients with BAD.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%. |
| Statement 4: In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, we suggest SeHCAT testing.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 80%. |
| Statement 5: In patients with chronic diarrhea including IBS-D and functional diarrhea, we suggest using a C4 assay to identify possible BAD.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 20%; yes, 60%; neutral, 20% |
| Statement 6: In patients with suspected BAD, we suggest against initiating empiric BAST over performing SeHCAT to establish a diagnosis of BAD.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: yes, 20%; no, 40%; strongly no, 40% |
| **Induction therapy for BAD (BAST)** |
| Statement 7: In patients with Type 1 or Type 3 BAD, we suggest the use of treatments for remediable causes (eg, Crohn's disease, microscopic colitis, SIBO) in addition to treatment for BAD for induction of clinical response.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 80%; yes, 20%. |
| Statement 8: In patients with BAD, we suggest using cholestyramine over no treatment for induction of clinical response.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: strongly yes, 60%; yes, 40%. |
| Statement 9: In patients with BAD, we suggest using cholestyramine over other BASTs as initial therapy for induction of clinical response.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%. |
| Statement 10: In patients with BAD who are unable to tolerate cholestyramine, we suggest using an alternate BAST for induction of clinical response.<br>GRADE: Conditional recommendation, low-certainty evidence. Vote on PICO question: strongly yes, 40%; yes, 60%. |
| Statement 11: In patients with BAD receiving empiric BAST, gradual daily dose titration should be used to minimize side effects.<br>Designated a good practice statement |
| Statement 12: In patients with Crohn's disease with extensive ileal involvement or resection, we suggest AGAINST using BAST.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question (Should we use BAST?): yes, 20%; no, 80%. |

| **Maintenance therapy for BAD (BAST)** |
|---|
| Statement 13: In patients with BAD who respond to BAST, we suggest that intermittent, on-demand dosing be tried.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: yes, 80%; neutral, 20%. |
| Statement 14: In patients with BAD who are unable to tolerate BAST, we suggest using alternative anti-diarrheal agents vs. no treatment for long-term symptomatic therapy.<br>GRADE: Conditional recommendation, very low-certainty evidence. Vote on PICO question: yes, 100%. |
| Statement 15: In patients with BAD receiving empiric BAST, maintenance therapy should be used at the lowest dose needed to minimize symptoms.<br>Designated a good practice statement |
| Statement 16: In patients with BAD and recurrent or worsening symptoms despite stable BAST, diagnostic re-evaluation should be conducted.<br>Designated a good practice statement |
| Statement 17: In patients being considered for BAST, a review of concurrent medications should be conducted to minimize the potential for drug interactions.<br>Designated a good practice statement |
| **Statements with no recommendations** |
| *No recommendation A: In patients with chronic diarrhea including IBS-D and functional diarrhea, the consensus group could not make a recommendation for or against the use FGF19 assay to identify possible BAD.*<br>*GRADE: NO recommendation, very low certainty evidence; Vote on PICO question: strongly yes, 20%; neutral, 80%.* |
| *No recommendation B: In patients receiving long-term maintenance therapy with BAST, the consensus group could not make a recommendation for or against measuring fat-soluble vitamin levels at baseline and annually thereafter.*<br>*GRADE: NO recommendation; very low-certainty evidence. Vote on PICO question: yes, 20%; neutral, 80%.* |

*The strength of each recommendation was assigned by the consensus group, per the GRADE system, as strong ("we recommend...") or conditional ("we suggest..."). A recommendation could be classified as strong despite low-certainty evidence to support it, or conditional despite the existence of high certainty evidence due to the 4 components considered in each recommendation (risk:benefit balance, patients' values and preferences, cost and resource allocation, and certainty of evidence).

*Table 2: Risk factors in patients with chronic non-bloody diarrhea most commonly associated with having a positive SeHCAT test suggestive of a BAD diagnosis*

| **Risk Factor** | **SeHCAT <10% (at least moderate)** | **SeHCAT <15% (at least mild)** |
|---|---|---|
| Cholecystectomy | 78%[26]<br>68% - OR 5.70 (95% CI, 2.42–13.46)[25]<br>21%[24] | 86% (CI, 71%–95%)[26]<br>68% - OR 2.51 (99% CI, 1.10–5.77)[24]<br>57% - OR 2.54 (95% CI, 1.36–4.74)[29] |
| TI resection or right hemicolectomy for Crohn's disease | 100%[44]<br>97%[28]<br>91% - OR 15.83 (95% CI, 2.62–95.69)[25]<br>87%[24] | 92% - OR 12.4 (99% CI, 2.42–63.8)[24]<br>91% (95% CI, 78%–87%)[26]<br>87% - OR 5.0 (95% CI, 2.20–11.4)[29] |
| TI resection or right hemicolectomy for reasons other than Crohn's disease | 76%[24]<br>71%[29] | 82% - OR 7.94 (99% CI, 1.02– 61.6)[24] |
| Radiotherapy without resection | 18%[30] | 62%[27]<br>36%[30] |
| Radiotherapy with resection | 71%[30] | 88%[30] |

CI, confidence interval; OR, odds ratio; TI, terminal ileum.

*Table 3: Prevalence of positive SeHCAT tests in patients with ileal Crohn's disease who have not undergone resection*

| SeHCAT | Prevalence |
|---|---|
| <10%<br>(at least moderate) | 80% - OR 3.76 (95% CI, 1.10–12.60)[25]<br>54%[28]<br>52%[26]<br>43%[29]<br>35%[24] |
| <15%<br>(at least mild) | 76% (95% CI, 57%–90%)[26]<br>52% - OR 1.88 (95% CI, 1.04–3.41)[29]<br>35%[24] |

CI, confidence interval; OR, odds ratio.

## FIGURE LEGEND

*Figure 1: Enterohepatic circulation of bile acids*

C4 is a metabolic intermediate in the rate limiting step for the synthesis of bile acids from hepatic cholesterol. FGF19 is a hormone released by ileal enterocytes after stimulation of nuclear farnesoid X receptors by absorbed bile acids. BA, bile acids; C4, 7 α-hydroxy-4-cholesten-3-one; CDCA, chenodeoxycholic acid; CA, cholic acid; FGF19, fibroblast growth factor 19; LCA, lithocholic acid. Reprinted from Gastroenterology, Vol 156, Vijayvargiya P, Camilleri M. Current practice in the diagnosis of bile acid diarrhea, Pages 1233-1238, ©2019, with permission from Elsevier.[53]

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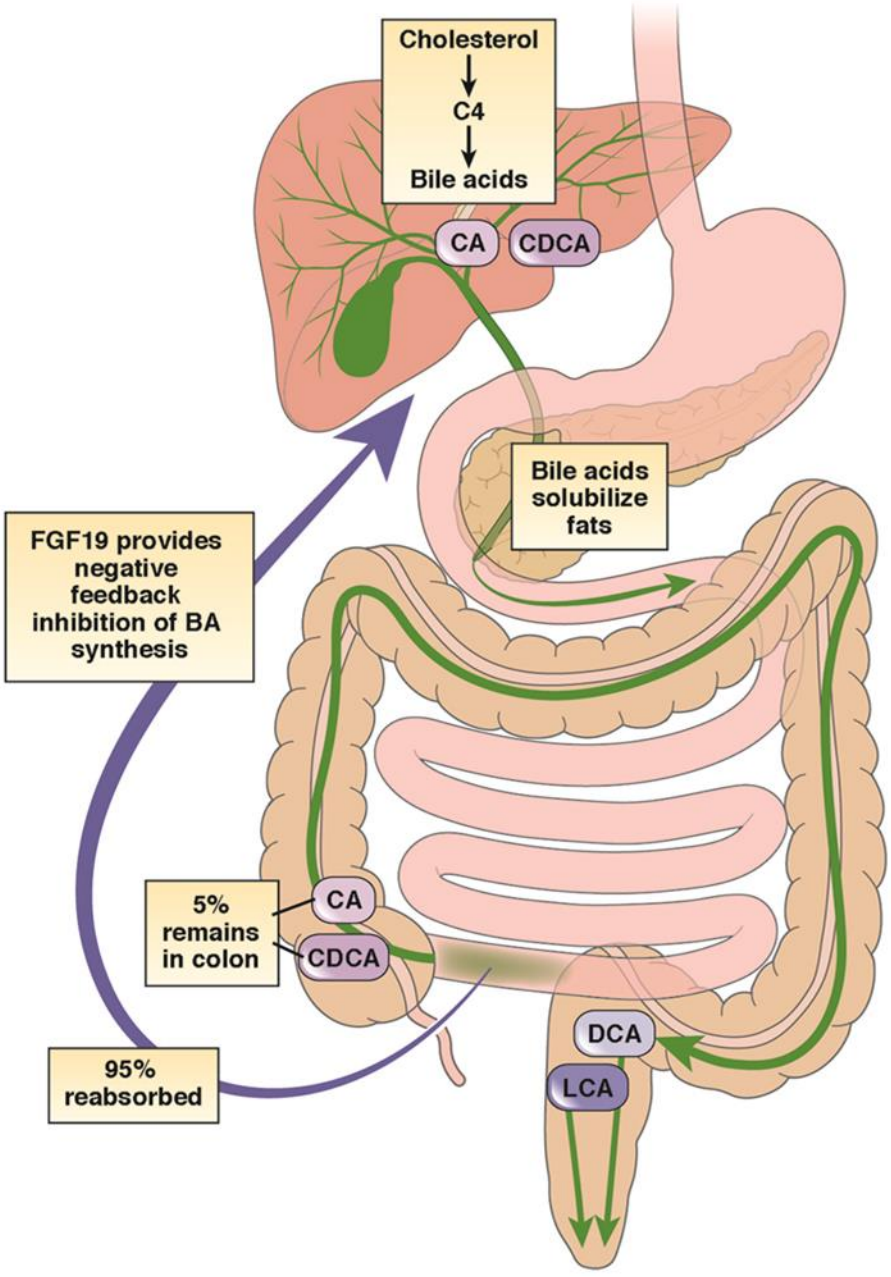

**What You Need to Know**

**Background and context**: Chronic diarrhea affects about 5% of the population, and can be related to bile acid diarrhea (BAD), a condition that is frequently underdiagnosed.

**New findings:** The group recommended using risk factors, but not additional symptoms to help diagnose BAD. Testing using $^{75}$selenium homocholic acid taurine (SeHCAT) or 7α-hydroxy-4-cholesten-3-one (C4) was suggested, and was preferred over empiric bile acid sequestrant therapy (BAST) depending on cost, available resources, local expertise, and patient preferences. Cholestyramine was suggested as initial therapy, with alternate BAST when tolerability was an issue. BAST maintenance treatment should be used at the lowest effective dose, with a trial of intermittent, on-demand dosing.

**Limitations:** The main challenge in BAD is the lack of a universally agreed-upon reference standard for diagnosis. Currently the condition is defined based on pathophysiologic mechanisms and its response to BAST.

**Impact:** This consensus provides guidance on the appropriate evidence-based use of diagnostic tests and medical therapies to help improve outcomes for patients with BAD. The gaps in evidence highlight the need for further research in this chronic condition.

**Appendix 1: Search strategies for BAD**

**Final search strategy for BAD:**

(from 1990 we have 1511 hits, then it was separated into RCTs or SRs, n=451; non-RCTs non SRs, n=1060).

Database: Embase <1974 to 2017 September 05>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 30, 2017>
Search Strategy:
---
1 diarrhea/ or chronic diarrhea/ (250921)
2 (diarrhea or diarrhoea or malabsorption).tw,kw. (251236)
3 1 or 2 (385404)
4 exp "Bile Acids and Salts"/ or exp bile acid/ (86671)
5 (bile acid or bile acids or biliary acid).tw,kw. (50328)
6 (SeHCAT or tauroselcholic acid).tw,kw. (381)
7 (Cholestyramine or colestyramine or Colestipol or Colestid or Colestipid or Colesevelam or Cholestagel or Welchol or Lodalis or Questran or Cholybar or Olestyr).tw,kw. (8017)
8 or/4-7 (107151)
9 3 and 8 (5049)
10 Conference Abstract.pt. or Congresses as Topic/ (2795323)
11 note/ or editorial/ or letter/ or Comment/ or news/ or (note or editorial or letter or Comment or news).pt. (4054984)
12 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rats or mice or mouse or cats or dogs or animal* or cell lines).ab.) not (humans/ or human/ or (human* or men or women or patients or subjects).ab.) (10259693)
13 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).ti.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).ti.) (4123598)
14 or/10-13 (20145364)
15 9 not 14 (3682)
16 limit 15 to english language [Limit not valid in CDSR; records were retained] (3093)
17 limit 16 to yr="1990 -Current" (2101)
18 remove duplicates from 17 (1511)
**********

Note: cholestyramine (colestyramine, trade names Questran, Questran Light, Cholybar, Olestyr); colestipol (Colestid, Colestipid); colesevelam (Cholestagel in Europe, Welchol in the USA, Lodalis in Canada)

**We then performed a separate search for SeHCAT before 1990, without limiting to adults, we have 13 hits:**

Database: Embase <1974 to 2017 September 06>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 7, 2017>
Search Strategy:
---
1 diarrhea/ or chronic diarrhea/ (251595)
2 (diarrhea or diarrhoea or malabsorption).tw,kw. (252683)
3 1 or 2 (387037)
4 (SeHCAT or tauroselcholic acid).tw,kw. (383)
5 Conference Abstract.pt. or Congresses as Topic/ (2801365)
6 note/ or editorial/ or letter/ or Comment/ or news/ or (note or editorial or letter or Comment or news).pt. (4065461)
7 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rats or mice or mouse or cats or dogs or animal* or cell lines).ab.) not (humans/ or human/ or (human* or men or women or patients or subjects).ab.) (10306801)
8 3 and 4 (314)
9 5 or 6 or 7 (16741255)
10 8 not 9 (202)
11 limit 10 to english language [Limit not valid in CDSR; records were retained] (179)
12 limit 11 to yr="1860 - 1989" (24)
13 remove duplicates from 12 (13)

**********

# Appendix 2: PICO questions and GRADE assessments of evidence on the management of bile acid diarrhea (BAD)

**Frances Tse & Grigorios Leontiadis**

**Feb 8, 2018 (Updated Oct 12, 2018, updated Jul 22, 2019)**

## Summary table

| **Role of risk factors and symptom presentation in the diagnosis of bile acid diarrhea (BAD)** |
|---|
| PICO 1: In patients with chronic non-bloody diarrhea, should risk factors (history of terminal ileal resection, cholecystectomy, or radiotherapy) be used as the initial assessment to identify patients with possible BAD?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 60%; yes, 40%. |
| PICO 2: In patients with chronic non-bloody diarrhea, should symptom presentation be used as the initial assessment to identify patients with possible BAD?<br>GRADE: Very low-quality evidence. Vote: no, 100%. |
| **Role of laboratory tests in the diagnosis of BAD** |
| PICO 3: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use SeHCAT testing to identify patients with BAD?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 20%; yes, 80%. |
| PICO 4: In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, should we use SeHCAT testing?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 20%; yes, 80%. |
| PICO 5: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a C4 assay to identify possible BAD?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 20%; yes, 60%; neutral, 20%. |
| **Role of BAST in the Diagnosis of BAD** |
| PICO 6: In patients with suspected BAD, should we initiate empiric BAST over performing SeHCAT to establish a diagnosis of BAD?<br>GRADE: Very low-quality evidence. Vote: yes, 20%; no, 40%; strongly no, 40%. |
| **Role of BAST in the induction treatment of BAD** |
| PICO 7: In patients with Type 1 or Type 3 BAD, should we use treatments for remediable causes (eg, Crohn’s, microscopic colitis, SIBO) in addition to treatment for BAD for induction of clinical response?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 80%; yes, 20%. |
| PICO 8: In patients with BAD, should we use cholestyramine over no treatment for induction of clinical response?<br>GRADE: Very low-quality evidence. Vote: strongly yes, 80%; yes, 20%. |

| |
|---|
| PICO 9: In patients with BAD, should we use cholestyramine over other BASTs as initial therapy for induction of clinical response?<br>GRADE: Very low-quality evidence. Vote: yes, 80%; neutral, 20%. |
| PICO 10: In patients with BAD who are unable to tolerate cholestyramine, should an alternate BAST be used for induction of clinical response?<br>GRADE: Low-quality evidence. Vote: strongly yes, 40%; yes, 60%. |
| PICO 11: In patients with BAD receiving empiric BAST, should gradual daily dose titration vs. no titration be used to minimize side effects?<br>DESIGNATED A GOOD PRACTICE STATEMENT. |
| PICO 12: In patients with Crohn's disease with extensive ileal involvement or resection, should we use BAST vs. no BAST?<br>GRADE: Very low-quality evidence. Vote: yes, 20%; no, 80%. |
| **Role of BAST in the maintenance treatment of BAD** |
| PICO 13: In patients with BAD who respond to BAST, should intermittent, on demand dosing be tried?<br>GRADE: Very low-quality evidence. Vote on PICO question: yes, 80%; neutral, 20%. |
| PICO 14: In patients with BAD who are unable to tolerate BAST, should alternative anti-diarrheal agents vs. no treatment be used for long-term symptomatic therapy?<br>GRADE: very low-quality evidence. Vote: yes, 100% |
| PICO 15: In patients with BAD receiving BAST, should maintenance therapy be used at the lowest dose needed to maintain symptom response vs. no dose titration?<br>DESIGNATED A GOOD PRACTICE STATEMENT. |
| PICO 16: In patients with BAD and recurrent or worsening symptoms despite stable BAST, should diagnostic re-evaluation or dose escalation be used?<br>DESIGNATED A GOOD PRACTICE STATEMENT. |
| PICO 17: In patients being considered for BAST, should concurrent medications be reviewed to minimize the potential for drug interactions?<br>DESIGNATED A GOOD PRACTICE STATEMENT. |
| **PICO questions with no recommendations** |
| *PICO A: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a FGF19 assay to identify possible BAD?*<br>*GRADE: Very low-quality evidence. Vote: strongly yes, 20%; neutral, 80%.* |
| *PICO B: In patients receiving long-term maintenance therapy with BAST, should fat-soluble vitamin levels be measured at baseline and annually, thereafter?*<br>*GRADE: very low-quality evidence. Vote: yes, 20%; neutral, 80%* |

| PICO questions that were not voted on, and for which no additional recommendation statements were developed |
|---|
| *PICO I: In patients with chronic diarrhea, should we use the absence of inflammatory markers or prior surgery to identify patients with possible primary bile acid diarrhea (Type II BAD)?*<br>*(Note: This PICO was not voted on, and no recommendation statement was developed because "prior surgery" was included in PICO 1, and no data were found regarding the use of inflammatory markers to identify patients with possible BAD)* |
| *PICO II: In patients with chronic diarrhea, should we use appropriate risk factors (e.g. ileal disease/disorders, post-surgical syndromes, enteropathies), to identify patients with likely bile acid malabsorption?*<br>*(Note: This PICO was not voted on, and no additional recommendation statement was developed because "risk factors" were included in PICO 1)* |
| *PICO III: In patients with BAD, should BAST be taken once daily to minimize interaction with other medications?*<br>*(Note: This PICO was not voted on, and no additional recommendation statement was developed because "drug interactions" were included in PICO 17)* |
| *PICO IV: In patients with BAD, should BAST be taken AM (or PM/ HS)?*<br>*(Note: This PICO was not voted on, and no recommendation statement was developed because there were no data to inform this issue, which is discussed in terms of future research needs)* |

## Role of risk factors and symptom presentation in the diagnosis of bile acid diarrhea (BAD)

**PICO 1: In patients with chronic non-bloody diarrhea, should risk factors be used as the initial assessment to identify patients with bile acid diarrhea (BAD)?**

**PICO 2: In patients with chronic non-bloody diarrhea, should symptom presentation be used as the initial assessment to identify patients with possible bile acid diarrhea (BAD)?**

Evidence for this PICO can be derived from two types of studies:

A. Diagnostic test accuracy (DTA) studies that assessed what is the diagnostic accuracy of "symptom presentation and/or risk factors" for the diagnosis of BAD - compared to a reference standard (positive SeHCAT, with/without positive response to BAS treatment)
B. RCTs that randomized patients to one strategy (assessing "symptom presentation and/or risk factors") vs. another strategy (not assessing "symptom presentation and/or risk factors") and then treated the patients according to the resulting diagnoses and captured clinical outcomes.

No such RCTs have been published; therefore the evidence will be derived from DTA studies.

Notes:

- Bannaga BMJ Open Gastro 2017[1] (UK): Online survey of patients with self-reported BAD. Serious limitations (only the first 100 responses out of 1300 members of the Bile Salt Malabsorption Facebook Group were analyzed; self-reported BAD). It does not directly answer this diagnostic PICO question, but it provides insight to patients' values: esp. the disappointment they felt because they "felt like they were not taken seriously by the medical professionals consulted" (35%) and because of the delay in diagnosis ("symptoms had been experienced for more than 5 years before diagnosis in 44% of respondents").
- We have also included 2 untagged studies that were cited in Gracie 2012[2] (see below):
  - Borghede EJIM 2011[3]
  - Ung EJGH 2000[4]

| DTA studies (QUADAS-II risk of bias domains) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Patient selection** | **Index test** (here: risk factors and symptom presentation) | **Reference standard** (here: SeHCAT) | **Flow and timing** | **Comments** |
| Gracie NGM 2012[2] | The criteria for referring some - but not all - chronic diarrhea patients for SeHCAT were not defined. | Retrospective cohort design: the data on risk factors were collected from medical records. **With the exception of the PMH of surgery**, these data cannot be adequately accurate. Unclear if the index test results were interpreted without knowledge of the results of the reference standard (it is not clear if medical records collected after the diagnosis of BAM, were also taken into account when data on risk factors and symptoms were extracted for this study: recall bias and directly questioning patients already diagnosed with BAM for recognized risk factors, would inflate | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (UK): Retrospective cohort study of 373 patients with chronic diarrhea undergoing SeHCAT scan. BAM = retention <15%:<br>● Overall: **50.9%** had BAM<br>● Previous cholecystectomy: **68.4%** had BAM (OR 2.51; 99% CI 1.10–5.77)<br>● TI resection or right hemicolectomy: **89.1%** had BAM<br>- TI resection or right hemicolectomy for Crohn's disease: OR 12.4; 99% CI 2.42–63.8<br>- TI resection or right hemicolectomy for other reasons: OR 7.94; 99% CI 1.02– 61.6<br>● IBS-D: **27.3%** had BAM<br>● Patients with no risk factors for a positive SeHCAT scan, other than chronic diarrhea: **37.5%** had BAM<br>- Significantly fewer individuals with BAM reported bloating (15.3% vs 24.9%, P = 0.02), or abdominal pain or discomfort (33.9% vs 43.6%, P = 0.05), and fewer met criteria for IBS-D (11.1% vs 30.6%, P < 0.001).<br>● History of acute enteric illness: 40.9% had BAM (not significantly associated with BAM)<br>● There were very few patients with microscopic colitis or celiac disease<br>● So, overall this study confirmed that (among patients with chronic diarrhea) previous cholecystectomy, and TI resection or R hemicolectomy were risk factors for BAM. Interestingly, patients with bloating, abdominal pain or discomfort (among those with chronic diarrhea) were less likely to have BAM. |

| | | | | | |
|---|---|---|---|---|---|
| | | the importance of these factors) | | | |
| Kurien SJG 2011[5] | The criteria for referring for SeHCAT were not defined. **Not all patients had chronic diarrhea**. | Retrospective cohort design: the data on risk factors were collected from medical records = inaccuracy. Unclear if the index test results were interpreted without knowledge of the results of the reference standard | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (UK): Retrospective cohort study of 273 patients undergoing SeHCAT scan. **39.2%** had BAM = retention <10%. It was unclear how many patients had chronic diarrhea. Only in the Discussion section it reads that "38% of patients with chronic diarrhea had evidence of BAM based on their SeHCAT result".<br>● Predictive factors reported in the pasted table below (for all patients, with or without diarrhea):<br>Table III. Features predictive of a positive SeHCAT.<br>Patient feature / *p* Value / Odds ratio / 95% CI<br>Ileal Crohn's: <0.01 / 3.76 / 1.10–12.60<br>Ileal resection: <0.01 / 15.83 / 2.62–95.69<br>Cholecystectomy: <0.01 / 5.70 / 2.42–13.46<br>● 33.6% of patients who had a positive SeHCAT also had Rome II D-IBS, but D-IBS was not a predictive factor. |
| Fernandez-Banares AJG 2007[6] | OK. | OK | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (Spain): prospective cohort study of 62 patients with a) **non-bloody chronic watery diarrhea**, defined as more than 3 loose or liquid BMs a day for at least 4 wk and a stool weight >200 g/day; (b**) fulfilling the Rome II criteria of either functional diarrhea or diarrhea predominant IBS**. They were assessed with a series of tests including SeHCAT (BAM=retention >11%).<br>● 59.7% had BAM by SeHCAT. The final diagnosis of **BAD** was given to those patients with BAM who responded to cholestyramine.<br>● Final diagnoses: 45.2% had BAD; an additional 3% had both BAD and sugar malabsorption.<br>● There were no significant differences between patients with functional diarrhea vs IBS-D in the final diagnoses: BAD was 46.7% vs. 43.8% respectively. |
| Galatola EJGH 1992[7] | OK | OK | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (Italy): prospective study on 98 patients **with IBS-D**: they all had SeHCAT scan: 56 patients (**57.1%**) had BAM (retention > 11.2%): of those 42 completed a course of cholestyramine and of those only 3 did not respond to the treatment.<br>● Predictive factor for BAM was **fecal wet weigh > 200 g/day**. |
| Aziz CGH 2015[8] | OK | OK | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (UK): cross-sectional study that showed that the prevalence of BAD (SeHCAT <15%) was 23.7% in 118 patients with **Rome III IBS-D**. No clinical characteristic was associated with BAD, other than **BMI** (patients with BAD had a higher mean BMI than patients without BAD (31.6 vs 26.4; P = .003) |
| Stotzer UEGJ 2015[9] | OK | High risk for differential verification bias: because the patients with less severe | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and | OK | (Sweden): Prospective cohort study. Assessed which of two definitions for diarrhea (≥3 loose stools/day vs. stool consistency mushy or loose) is the best predictor of having an organic cause of the diarrhoea.<br>The most common of the organic causes of diarrhea in this study was BAD (48 out of 91 patients with organic diarrhea). Among patients with BAD 44% had ≥3 |

| | | | | | |
|---|---|---|---|---|---|
| | | diarrhea were less rigorously investigated and therefore were less likely to be diagnosed with organic diarrhea. | symptoms): probably not. | | loose stools/day and 81% had mushy or loose stools; among functional diarrhea patients the proportions were 21% and 35%. Therefore, the **consistency of stools would have a better discriminator ability** than the frequency. The diagnostic accuracy for BAD among patients with diarrhea was not calculated but it is obvious that this criterion alone cannot be extremely useful in clinical practice. |
| Borghede EJIM 2011[3] | The criteria for referring for SeHCAT patients with chronic watery diarrhea were not defined. | Retrospective cohort design: the data on risk factors were collected from medical records = likely inaccurate. Unclear if the index test results were interpreted without knowledge of the results of the reference standard | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | OK | (Denmark): Retrospective cohort study of 289 patients with chronic watery diarrhea undergoing SeHCAT scan. BAM = retention <15%:<br>● Overall: **68%** had BAM<br>● Previous cholecystectomy: **89%** (CI 71%–95%) had BAM<br>● Crohn's disease in TI without resection: **76%** (CI 57%–90%) had BAM<br>● Crohn's disease with ileal resection: **91%** (CI 78%–87%) had BAM<br>● Patients with no known cause for diarrhea (and no risk factors for BAM other than chronic diarrhea): **60%** (CI 52%–67%) had BAM |
| Ung EJGH 2000[4] | OK | OK | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | Data on symptoms were missing in 22% of the patients | (Denmark): Prospective cohort study of 94 patients with chronic diarrhea undergoing SeHCAT scan. BAM = retention <10%:<br>● Overall: 44.6% had BAM<br>● Patients with BAD type II had more frequent and looser stools compared to patients with functional diarrhea, but there was no difference in abdominal pain, distention or flatulence. |
| Williams Gut 1991[10] | The criteria for referring for SeHCAT were not defined. | Retrospective cohort design: the data on clinical characteristics were collected from medical records = likely inaccurate. Unclear if the index test results were interpreted without knowledge of the results of the reference standard. | Unclear if the SeHCAT results were interpreted without knowledge of the results of the index test (risk factors and symptoms): probably not. | Data on clinical characteristics (as shown in tables I-III) were missing for many patients. | (UK): retrospective study on 181 patients with chronic diarrhoea (that remained unexplained after full investigation), who had SeHCAT scan, and if, positive, were treated with cholestyramine.<br>● 11.6% had mild BAM (SeHCAT retention 10-15%)<br>● 8.8% had moderate BAM (SeHCAT retention 5-10%)<br>● 12.7% had severe BAM (SeHCAT retention < 5%)<br>No predictive factors for BAM were reported<br>It was noted that the nocturnal component of the diarrhea was only present in severe BAM (11 out of 23) and in no patient with moderate or mild BAM. However, the prevalence of the nocturnal component in non-BAM patients was not reported. Therefore, it is unknown if this criterion has any diagnostic value when trying to predict if a patient which chronic diarrhea is likely to have BAM or not.<br>**Very serious indirectness.** |

## QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies- 2) tool

| **Domain 1: Patient Selection** |
|---|
| **Risk of Bias**: Could the Selection of Patients Have Introduced Bias?<br>• Signaling question 1: Was a consecutive or random sample of patients enrolled? |

- Signaling question 2: Was a case–control design avoided?
- Signaling question 3: Did the study avoid inappropriate exclusions?

**Applicability**: Are There Concerns That the Included Patients and Setting Do Not Match the Review Question?

**Domain 2: Index Test**

**Risk of Bias:** Could the Conduct or Interpretation of the Index Test Have Introduced Bias?

- Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?
- Signaling question 2: If a threshold was used, was it prespecified?

**Applicability:** Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?

**Domain 3: Reference Standard**

**Risk of Bias:** Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?

- Signaling question 1: Is the reference standard likely to correctly classify the target condition?
- Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

**Applicability:** Are There Concerns That the Target Condition as Defined by the Reference Standard Does Not Match the Question?

**Domain 4: Flow and Timing**

**Risk of Bias:** Could the Patient Flow Have Introduced Bias?

- Signaling question 1: Was there an appropriate interval between the index test and reference standard?
- Signaling question 2: Did all patients receive the same reference standard?
- Signaling question 3: Were all patients included in the analysis?

**Quality of evidence assessment**

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
|---|---|---|---|---|---|---|---|
| **TI resection, TI disease or cholecystectomy as risk factors for BAM among patients with chronic diarrhea** | | | | | | | |
| Multiple observational studies | Serious [a] | Not serious | Not serious | Not serious | None | ⨁◯◯◯ VERY LOW | ⨁◯◯◯ VERY LOW |
| **Symptom presentation** | | | | | | | |
| Multiple observational studies | Serious [b] | Serious [c] | Not serious | Serious [d] | None | ⨁◯◯◯ VERY LOW | ⨁◯◯◯ VERY LOW |

a. All studies are at either high or unclear risk of bias
b. The studies that identified specific symptoms and clinical characteristics as risk factors for BAM (among patients with chronic diarrhea) were all at high risk of bias. There were only three studies at unclear risk of bias (Fernandez-Banares AJG 2007, Galatola EJGH 1992, Aziz CGH 2015) but these included selected sub-populations with chronic diarrhea (functional diarrhea and/or IBS-D) and did not identify any symptoms as risk factors for BAM. There were no studies at low risk of bias.
c. The specific symptoms and clinical characteristics were inconsistently identified as risk factors for BAM among the studies
d. Small sample size, the studies were not powered to identify weak risk factors.

**Overall QoE for PICO 1:**

There are no diagnostic-strategy RCTs informing this PICO.

There are several observational studies that have not been designed and executed as diagnostic accuracy studies, but diagnostic accuracy data can still be extracted.

- There is **VERY LOW** quality evidence supporting the use of **TI resection, TI disease or cholecystectomy** as the initial assessment to identify patients at higher risk for having BAD. The quality of evidence was downrated for study limitations (risk of bias) but the results of the studies were consistently in favor of this PICO
- There is **VERY LOW** quality evidence supporting the use of **symptom presentation** as the initial assessment to identify patients at higher risk for having BAD. The quality of evidence was downrated for study limitations (risk of bias), inconsistency and imprecision: it remains very uncertain if symptom presentation has any diagnostic/prognostic utility in this clinical setting.

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms**: Consider the potential harms (clinical consequences of false positive (unnecessary diagnostic tests and /or treatments) or false negative classifications (missed diagnoses)) when using clinical risk factors as triage test for BAM
- **Patient values and preferences**: See Bannaga BMJ Open Gastro 2017.[1]
- **Cost:** The cost of using clinical risk factors as triage test for BAM is very low.

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

- **Wedlake APT 2009 (**Wedlake L, A'Hern R, Russell D, et al. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2009;30:707-17): Systematic review and meta-analysis that allows estimation of the prevalence of BAM among patients with IBS-D:
    - 5 studies (429 patients) indicated that 10% (CI: 7–13) patients had severe bile acid malabsorption (SeHCAT 7-day retention <5% of baseline value)
    - 17 studies (1073 patients) indicated that 32% (CI: 29–35) patients had moderate bile acid malabsorption (SeHCAT<10%)
    - 7 studies (618 patients) indicated that 26% (CI: 23–30) patients had mild (SeHCAT <15%) bile acid malabsorption
    - No data on the diagnostic accuracy of specific symptoms and risk factors. The estimated prevalence is equal to the pretest probability of BAM in patients with IBS-D, but it is not known if this prevalence is statistically higher that the prevalence of BAM in other conditions presenting with chronic diarrhea, such as functional diarrhea. Therefore, these results cannot help us decide if IBS-D is a risk factor for BAM among patients with chronic diarrhea.
- **Lacy Gastro 2016 (**Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393-1407. e5): Narrative review, classifying and describing functional bowel disorders. In the IBS-D chapter, it states that BAM may be the cause of persistent, watery diarrhea in some patients; in the Functional Diarrhea

chapter it states that BAM is an often-overlooked diagnosis in patients with longstanding diarrhea. However, there are no detailed data to allow us to quantify the diagnostic accuracy of "symptom presentation and risk factors" for the diagnosis of BAD.

- **Peleman CGH 2017 (**Peleman C, Camilleri M, Busciglio I, et al. Colonic transit and bile acid synthesis or excretion in patients with irritable bowel syndrome-diarrhea without bile acid malabsorption. Clin Gastroenterol Hepatol 2017;15:720-727 e1): elaborate study that in the absence of overt BAM, the total, primary, and secretory BAs in stool contribute to the acceleration of colonic transit and fecal weight in the diarrhea of patients with IBS-D.
- **Camilleri NGM 2014 (**Camilleri M, Shin A, Busciglio I, et al. Validating biomarkers of treatable mechanisms in irritable bowel syndrome. Neurogastroenterol Motil 2014;26:1677-85)**:** Assessed potential biomarkers for IBS-D and IBS-C. Found that IBS-D patients had higher total fecal bile acid secretion and evidence of increased BA synthesis (C4 and FGF19) compared to healthy volunteers (who did not have diarrhea). Does not answer this PICO question.
- **Shin CGH 2013 (**Shin A, Camilleri M, Vijayvargiya P, et al. Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2013;11:1270-1275 e1)**:** Assessed the association between individual unconjugated BAs and stool characteristics in patients with IBS. Does not answer this PICO question.
- **Thomas Gut 2003 (**Thomas PD, Forbes A, Green J, et al. Guidelines for the investigation of chronic diarrhoea, 2nd edition. Gut 2003;52 Suppl 5:v1-15): BSG CPG for the investigation of chronic diarrhea. It highlights the risk factors for BAM among patients with chronic diarrhea: "Patients with Crohn's disease or other terminal ileal abnormality or resection are particularly at risk of BAM, but the condition has also been well documented following cholecystectomy, post-infectious diarrhoea, and in idiopathic diarrhoea." It did not provide qualitative data that would allow us calculate the diagnostic accuracy of specific symptoms and risk factors

**Evidence to Decision framework (diagnostic question)**

**PICO 1: In patients with chronic non-bloody diarrhea, should risk factors (history of terminal ileal resection, cholecystectomy, or radiotherapy) be used as the initial assessment to identify patients with possible bile acid diarrhea (BAD)?**

| | JUDGEMENT |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |

| | |
|---|---|
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High |

| | |
|---|---|
| | ○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?** |

| | |
|---|---|
| | ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

**Evidence to Decision framework (diagnostic question)**

**PICO 2: In patients with chronic non-bloody diarrhea, should risk factors should symptom presentation be used as the initial assessment to identify patients with possible bile acid diarrhea (BAD)?**

| | **JUDGEMENT** |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate |

| | |
|---|---|
| | ○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?** |

| | |
|---|---|
| | ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes |

| | |
|---|---|
| | ○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 1 & 2*


1. Bannaga A, Kelman L, O'Connor M, et al. How bad is bile acid diarrhoea: an online survey of patient-reported symptoms and outcomes. BMJ Open Gastroenterol 2017;4:e000116.
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9. Stotzer PO, Abrahamsson H, Bajor A, et al. Are the definitions for chronic diarrhoea adequate? Evaluation of two different definitions in patients with chronic diarrhoea. United European Gastroenterol J 2015;3:381-6.
10. Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut 1991;32:1004-6.

**PICO I (no vote): In patients with chronic diarrhea, should we use the absence of inflammatory markers or prior surgery to identify patients with possible primary bile acid diarrhea (Type II BAD)?**

Evidence for this PICO can be derived from two types of studies:

A. Diagnostic test accuracy (DTA) studies that assessed what is the diagnostic accuracy of "absence of inflammatory markers or prior surgery" for the diagnosis of primary BAD, among patients with chronic diarrhea - compared to a reference standard (positive SeHCAT, with/without positive response to BAS treatment)
B. RCTs that randomized patients to one strategy (considering "absence of inflammatory markers or prior surgery") vs. another strategy (not considering "absence of inflammatory markers or prior surgery") and then treated the patients according to the resulting diagnoses and captured clinical outcomes.

There was only one study tagged to this PICO: **Gothe JCC 2014**. However, this was a pediatric study and the committee had *a priori* decided to exclude pediatric studies. Even if we had not decided to exclude pediatric studies, this study would not provide results relevant to this PICO: the study population was patients with IBD (not patients with chronic diarrhea).

Therefore, **we were not able to find any evidence in favor or against this PICO**.
**The quality of evidence could not be assessed.**

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms**:
- **Patient values and preferences**:
- **Cost**

**Evidence to Decision framework (diagnostic question)**
**PICO I (no vote): In a patient with chronic diarrhea, should we use the absence of inflammatory markers or prior surgery to identify patients with primary bile acid diarrhea (Type II BAD)?**

The EtD framework was not completed, there was no vote, and no recommendation statement was developed because "prior surgery" is included in PICO 1, and no data were found regarding the use of inflammatory markers to identify patients with possible BAD.

*References for PICO I*

Not applicable

**PICO II (no vote): In patients with chronic diarrhea, should we use appropriate risk factors (e.g. ileal disease/disorders, post-surgical syndromes, enteropathies), to identify patients with likely bile acid diarrhea**

Evidence for this PICO can be derived from two types of studies:

A. Diagnostic test accuracy (DTA) studies that assessed what is the diagnostic accuracy of "appropriate risk factors (e.g. ileal disease/disorders, post-surgical syndromes, enteropathies)" for the diagnosis (as a triage test) of BAD, among patients with chronic diarrhea – compared to a reference standard (positive SeHCAT, with/without positive response to BAS treatment)
B. RCTs that randomized patients to one strategy (considering "appropriate risk factors") vs. another strategy (not considering "appropriate risk factors") and then treated the patients according to the resulting diagnoses and captured clinical outcomes.

22 supportive studies have been tagged. The studies that reported the prevalence of positive SeHCAT in at least 10 patients with a specific risk factor were the following:

- Ludgate CR 1985:[1] 26 patients with post-irradiation chronic diarrhea (81% positive SeHCAT)
- Murray SJG 2017:[2] retrospective observational study of 387 consecutive patients undergoing SeHCAT. Binary logistic regression was used to define which variables were statistically significant predictors of a positive SeHCAT.

**Table 2.** Predictors of a positive $^{75}$SeHCAT test.

| | | | 95% CI for odds ratio | |
|---|---|---|---|---|
| | Significance | Odds ratio | Lower | Upper |
| Cholecystectomy | 0.003 | 2.540 | 1.361 | 4.737 |
| Right Hemicolectomy | <0.001 | 4.997 | 2.197 | 11.362 |
| Crohn's | 0.038 | 1.879 | 1.036 | 3.407 |

- Gracie NM 2012[3] (UK): Retrospective cohort study of 373 patients with chronic diarrhea
  - Overall: 50.9% had BAM
  - Previous cholecystectomy: 68.4% had BAM OR 2.51; 99% CI 1.10–5.77
  - TI resection or right hemicolectomy: 89.1% had BAM

  - TI resection or right hemicolectomy for Crohn's disease: OR 12.4; 99% CI 2.42–63.8
  - TI resection or right hemicolectomy for other reasons: OR 7.94; 99% CI 1.02– 61.6
- Patients with no risk factors for a positive SeHCAT scan, other than chronic diarrhea: 37.5% had BAM

- Smith JRCPL 2000[4] (UK):
  - 37 patients with Crohn's with ileal resection in remission (97% SeHCAT positive)
  - 44 patients with Crohn's unoperated, in remission (54% SeHCAT positive
  - Vagotomy and pyloroplasty, with/without cholecystectomy (58% SeHCAT positive)
- Valdes Olmos EJNM 1991[5] (Netherlands):

  All 39 patients had a history of abdominal irradiation for malignancies of the cervix, endometrium, ovary, rectum or bladder. At the time of the investigation patients complained of diarrhoea, pain or both.
  - in 22 cases no ileal resection had been performed (group A): SeHCAT positive 36.4%
  - In 17 patients a ileal resection had been performed because of obstructing radiation damage to the terminal ileum (group B): SeHCAT positive 88.2%

The assessment of the quality of evidence is similar to the assessment done for the one of the two underlying sub-questions for PICO 1 (regarding risk factors):

| **Quality of evidence assessment** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
| **TI resection, TI disease or cholecystectomy as risk factors for BAM among patients with chronic diarrhea** | | | | | | | |
| Multiple observational studies | Serious [a] | Not serious | Not serious | Not serious | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW |

a. All studies are at either high or unclear risk of bias

Therefore, overall, there is **VERY LOW** quality evidence (rated down due to risk of bias), that is supporting the use of appropriate risk factors (e.g. ileal disease/disorders, post-surgical syndromes, enteropathies), to identify patients with likely bile acid malabsorption

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms**:
- **Patient values and preferences**:
- **Cost**

**Evidence to Decision framework (diagnostic question)**
**PICO II (no vote): In patients with chronic diarrhea, should we use appropriate risk factors (e.g. ileal disease/disorders, post-surgical syndromes, enteropathies), to identify patients with likely bile acid diarrhea**

The EtD framework was not completed, there was no vote, and no additional recommendation statement was developed because "risk factors" are included in PICO 2.

*References for PICO II*
Not applicable

## Role of laboratory tests in the diagnosis of BAD

**PICO 3: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use SeHCAT testing to identify patients with BAD?**

Evidence for this PICO can be derived from three types of studies:

A. Diagnostic test accuracy (DTA) studies that assessed what is the diagnostic accuracy of SeHCAT testing for the diagnosis of BAD, among patients with chronic diarrhea - compared to a reference standard (measurement of fecal bile acids)

B. DTA studies that assessed what is the diagnostic/prognostic accuracy of SeHCAT testing for predicting "symptomatic response to BAS treatment", among patients with chronic diarrhea compared to the reference standard which is a symptomatic response to BAS regardless of the result of SeHCAT (in such studies, all patients undergo SeHCAT testing and all patients receive BAS treatment -regardless of the result of SeHCAT)

C. RCTs that randomized patients to one strategy (SeHCAT) vs. another strategy (no SeHCAT, or use of another test) and then treated the patients according to the resulting diagnoses and captured clinical outcomes.

**Contributing to GRADE assessment**

**Riemsma HTA 2013**:[6] This is a rigorous and detailed HTA (UK) report: a SR and CE analysis on SeHCAT for the investigation of BAM and measurement of BA pool loss. This HTA has searched for all three study designs mentioned above, using a very rigorous literature search.

- The HTA conclusions: *"The results of our systematic review suggest that the accuracy of the SeHCAT test in predicting either BAM or response to treatment, and the clinical effectiveness of BAS for the treatment of chronic diarrhoea caused by BAM, are uncertain. Additionally, the results of our economic evaluation showed that for both populations studied, the lifetime perspective gave different results for different scenarios meaning that all strategies may potentially be the most cost-effective. Therefore, the implications for service provision of SeHCAT are equally uncertain. The main reason for this uncertainty is the lack of good-quality evidence."*
- The HTA project decided to focus on two populations with chronic diarrhea: IBS-D and Crohn's disease (without TI resection).
- They did not identify any RCTs ("type C" studies)
- They did not find any ("type A") DTA studies that assessed the diagnostic accuracy of SeHCAT testing for the diagnosis of BAD compared to a gold standard: "*None of the studies evaluated in this report, including the studies described in the literature as accuracy studies, was included in this review as diagnostic test accuracy (DTA) studies, because they either do not use an acceptable reference standard or they include a population not in line with the scope (i.e. healthy volunteers or people with ileal resection)*"
    - We independently confirmed this: there are **no studies** that attempted to measure the diagnostic accuracy of SeHCAT among patients with chronic diarrhea, using a reference standard, and avoiding the case-control design:
        - Even the two Sciarretta studies[7, 8] (mentioned below) that were the only two studies that allowed calculation of the diagnostic accuracy of SeHCAT for predicting response to BAST, were actually designed as case-control studies that assessed the ability of SeHCAT to discriminate between cases and controls. The DTA calculations that the HTA project did, were post-hoc calculations using other secondary results that these studies reported.
        - We also assessed older studies that have been classically cited as the DTA studies that validated the diagnostic accuracy of SeHCAT, and we found that none of these studies actually provides true DTA results:
            - Boyd JNM 1981 (Boyd GS, Merrick MV, Monks R, Thomas IL. Se-75-labeled bile acid analogs, new radiopharmaceuticals for investigating the enterohepatic circulation. J Nucl Med 1981;22:720-5): **animal (rabbit) study**
            - Thaysen Gut 1982 (Thaysen EH, Orholm M, Arnfred J, Carl J, Rddbro P. Assessment of ileal function by abdominal counting of the retention of a gamma emitting bile acid analogue. Gut 1982;23:862-5: **The reference standard was clinical features and 14C-cholylglycine breath test.**
            - Blankestein van M, van den Berg JWO, Delhez H. The use of 75SeHCAT for testing ileal function. Proceedings of the 3rd World Congress of Nuclear Medicine and Biology, Paris, 1982:2434-6: **the proceedings could not be assessed**

- Nyhlin Gastro 1983 (Nyhlin H, Merrick MV, Eastwood MA, Brydon WG. Evaluation of ileal function using 23-selena-25-homotaurocholate, a rlabeled conjugated bile acid. Gastroenterology 1983;84:63-8): **Used a case-control design (patients with disease of the small intestine, colon, or ileocecal region vs. healthy controls), i.e. the reference standard was the initial classification as case or control (this study assessed the ability of SeHCAT to discriminate cases vs. controls). Also measured total fecal and primary bile acids and found a "significant relationship" with SeHCAT results, but, again, this was a case-control study.**
- Fagan Digestion 1983 (Fagan EA, Chadwick VS, Baird McL. SeHCAT absorption: a simple test of ileal dysfunction. Digestion 1983;26:159-85): **Used a case-control design (patients with IBD vs. healthy controls), i.e. the reference standard was the initial classification as case or control (this study assessed the ability of SeHCAT to discriminate IBD patients vs. controls). SeHCAT was also compared with tests of vitamin B12 absorption (Schilling test and whole body retention) and the cholylglycine-1-14C breath test and faecal isotope excretion, but, again, this was a case-control study.**

- The HTA report concluded that there is no feasible gold standard for the diagnosis of BAM, so as to compare it with SeHCAT: *"there is no direct comparator for SeHCAT. Current diagnostic options include analysis of a patient's history, investigations to exclude 'red flag' symptoms and a variety of other diagnostic tests such as blood tests and lactose tolerance tests. Trial of treatment and measurement of faecal bile acids are two methods used, with mixed results, to diagnose BAM. They are, however, not widely used in current practice."*
- The HTA project did not identify any ("type B") DTA studies that assessed the diagnostic accuracy of SeHCAT testing for the predicting response to BAS, in patients with CD without resection.
- The HTA project only found 3 ("type B") DTA studies that assessed the diagnostic accuracy of SeHCAT testing for the predicting response to BAS, in patients with IBS-D (Sciarretta Gastro 1986;[7] Sciarretta Gut 1987;[8] Merrick BMJ 1985[9]). They did not proceed to a meta-analysis: "*Meta-analysis of test accuracy studies was considered inappropriate, owing to the small number of studies with varying diagnostic thresholds and between-study heterogeneity in other study design categories (principal diagnosis, treatment dose, definition of response, follow-up period and SeHCAT administration)*"
    - However, we are very confident that Merrick BMJ 1985[9] was included in the HTA report by mistake: there are no diagnostic accuracy data for the IBS-D group. Therefore, there are **only 2 studies** providing DTA evidence for IBS-D patients: Sciarretta Gastro 1986;[7] Sciarretta Gut 1987:[8] **see QUADAS-II risk of bias assessments and comments below**

| **DTA studies (QUADAS-II risk of bias domains)**<br>**Note: the risk of bias assessment refers to the data extracted on DTA of SeHCAT for predicting response to BAST** (if we attempt to assess the studies for the DTA of SeHCAT for diagnosing "BAD", then the risk of bias is substantially higher) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Patient selection** | **Index test** (here: SeHCAT) | **Reference standard** (here: response to BAST) | **Flow and timing** | **Comments** |
| Sciarretta Gastro 1986[7] | Unclear if the enrolled patients were consecutive | The threshold was not pre-specified | The reference standard results (response to BAST) were not interpreted without knowledge of the results of the index test (SeHCAT results) | OK | (Italy): Prospective study of SeHCAT and results on response to BAST (all patients received BAST regardless of the results of SeHCAT test). The study included four groups of patients:<br>(a) healthy controls<br>(b) patients with resected pathological distal ileum<br>(c) patients with intestinal pathology, but normal distal ileum<br>(d) patients with diarrhoea, but no evidence of intestinal or extraintestinal pathology |

| | | | | | |
|---|---|---|---|---|---|
| | | | The dose and duration of BAST and the definition of response are unclear | | Data were extracted for group D (n= 13)<br><br>**Applicability concerns**<br>• **indirectness of population**: 3/13 (23%) of patients in group D ("chronic unexplained diarrhea") had cholecystectomy (in 2 of these, diarrhea started after the cholecystectomy)<br>• **Indirectness of Index Test**: 3rd day SeHCAT retention values were used |
| Sciarretta Gut 1987[8] | Unclear if the enrolled patients were consecutive.<br><br>Unclear if the study population partially overlaps with the patients used in Sciarretta Gastro 1986[7] (for sure they used the same controls for both studies) | OK | The reference standard results (response to BAST) were not interpreted without knowledge of the results of the index test (SeHCAT results) | OK | (Italy): Prospective study of SeHCAT and results on response to BAST (all patients received BAST regardless of the results of SeHCAT test). The study included 46 patients (38 with IBS-D and 8 with cholecystectomy). No separate results for IBS-D.<br><br>**Applicability concerns**<br>• **indirectness of population**: 8/46 (17%) of patients had cholecystectomy (no separate results for the IBS-D patients)<br>• **(moderate) Indirectness of Index Test**: 7th day SeHCAT retention value of < 8% was used as cut-off point |

The calculated sensitivity and specificity of SeHCAT for predicting response to BAST (copy-pasted from the HTA report – deleted Merrick 1985[9])[6]

TABLE 4 Accuracy of SeHCAT for the assessment of treatment response – studies in which all patients were treated

| Study ID | Patient data, *n* | Index test or comparator | Reference standard | TP | FN | FP | TN | Sensitivity (95% CI) | Specificity (95% CI) | Tested/treated, *n* patients |
|---|---|---|---|---|---|---|---|---|---|---|
| *Inclusion criteria: chronic diarrhoea with unknown cause/IBS* | | | | | | | | | | |
| Sciaretta 1986[42] | 13 patients (group D only) | SeHCAT; 5% cut-off | Response[c] | 6 | 1 | 0 | 6 | 0.857 (0.421 to 0.996) | 1.000 (0.541 to 1.000) | All treated |
| Sciaretta 1987[43] | 46 patients (group B only) | SeHCAT; 8% cut-off | Response[d] | 19 | 1 | 1 | 25 | 0.950 (0.751 to 0.999) | 0.962 (0.804 to 0.999) | All treated |

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.
a Definition of response: 'asymptomatic' or 'free of small bowel disease'.
b These patients were not actually treated with cholestyramine, but were considered true-negatives based on follow-up: 'None of the 31 patients with irritable bowel disease who retained more than 15% at seven days showed any evidence of small bowel disease, and none appeared during a follow up of at least 12, and in some up to 24 months. Simple conservative treatment resolved or eased most symptoms'. Two equivocal patients responded to cholestyramine.
c Definition of response: 'Disappearance of diarrhoea' – no further details reported.
d Definition of response: the test was considered positive when diarrhoea stopped with cholestyramine administration, and recurred without it.

Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236.

Added post hoc in response to peer-reviewers' comments:

- Downstream clinical consequences of FP results: patients with diarrhea without BAD will be erroneously be diagnosed as having BAD and will be treated with BAST, thus delaying the true diagnosis and using a costly treatment, that will be unlikely to be effective and has common, although usually non-serious, adverse effects
- Downstream clinical consequences of FN results: patients with BAD will be erroneously diagnosed as not having BAD and will be denied BAST, and will continue suffering from diarrhea while undergoing unnecessary additional investigations and treatments.

Figure showing the confidence intervals for sensitivity and specificity of SeHCAT for predicting response to BAST (copy-pasted from the HTA report – Merrick 1985[9] should be ignored; also there is a typo in the legend of X-axis: it should read "1-specificity"[6]

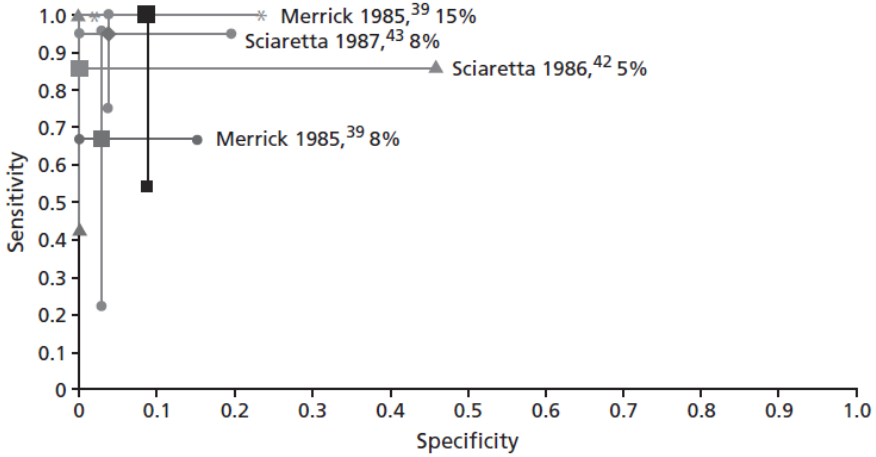


FIGURE 5 'Accuracy' of SeHCAT to predict a response to treatment at different cut-offs. The centre dots represent the point estimates for sensitivity and specificity of SeHCAT in predicting response to treatment in the three studies at different cut offs (5%, 8% and 15%). The vertical and horizontal lines represent the 95% CIs for sensitivity and specificity respectively; see data in *Table 4*.

Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236.

Our assessment of the quality of evidence:

**Quality of evidence assessment**

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
|---|---|---|---|---|---|---|---|
| Two DTA studies (Sciarretta Gastro 1986;[7] Sciarretta Gut 1987[8]) | Serious [a] | Not serious | Serious [b] | **Very** serious [c] | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW |

a. High risk of bias for Index test and Reference standard (see QUADAS-2 table)
b. indirectness of population and index test (see applicability concerns in QUADAS-2 table)

c. The lower limits of the confidence intervals for sensitivity and specificity cross the threshold for clinically useful diagnostic tests; very small sample sizes (13 and 46 patients; there might even be overall among the populations of the two studies)

In conclusion, the only diagnostic accuracy results for SeHCAT, are derived from two studies conducted by one group of investigators. There is serious risk of bias, serious indirectness and very serious imprecision. There is **VERY LOW** quality evidence, which seems to be inefficient to support or refute the clinical utility of SeHCAT in patients with IBS-D. There is **no evidence** on the diagnostic accuracy of SeHCAT for patients with Crohn's disease without TI resection

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms**: The harms of using SeHCAT should be considered
  - Radiation risks (for the patients (esp. the gallbladder), the personnel and the environment)
  - Inconvenience, anxiety while awaiting to have the test, delay in initiating BAST
  - Not trying BAST in false negative results
- **Patient values and preferences**
- **Cost and recourse requirements**

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Sciarretta IJG 1988 (**Sciarretta G, Furno A, Fagioli G, et al. The SeHCAT test: a new radioisotopic diagnostic tool for bile acid malabsorption. Ital J Gastroenterol 1988;20:83-87): Review article (no access to the full-text pdf)

**Merrick BMJ 1985** (Merrick MV, Eastwood MA, Ford MJ. Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention. Br Med J (Clin Res Ed) 1985;290:665-8) (UK): compared the **diagnostic yield** of SeHCAT in normal controls and in various groups of patients with chronic diarrhea (small bowel resection, PUD surgery, IBS, etc.). The positivity rate was high in these patients, but there were no results on the diagnostic accuracy of SeHCAT for BAD, because there is no comparison with a gold standard).
Some (not very detailed) results on clinical response to cholestyramine are available, but only for those who tested positive for the SeHCAT (most, but not all responded). There are no results on the response to cholestyramine for the patients with negative SeHCAT, therefore we cannot calculate the diagnostic accuracy of SeHCAT for response to cholestyramine response either. NOTE: The UK HTA report (Riemsma HTA 2013) concluded that this study reported the efficacy of cholestyramine treatment in the IBS-D patients who had negative SeHCAT, but we are confident that this is a mistake: such results are not reported anywhere in the paper.

**Slattery APT 2015 (**Slattery SA, Niaz O, Aziz Q, et al. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther 2015;42:3-11)**:** SRMA that assessed the diagnostic yield of SeHCAT in IBS-D. No results on diagnostic accuracy.

**Wedlake APT 2009 (**Wedlake L, A'Hern R, Russell D, et al. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2009;30:707-17)**:** SRMA that assessed the diagnostic yield of SeHCAT in IBS-D. No results on diagnostic accuracy. It found a "dose-response relationship according to severity of malabsorption to treatment with a bile acid binder: response to colestyramine occurred in

96% of patients with <5% retention, 80% at <10% retention and 70% at <15% retention" but the studies were not blinded and there were no results for patients with negative SeHCAT (retention > 15%)

**Pattni BMB 2009 (**Pattni S, Walters JR. Recent advances in the understanding of bile acid malabsorption. Br Med Bull 2009;92:79-93): Narrative review of the pathophysiology of idiopathic BAM. No specific data or references to studies with data on the diagnostic accuracy of SeHCAT.

**Murray SJG 2017 (**Murray IA, Murray LK, Woolson KL, et al. Incidence and predictive factors for positive (75)SeHCAT test: improving the diagnosis of bile acid diarrhoea. Scand J Gastroenterol 2017;52:698-703) (UK): retrospective observational study of 387 consecutive patients undergoing SeHCAT. There were no significant differences in the response rates to cholestyramine treatment according to the severity of the SeHCAT results: response 66.7% (mild), 78.6% (moderate), and 75.9% (severe BAD). The response rate of those with normal SeHCAT was not mentioned.

**Summers BMJOG 2016 (**Summers JA, Peacock J, Coker B, et al. Multicentre prospective survey of SeHCAT provision and practice in the UK. BMJ Open Gastroenterol 2016;3:e000091) (UK): prospective multicentre observational study of 1036 patients undergoing SeHCAT. No diagnostic accuracy data. Follow up information (with info regarding treatment with BAS and response) was reported for only 340 out of 1036 patients.

**Orekoya CM 2015 (**Orekoya O, McLaughlin J, Leitao E, et al. Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clin Med (Lond) 2015;15:252-7) (UK): retrospective observational study of 264 consecutive patients undergoing SeHCAT. "Response to BAS therapies decreased with reduced severity of BAM, although not reaching statistical significance". No diagnostic accuracy data.

**Vijayvargiya CGH 2013 (**Vijayvargiya P, Camilleri M, Shin A, et al. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol 2013;11:1232-9): narrative review of methods for diagnosis of bile acid malabsorption in clinical practice. For the diagnostic accuracy of SeHCAT, the results from Sciarretta Gastro 1986 are used (we have assessed the original study separately)

**Smith NMC 2013 (**Smith MJ, Perkins AC. A survey of the clinical use of SeHCAT in the UK. Nucl Med Commun 2013;34:306-13) (UK): survey of the clinical use of SeHCAT in the UK. No original diagnostic accuracy data.

**Borghede EJIM 2011 (**Borghede MK, Schlutter JM, Agnholt JS, et al. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med 2011;22:e137-40) (Denmark): Retrospective cohort study of 289 patients with chronic watery diarrhea undergoing SeHCAT scan. No diagnostic accuracy data.

**Seetharam SJG 2011 (**Seetharam P, Rodrigues G. Short bowel syndrome: a review of management options. Saudi J Gastroenterol 2011;17:229-35): Narrative review of the management options for sort bowel syndrome.

**Bajor DDS 2008** (Bajor A, Kilander A, Sjovall H, et al. The bile acid turnover rate assessed with the (75)SeHCAT test is stable in chronic diarrhoea but slightly decreased in healthy subjects after a long period of time. Dig Dis Sci 2008;53:2935-40) (Sweden): Assessment of repeat SeHCAT tests in patients with diarrhea (median interval 44 months) and in healthy volunteers (interval 16 years). No diagnostic accuracy data.

## Evidence to Decision framework (diagnostic question)

## PICO 3: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use SeHCAT testing to identify patients with BAD?

| | JUDGEMENT |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate |

| | |
|---|---|
| | ○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High |

| | |
|---|---|
| | ○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate |

| | |
|---|---|
| | ○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



*References for PICO 3*

1. Ludgate SM, Merrick MV. The pathogenesis of post-irradiation chronic diarrhoea: measurement of SeHCAT and B12 absorption for differential diagnosis determines treatment. Clin Radiol 1985;36:275-8.
2. Murray IA, Murray LK, Woolson KL, et al. Incidence and predictive factors for positive (75)SeHCAT test: improving the diagnosis of bile acid diarrhoea. Scand J Gastroenterol 2017;52:698-703.
3. Gracie DJ, Kane JS, Mumtaz S, et al. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. Neurogastroenterol Motil 2012;24:983-e538.
4. Smith MJ, Cherian P, Raju GS, et al. Bile acid malabsorption in persistent diarrhoea. J R Coll Physicians Lond 2000;34:448-51.

5. Valdes Olmos R, den Hartog Jager F, Hoefnagel C, et al. Imaging and retention measurements of selenium 75 homocholic acid conjugated with taurine, and the carbon 14 glycochol breath test to document ileal dysfunction due to late radiation damage. Eur J Nucl Med 1991;18:124-8.
6. Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236.
7. Sciarretta G, Vicini G, Fagioli G, et al. Use of 23-selena-25-homocholyltaurine to detect bile acid malabsorption in patients with illeal dysfunction or diarrhea. Gastroenterology 1986;91:1-9.
8. Sciarretta G, Fagioli G, Furno A, et al. 75Se HCAT test in the detection of bile acid malabsorption in functional diarrhoea and its correlation with small bowel transit. Gut 1987;28:970-5.
9. Merrick MV, Eastwood MA, Ford MJ. Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention. Br Med J (Clin Res Ed) 1985;290:665-8.

**PICO 4: In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, should we use SeHCAT testing?**

In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, we suggest SeHCAT testing.

The underlying questions:

- In patients with small intestinal Crohn's disease and persistent diarrhea despite adequate IBD therapy, what is the diagnostic accuracy of SeHCAT testing (compared to a reference standard) for
    - (a) diagnosing BAD and
    - (b) for predicting response to BAST?
- In patients with small intestinal Crohn's disease and persistent diarrhea despite adequate IBD therapy, does the use of SeHCAT testing improve clinical outcomes (compared to not using SeHCAT testing)

None of the 7 tagged papers provide any information related to the above questions. The UK HTA report (Riemsma HTA 2013)[1] has very rigorously searched for evidence for these questions, and concluded that there is no relevant study (see comments for PICO #4)

An observational cohort study (Smith. JRCPL 2000)[2] appeared relevant, but on close inspection does not provide direct qualitative data for this PICO. This study included patients with diarrhea and underlying GI diseases (Crohn’s disease with ileal resection, unoperated Crohn’s disease;

post-vagotomy and pyloroplasty +/- cholecystectomy). There were 44 patients with unoperated Crohn's disease in clinical remission (other than diarrhea) and with normal hematology, plasma viscosity and CRP. SeHCAT testing was abnormal (<10% retention) in 24/44 (54%). Of the 24 with positive SeHCAT, 20 received treatment: Initial treatment was convectional (prednisolone +/- 5 ASA) with BAST used when conventional treatment failed: 11 responded to prednisolone +/- 5 ASA, 8 responded to BAST and 1 failed both treatments. The duration of the treatments was not stated. The outcome assessment was not described. It is unclear why some patients positive SeHCAT did not receive treatment and what the outcome was. It is unclear if patients with negative SeHCAT received treatment and what the outcome was.

| **DTA studies (QUADAS-II risk of bias domains)**<br>**Note: the risk of bias assessment refers to the data extracted on DTA of SeHCAT for predicting response to BAST** (if we attempt to assess the studies for the DTA of SeHCAT for diagnosing "BAD", then the risk of bias is substantially higher) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Patient selection** | **Index test** (here: SeHCAT) | **Reference standard** (here: response to BAST) | **Flow and timing** | **Comments** |
| Smith 2000[2] | Unclear if the enrolled patients were consecutive | OK | Response to BAST was reported only for 20/24 positive SeHCAT. No outcomes for those with negative SeHCAT<br><br>The reference standard results (response to BAST) were not interpreted without knowledge of the results of the index test (SeHCAT results)<br><br>The dose and duration of BAST and the definition of response are unclear | Results have not been reported for all patients | It is impossible to calculate diagnostic accuracy or the effects of the management that is guided by the test results, without knowledge of results in the control group (those with negative SeHCAT).<br><br>**Applicability concerns**<br>• **indirectness of intervention/reference standard**: patients were treated with conventional treatment first |

Quality of evidence:

| **Quality of evidence assessment** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
| 1 DTA study (Smith 2000[2]) | Very serious [a] | Not serious | Not serious [b] | **Very** serious [c] | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW |

a. High risk of bias for Reference standard and flow (see QUADAS-2 table)
b. There is moderate indirectness of intervention/reference standard (see applicability concerns in QUADAS-2 table)
c. Very small sample size

There is VERY LOW-quality evidence in support of this PICO.

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms** when using vs. not using SeHCAT in this situation
- **Patient values and preferences**
- **Cost and recourse utilization**

**Evidence to Decision framework (diagnostic question)**
**PICO 4: In patients with small intestinal Crohn's disease without objective evidence of inflammation and persistent diarrhea, should we use SeHCAT testing?**

| | JUDGEMENT |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |

| | |
|---|---|
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?** |

| | |
|---|---|
| | ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?** |

| | |
|---|---|
| | ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 4*

1. Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236.
2. Smith MJ, Cherian P, Raju GS, et al. Bile acid malabsorption in persistent diarrhoea. J R Coll Physicians Lond 2000;34:448-51.

**PICO 5: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a C4 assay to identify possible BAD?**

***PICO A (no recommendation): In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a FGF-19 assay to identify possible BAD?***

The underlying questions:

- In patients with chronic diarrhea and clinical features suggestive of BAD, what is the diagnostic accuracy of C4 and FGF assays compared to a reference standard for
  - (a) diagnosing BAD and
  - (b) for predicting response to BAST?
- In patients with chronic diarrhea and clinical features suggestive of BAD, does the use of C4 and FGF assays improve clinical outcomes (compared to not using C4 and FGF assays)

**Supporting evidence**

Important note about the reference standard: SeHCAT has been formally assessed for a previous PICO for this guideline and it was concluded that there is very low quality of evidence for the diagnostic accuracy of SeHCAT (derived from only 2 studies conducted by one group of investigators, with serious risk of bias, serious indirectness and very serious imprecision). Therefore, unless we have high quality of evidence for

an almost perfect diagnostic accuracy for SeHCAT, it cannot be considered reference standard in studies that aim to measure the diagnostic accuracy of other tests (such as C4 and FGF assays). The following studies compared C4 and/or FGF against SeHCAT as reference standard:

**Johnston AJG 2016**[1] (UK): exhaustive study of possible pathophysiology mechanisms for low serum FGF19 in patients with primary BAD. Did not compare with a gold standard other than SeHCAT

**Borup JGH 2015**[2] (Denmark): Assessed if single postprandial sampling of FGF19 has greater discriminative value than fasting FGF19 for detection of BAD among patients with diarrhea. Did not compare with a gold standard other than SeHCAT

**Pattni APT 2013**[3] (UK): compared prospectively SeHCAT and FGF19 in patients with chronic diarrhoea of unknown aetiology. No gold standard other than SeHCAT. Limited (retrospective data, most patients missing) report of response to BAST, but only for the SeHACT positive group.

**Sauter DDS 1999**[4] (Germany): compared prospectively SeHCAT and C4 in patients with chronic diarrhea. No gold standard other than SeHCAT.

**Farkkila CS 1996**[5] (Finland): case-control design DTA: patients with CD who had TI resections vs. healthy controls. Compared various plasma cholesterol precursors with SeHCAT and with fecal bile acids (but did not describe the methods). Unable to estimate diagnostic accuracy for patients with chronic diarrhea of unknown etiology

**Brydon EJGH 1996**[6] (UK): assessed the association between C4 and SeHCAT in a group of patients with chronic diarrhea (IBS-D and various diseases). Reported response rates to BAST, but only for SeHACT positive patients. No gold standard other than SeHCAT.

**Eusufzai Gut 1993**[7] (Sweden): assessed the association between C4 and SeHCAT in a group of patients with chronic diarrhea (most had various organic diseases). No gold standard other than SeHCAT.

Overall, the above studies showed good correlation between C4 and SeHCAT and between FGF and SeHCAT. After a discussion at the face-to-face meeting, it was agreed to include these studies is the Evidence Tables, acknowledging that the true diagnostic accuracy cannot be estimated and that the quality of evidence from such studies will be very low.

Among the identified papers, only one study (Vijayvargiya APT 2017[8]) provides evidence on DTA outcomes for this PICO compared to a reference standard that directly measures bile acid malabsorption (28 h fecal BA). No study has reported clinical outcomes from the use vs. not use of these assays.

The Risk of Bias assessment and the QoE assessment are identical for both C4 and FGF19:

| **DTA studies (QUADAS-II risk of bias domains)** | | | | | |
|---|---|---|---|---|---|
| **Study** | **Patient selection** | **Index test** (here: C4 or FGF19) | **Reference standard** (here: 28 h fecal bile acids) | **Flow and timing** | **Comments** |
| Vijayvargiya APT 2017[8] | Unclear if the enrolled patients were consecutive or random. | Unclear if the index test results (C4 or FGF19) were interpreted without knowledge of the results of the reference standard (28 h | Unclear if the reference standard results (28 h fecal BA) were interpreted without knowledge of the results of the index test (C4 or FGF19) | Unclear if there was there an appropriate interval between the index test and reference | (US): DTA study on patients with IBS-D (some have had cholecystectomy) who underwent measurement of C4 and FGF19.<br>For a proportion of the patients (30 patients), older (measured probably 5 years previously) values of **28 h fecal bile acids** were available and these were used as gold standard for BAD. These 30 patients had C4 and FGF19 measured both at the time of the study and 5 years earlier. Unclear if the new or the old measurements (for C4 and FGF19) were used for the calculation of DTA compared to the old fecal BA measurements<br>• When patients with cholecystectomy were excluded, **serum C4** showed 40% sensitivity, 85% specificity, 40% PPV and 85% NPV to diagnose BAD. |

| | | | | | |
|---|---|---|---|---|---|
| | | fecal BA) | | standard | • For **FGF19**, exclusion of patients with prior cholecystectomy resulted in 20% sensitivity, 75% specificity, 17% PPV and 79% NPV to diagnose BAD.<br><br>Note: the assay and method of measurement of fecal BA is not described in detail in this paper. The reference is a paper on an assay for measurement of BA in plasma, not feces (Tagliacozzi et al. Quantitative analysis of bile acids in human plasma by liquid chromatography-electrospray tandem mass spectrometry: a simple and rapid one-step method. Clin Chem Lab Med. 2003;41:1633-1641). However, we are aware that this group has successfully adapted a method used with serum samples to measure fecal total and individual BAs (Shin CGH 2013).<br><br>**Applicability concerns:** no concerns (provided that we use the results produced after the exclusion of patients with prior cholecystectomy) |

**Quality of evidence assessment**

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
|---|---|---|---|---|---|---|---|
| 1 DTA study (Vijayvargiya APT 2017) N < 30 | Moderately serious [a] | Not serious | Not serious | **Very** serious [b] | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW |
| Multiple DTA studies that used SeHCAT as reference standard [c] | Very serious [d] | Not serious | Serious | Not serious | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW |

a. Unclear risk of bias for all domains (see QUADAS-2 table)
b. The lower limits of the confidence intervals for sensitivity and specificity cross the threshold for clinically useful diagnostic tests *; small sample sizes (30 patients in the initial analysis; final analysis had even less patients after excluding those with previous cholecystectomy
c. Pattni APT 2013, Johnston AJG 2016; Borup JGH 2015; Sauter DDS 1999; Farkkila CS 1996; Brydon EJGH 1996; Eusufzai Gut 1993
d. Downrated by two levels due to very low quality of evidence on the diagnostic accuracy of SeHCAT (used as reference standard here)

*The paper does not report 95% CIs for the DTA results. We cannot calculate the CIs for the final results (excluding prior cholecystectomy) because the 2x2 raw data are not shown. However, we are able to do so for the initial results (see our table below), and this showed that the 95% CI were very wide (about 20 decimal points lower than the point estimate; see results for sensitivity and specificity highlighted in the red box in the second table below). The 95% CIs for the final results will be slightly wider because the sample size becomes smaller.

**Results as reported in Vijayvargiya APT 2017[8]**

**TABLE 2** Statistical comparison of the diagnostic value of fasting serum C4 and FGF19 as compared to 48 hours faecal bile acids

| Bile acid biomarker | >2619 μmol/48 hours (+bile acid diarrhoea) | <2619 μmol/48 hours (−bile acid diarrhoea) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| C4 | | | | |
| ≥52.5 ng/mL (+bile acid diarrhoea) | 2 | 4 | 33 | NA |
| ≤52.5 ng/mL (−bile acid diarrhoea) | 5 | 19 | NA | 79 |
| Sensitivity (%) | 29 | NA | | |
| Specificity (%) | NA | 83 | | |
| FGF19 | | | | |
| ≤61.7 pg/mL (+bile acid diarrhoea) | 2 | 5 | 29 | NA |
| >61.7 pg/mL (−bile acid diarrhoea) | 5 | 18 | NA | 78 |
| Sensitivity (%) | 29 | NA | | |
| Specificity (%) | NA | 78 | | |

PPV, positive predictive value; NPV, negative predictive value.

Vijayvargiya P, Camilleri M, Carlson P, et al. Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. Aliment Pharmacol Ther 2017;46:581-588.

Our calculation of the 95% CIs for the DTA results for C4:

| | Condition | | |
|---|---|---|---|
| | Absent | Present | Totals |
| Test Positive | 4 | 2 | 6 |
| Test Negative | 19 | 5 | 24 |
| Totals | 23 | 7 | 30 |

Calculate Reset

| | Estimated Value | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Limit | Upper Limit |
| Prevalence | 0.233333 | 0.10635 | 0.427002 |
| Sensitivity | 0.285714 | 0.051124 | 0.697439 |
| Specificity | 0.826087 | 0.604523 | 0.942762 |
| For any particular test result, the probability that it will be: | | | |
| Positive | 0.2 | 0.084048 | 0.391307 |
| Negative | 0.8 | 0.608693 | 0.915952 |
| For any particular positive test result, the probability that it is: | | | |
| True Positive (Positive Predictive Value) | 0.333333 | 0.05999 | 0.758921 |
| False Positive | 0.666667 | 0.241079 | 0.94001 |
| For any particular negative test result, the probability that it is: | | | |
| True Negative (Negative Predictive Value) | 0.791667 | 0.572935 | 0.92064 |
| False Negative | 0.208333 | 0.07936 | 0.427065 |
| likelihood Ratios: [C] = conventional [W] = weighted by prevalence [definitions] | | | |
| Positive [C] | 1.642857 | 0.377172 | 7.155833 |
| Negative [C] | 0.864662 | 0.531593 | 1.406414 |
| Positive [W] | 0.5 | 0.141099 | 1.77181 |
| Negative [W] | 0.263158 | 0.118081 | 0.586478 |

Therefore, there is VERY LOW quality evidence regarding the use of C4 or FGF assays in this population (patients with chronic diarrhea and clinical features suggestive of BAD).

**Other factors** that should influence the strength (or direction) of recommendation:

- **Balance between benefits and harms** when using vs. not using C4/ FGF19 in this situation
- **Patient values and preferences**
- **Cost and recourse utilization**

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Valentin Gut 2016 (**Valentin N, Camilleri M, Altayar O, et al. Biomarkers for bile acid diarrhoea in functional bowel disorder with diarrhoea: a systematic review and meta-analysis. Gut 2016;65:1951-1959): SRMA of the **diagnostic yield** of SeHCAT, C4 and FGF19 in patients with functional bowel disorder with diarrhea (due to lack of gold standard no diagnostic accuracy results could be calculated)

**Prost CMS 2017 (**Prost J-C, Brunner F, Bovet C, et al. A UHPLC–MS/MS method for the quantification of 7α-hydroxy-4-cholesten-3-one to assist in diagnosis of bile acid malabsorption. Clin Mass Spectrometry 2017;3:1-6): description of a new method (ultra high-performance liquid chromatography–tandem mass spectrometry) to measure C4 in human serum. Did not compare with a gold standard.

**Walters NRGH 2014 (**Walters JR. Bile acid diarrhoea and FGF19: new views on diagnosis, pathogenesis and therapy. Nat Rev Gastroenterol Hepatol 2014;11:426-34): Narrative review. No data on diagnostic accuracy of C4 or FGF19, through comparison with a gold standard other than SeHCAT

**Vijayvargiya CGH 2013 (**Vijayvargiya P, Camilleri M, Shin A, et al. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol 2013;11:1232-9): narrative review of methods for diagnosis of bile acid malabsorption in clinical practice, including C4. No DTA results, other than via comparison with SeHCAT.

**Pattni CTG 2012 (**Pattni SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 and 7alpha-hydroxy-4-cholesten-3-one in the diagnosis of patients with possible bile acid diarrhea. Clin Transl Gastroenterol 2012;3:e18) (UK): compared C4 and FGF19 in patients with chronic diarrhea. No gold standard was used.

**Brydon CGH 2011 (**Brydon WG, Culbert P, Kingstone K, et al. An evaluation of the use of serum 7-alpha-hydroxycholestenone as a diagnostic test of bile acid malabsorption causing watery diarrhea. Can J Gastroenterol 2011;25:319-23) (UK): assessed C4 in patients with chronic diarrhea. No gold standard was used. This study was discussed at the face-to-face meeting because it appeared relevant initially, but on close inspection, it was confirmed that the reference standard was not adequately valid. The reference standard was the “final diagnosis [that] was determined based on medical history and investigations, serum levels of 7HCO [C4] and response to cholestyramine”. There is serious incorporation bias (index test being part of the reference standard) and differential verification bias (patients who had negative C4 test were not assessed for BAD with the “reference standard”). Therefore there are no data on false negatives and true negatives, therefore diagnostic accuracy cannot be possibly calculated (it is unclear how the ROC curves shown in the paper were produced)

**Camilleri NGM 2009 (**Camilleri M, Nadeau A, Tremaine WJ, et al. Measurement of serum 7alpha-hydroxy-4-cholesten-3-one (or 7alphaC4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. Neurogastroenterol Motil 2009;21:734-e43) (US): described the development of a serum 7aC4 assay, normal values, and compared results from healthy controls, patients with ileal CD or resection, and patients with IBS-D or IBS-C. No diagnostic accuracy data (no gold standard was used)

**Evidence to Decision framework (diagnostic question)**

**PICO 5: In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a C4 assay to identify possible BAD?**

| | JUDGEMENT |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High |

| | |
|---|---|
| | ○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention |

| | |
|---|---|
| | ○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies |

| | |
|---|---|
| | ○ Don't know |

**Evidence to Decision framework (diagnostic question)**

***PICO A (no recommendation): In patients with chronic diarrhea including IBS-D and functional diarrhea, should we use a FGF-19 assay to identify possible BAD?***

| | **JUDGEMENT** |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or** |

| | |
|---|---|
| OF TEST'S EFFECTS | **burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |

| | |
|---|---|
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 5 & PICO A*


1. Johnston IM, Nolan JD, Pattni SS, et al. Characterizing factors associated with differences in FGF19 blood levels and synthesis in patients with primary bile acid diarrhea. Am J Gastroenterol 2016;111:423-32.
2. Borup C, Syversen C, Bouchelouche P, et al. Diagnosis of bile acid diarrhoea by fasting and postprandial measurements of fibroblast growth factor 19. Eur J Gastroenterol Hepatol 2015;27:1399-402.
3. Pattni SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. Aliment Pharmacol Ther 2013;38:967-76.
4. Sauter GH, Munzing W, von Ritter C, et al. Bile acid malabsorption as a cause of chronic diarrhea: diagnostic value of 7alpha-hydroxy-4-cholesten-3-one in serum. Dig Dis Sci 1999;44:14-9.
5. Farkkila MA, Kairemo KJ, Taavitsainen MJ, et al. Plasma lathosterol as a screening test for bile acid malabsorption due to ileal resection: correlation with 75SeHCAT test and faecal bile acid excretion. Clin Sci (Lond) 1996;90:315-9.
6. Brydon WG, Nyhlin H, Eastwood MA, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one and selenohomocholyltaurine (SeHCAT) whole body retention in the assessment of bile acid induced diarrhoea. Eur J Gastroenterol Hepatol 1996;8:117-23.
7. Eusufzai S, Axelson M, Angelin B, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. Gut 1993;34:698-701.
8. Vijayvargiya P, Camilleri M, Carlson P, et al. Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. Aliment Pharmacol Ther 2017;46:581-588.


## Role of BAST in the diagnosis of BAD

**PICO 6: In patients with suspected BAD, should we initiate empiric BAST over performing SeHCAT to establish a diagnosis of BAD?**

The underlying questions:

A. In patients with suspected BAD, what is the diagnostic accuracy of BAST (compared to a reference standard- which has to be better than SeHCAT) for diagnosing BAD
B. In patients with suspected BAD, does the use of BAST improve clinical outcomes (compared to using one of the tests for BAD (SeHCAT, C4, FGF19))

Four papers have been tagged to this PICO. None provides evidence for underlying question A.

One paper provides evidence for underlying question B:

- **Riemsma HTA 2013[1]:** This is a rigorous UK HTA project, presented in detail under PICO 4. One of the questions that the UK HTA project has assessed is in fact assessed is almost the inverse of our "underlying question B": in patients with IBS-D or Crohn's without resection, does the use of SeHCAT improve clinical outcomes and is it cost-effective compared to using BAST (without SeHCAT)?
- There were no primary studies that assessed such outcomes, however the HTA team conducted a cost-effectiveness analysis: the conclusion was that "considerable decision uncertainty exists and that no firm conclusions can be formulated about which strategy is optimal"

Therefore, there are no comparative or diagnostic primary studies addressing the underlying questions.

Through a CE analysis, there is **VERY LOW** quality of evidence for uncertainty regarding the optimal strategy.

| **Quality of evidence assessment** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
| 1 CE study (Riemsma HTA 2013)[1] | Serious [a] | Serious [b] | Serious [c] | Not serious | None | ⨁⊖⊖⊖ VERY LOW | ⨁⊖⊖⊖ VERY LOW |

a. High risk of bias of the studies that informed the CE analysis (see QUADAS-2 table for PICO 4)
b. Various scenarios in the CE analysis showed widely differing and/or opposite results
c. No direct studies have been identified; the CE analysis can only provide indirect evidence.

**Evidence to Decision framework (diagnostic question)**

**PICO 6: In patients with suspected BAD, should we initiate empiric BAST over performing SeHCAT to establish a diagnosis of BAD?**

| | **JUDGEMENT** |
|---|---|
| TEST ACCURACY | **How accurate is the test?**<br>○ Very inaccurate<br>○ Inaccurate<br>○ Accurate<br>○ Very accurate<br><br>○ Varies<br>○ Don't know |

| | |
|---|---|
| DESIRABLE EFFECTS | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| UNDESIRABLE EFFECTS | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF THE EVIDENCE OF TEST ACCURACY | **What is the overall certainty of the evidence of test accuracy?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS | **What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS | **What is the overall certainty of the evidence of effects of the management that is guided by the test results?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT | **How certain is the link between test results and management decisions?**<br>○ Very low<br>○ Low<br>○ Moderate |

| | |
|---|---|
| | ○ High<br><br>○ No included studies |
| CERTAINTY OF EFFECTS | **What is the overall certainty of the evidence of effects of the test?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| VALUES | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| BALANCE OF EFFECTS | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| RESOURCES REQUIRED | **How large are the resource requirements (costs)?**<br>○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br><br>○ Varies<br>○ Don't know |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | **What is the certainty of the evidence of resource requirements (costs)?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| COST EFFECTIVENESS | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?** |

| | |
|---|---|
| | ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ No included studies |
| ACCEPTABILITY | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| FEASIBILITY | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



*References for PICO 6*

1. Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236.

## Role of BAST in the induction treatment of BAD

**PICO 7: In patients with Type 1 or Type 3 BAD, should we use treatments for remediable causes (e.g. Crohn's, microscopic colitis, SIBO) in addition to treatment for BAD for induction of clinical response?**

| Cohort studies | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Smith 2000[1] (n=56, excluding IBS-D) | Unlikely | No "successful response was whether patients felt there had been a marked improvement in the QoL" - subjective | No "Treatment and F/U information available in 96/140 patients with BAM" | No | • Open label, non-randomized cohort study (Group 1: CD with ileal resection, in remission; Group 2: CD, unoperated, in remission; Group 3: vagotomy and pyloroplasty +/- choly; Group 4: IBS-D. All tested for BAM with 7d SeHCAT (< 10%).<br>• BAM found in a significant proportion of patients n = 75 (97% vs. 54% vs. 58% vs. 33%).<br>• Treated with conventional therapy first n = 56 (prednisolone +/- ASAs, anti-diarrheal) and if no response -> BAS.<br>• A significant proportion of patients responded to conventional treatment (32% vs 55% vs 18% vs 15%) and to BAS (60% vs. 40% vs. 64% vs. 70%). Did not subgroup response based on SeHCAT result (BAM + vs. BAM -) |

## GRADE report

| Quality Assessment | | | | | | | | Summary of Findings | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | No of patients | Effect | |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Efficacy of "Conventional treatment" before BAST | Relative (95% CI) | Absolute (95% CI) |
| **Efficacy (Clinical response felt by patients)** | | | | | | | | | | |
| 1 Observational study (Cohort Study) n = 56 | Serious[a] | Not serious | Serious[b] | Serious[c] | None | ⊕⊖⊖⊖ VERY LOW | ⊕⊖⊖⊖ VERY LOW | 21 / 56 (37.5%) | NA | NA |

a. High risk for selection bias, incomplete follow-up, and outcome detection bias.
b. Not a direct comparison of treatment for "remediable causes" vs. BAST.
c. Small sample size and low event rates.

**Overall QoE for PICO 7:**

There are no RCTs or observational studies that directly compared treatment for remediable causes vs. BAST in patients with Type 1 or Type 3 BAD.

One observational cohort study (Smith 2000[1]) included 75 patients with BAD (diagnosed by 7d SeHCAT) and underlying GI diseases (unoperated and operated Crohn's disease with ileal resection; post-vagotomy and pyloroplasty +/- cholecystectomy). Only 56 patients were treated. Patients were first treated with "conventional treatment" including prednisolone +/- 5 ASA in Crohn's and anti-diarrheals in the others) before BAST was used. A proportion of patients (37.5%) responded to conventional treatment (32%

Crohn's with ileal resection, 55% Crohn's with no resection, 18% post-vagotomy and pyloroplasty). When conventional treatment failed, BAST was successful in achieving symptom control in a significant proportion (55.3% of 56) of patients (60% Crohn's with ileal resection, 40% Crohn's with no resection, 64% post vagotomy and pyloroplasty). However, there was no control group or blinding of interventions, and the outcome was highly subjective with unclear duration of follow-up. The evidence was downgraded for risk of bias, imprecision and indirectness (not a direct comparison between treatments for remediable causes vs. BAST).

Overall, there is **VERY LOW** quality evidence supporting the treatment of remediable causes (e.g. Crohn's disease, vagotomy) prior to the use of BAST in patients with Type I and III BAD. We found no evidence for other conditions (e.g. SIBO). The decisions to treat remediable causes first as opposed to using BAST first may be dependent on the underlying disease.

**Other factors** that should influence the strength (or direction) of recommendation:
**Balance between benefits and harms**: treatment of remediable causes of diarrhea (e.g. Crohn's, SIBO) as opposed to BAST may achieve better control of symptoms and stop disease progression. Depending on the conditions, the treatment for remediable causes may also carry more risks or side effects than BAST treatment (e.g. steroids, immunosuppressives, biologics). The investigations for remediable causes may also be invasive and costly (e.g. colonoscopy).
**Patient values and preferences**: it is uncertain how patients value side effects or risks of medications that are used to treat the remediable causes (e.g. immunosuppressive / biologics for Crohn's disease, antibiotics for SIBO) as opposed to BAST.
**Cost:** depending on the remediable conditions, treatment cost may be higher (or lower) than with BAST. However, this may be offset by downstream savings through more effective control of symptoms and disease?

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Chande CDBSR 2008** (Chande N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis. Cochrane Database Syst Rev 2008:CD003575): SR of 10 RCTs comparing various therapies to either placebo or active comparator in patients with collagenous or microscopic colitis. Most trials did not specify if patients also had BAD. 1 RCT (Munck 2003) excluded patients with BAD.

**Gupta SCC 2015** (Gupta A, Muls AC, Lalji A, et al. Outcomes from treating bile acid malabsorption using a multidisciplinary approach. Support Care Cancer 2015;23:2881-90): retrospective cohort study of patients with BAD (based on 7-day SeCHAT scan < 20%) post-cancer treatment (GI, GU, gyne, heme, etc). 90/143 patients with BAD also had other major GI diagnoses (SIBO, pancreatic insufficiency, lactose intolerance, IBD). Followed algorithm to manage BAD (low fat diet, Colesevelam). Did not report whether patients were treated for their other major GI diagnoses / "remediable causes".

**Vitek IBD 2013** (Vitek L. Bile acid malabsorption in inflammatory bowel disease. Inflamm Bowel Dis 2015;21:476-83): review article on BAM in IBD

**Jahnel DMD 2014** (Jahnel J, Fickert P, Hauer AC, et al. Inflammatory bowel disease alters intestinal bile acid transporter expression. Drug Metab Dispos 2014;42:1423-31): ex vivo study of mucosal biopsy specimens from IBD patients assessed for mRNA expression of intestinal BA transporters, BA detoxifying systems, and nuclear receptors that regulate BA transport and detoxification. BA handling in IBD is altered.

**Baert ACB 2004** (Baert D, Coppens M, Burvenich P, et al. Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. Acta Clin Belg 2004;59:258-62): case series of 20 patients with microscopic colitis treated with cholestyramine. Did not specify if patients also had BAD.

**Nyhlin Gut 1994** (Nyhlin H, Merrick MV, Eastwood MA. Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. Gut 1994;35:90-3): case series of 51 patients with CD who had failed to respond to conventional treatment tested for BAM with SeHCAT. A small subgroup of patients was given cholestyramine with good response (19/22).

**Evidence to Decision framework (management question)**

**PICO 7: In patients with Type 1 or Type 3 BAD, should we use treatments for remediable causes (e.g. Crohn's, microscopic colitis, SIBO) in addition to treatment for BAD for induction of clinical response?**

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |

| | |
|---|---|
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



*References for PICO 7*

1. Smith MJ, Cherian P, Raju GS, et al. Bile acid malabsorption in persistent diarrhoea. J R Coll Physicians Lond 2000;34:448-51.

**PICO 8: In patients with BAD, should we use cholestyramine over no treatment for induction of clinical response?**

**PICO 9: In patients with BAD, should we use cholestyramine over other BASTs as initial therapy for induction of clinical response?**

| RCTs |
|---|

| Study | Adequate sequence generation | Allocation concealment | Blinding | Incomplete outcome data addressed | Free of selective reporting | Free of other bias | Comments |
|---|---|---|---|---|---|---|---|
| Fernandez-Banares 2015[1] | OK | OK | OK | OK | OK | OK | • 26 patients with chronic functional watery diarrhea or IBS-D (**SeHCAT 7-d retention ≤ 20%)** randomized to **cholestyramine 4g bid vs. hydroxypropyl cellulose** x 8 wks.<br>• Clinical remission: < 3 BMs/d x 1 wk before visit (< 1 watery stool/d). **No difference in clinical remission (53.8% vs. 38.4%; P = 0.43; ITT). Higher mean % decrease in watery stool number with cholestyramine** (-92.4+/- 3.5% vs. -75.8+/-7.1%; P = 0.048).<br>• **No difference in adverse events**<br>• Presence of BAM (SeHCAT < 10%) was not a prerequisite for inclusion (77% vs. 54%).<br>• Hydroxypropyl cellulose may be an active drug (bulking effect) – no placebo group for comparison. |

| **SR of Observational Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Wilcox 2014[2] (included studies in Wedlake 2009[3]) | No | No | Unclear | No<br>High risk for performance bias, selection bias etc | • SR of 23 cohort studies (n = 801) of BAM patients treated with cholestyramine.<br>• **Treatment success in 67% of patients with < 5% retention, 73% of patients with < 8 -11.7% retention, 59% of patients with < 15% retention on SeHCAT**<br>• **11% patients found cholestyramine intolerable due to unpalatability or side effects**<br>• Variation in diagnostic testing used for BAM and cut-off value, treatment dose and timing of administration, and definition of clinical response<br>• No quality assessment of included studies |
| Wedlake 2009[3] | No | No<br>Outcomes were not standardized – objective and subjective reports of symptomatic improvement | Unclear | No<br>High risk for performance bias, selection bias etc | • SR of 15 cohort studies (n = 268) patients with I-BAM from IBS-D treated with cholestyramine<br>• **Response in 96% with < 5% retention, 80% with < 10% retention and 70% with < 15% retention on SeCHAT**<br>• No report of adverse effects<br>• Variation in cut-off values for SeHCAT, treatment dose and timing of administration, and definition of response<br>• No quality assessment of included studies |

| **Cohort Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |

| | | | | | |
|---|---|---|---|---|---|
| Lin 2016[4] | No | OK | No<br>54% of BAD patients who were started on BAS were contactable and agreed to f/u | No<br>High risk for selection bias, performance bias, etc | • Retrospective cohort study (107/207 patients diagnosed with Type 1 – 3 BAD with 10% SeHCAT and started on BAS, only 58 were contactable and had f/u data (median f/u was 6.8 yrs)<br>• Only 38% of patients were still on BAS during f/u (cholestyramine / colestipol / colesevelam) with decreased median bowel freq (6 vs 3). Did not provide subgroup data on cholestyramine vs. other BAST.<br>• Assumed 17 patients who stayed on cholestyramine were responders<br>• **Unclear if cholestyramine were used as first line / second line treatments**<br>• 28% used alternative tx (loperamide, diet, octreotide) had decreased median bowel freq (7.5 vs. 3)<br>• **34% d/c tx (poor tolerability of BAS) had no change in stool freq (6 vs. 5)** |
| Orekoya 2015[5] (not tagged) | No | No<br>Subjective report of symptom improvement or improved QoL | No | No<br>High risk for selection bias, outcome detection bias, performance bias etc | • Retrospective cohort study of 92 patients with BAM (SeHCAT < 15%) treated with BAS with f/u data available<br>• Subjective improvement in frequency, consistency, QOL<br>• Cholestyramine as 1st line (49/87, 56%) had successful response<br>• **Only 45% of cholestyramine non-responders were offered colesevelam as 2nd line treatment.** Colesevelam as 1st line (2/5, 40%) had successful response, as 2nd line (7/15, 47%) had successful response<br>• **20% of patients had Intolerance to cholestyramine**<br>• **No patient reported intolerance to colesevelam** |

## GRADE report

| Quality Assessment | | | | | | | | Summary of Findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | No of patients | | Effect | |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Cholestyramine | Comparator | Relative (95% CI) | Absolute (95% CI) |
| **Efficacy (subjective / objective clinical response – highly variable definitions among studies)** | | | | | | | | | | | |
| 1 RCT<br>n = 26 | Not serious | Not serious | Very serious[a] | Serious[b] | None | ⊕⊖⊖⊖<br>VERY LOW | ⊕⊖⊖⊖<br>VERY LOW | 7/13<br>(53.8%) | 5/13<br>(38.5%)<br>Hydroxypropyl cellulose<br>(possible active drug) | RR 1.87<br>(0.39 to 8.89) | 335 more per 1000<br>(from 235 fewer to 1000 more) |
| 1 SR of Observational Studies (Cohort studies)<br>n = 801 | Serious[c] | Not serious | Serious[d] | Serious[e] | Variation in diagnostic testing used for BAD and cut-off values, treatment dose and timing of administration, | ⊕⊖⊖⊖<br>VERY LOW | | 559 / 801<br>(69.8%)<br>range: 63 to 100%<br>Cholestyramine as first-line treatment in all studies | NA | NA | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | and definition of clinical response (subjective / objective) | | | | | | |
| 1 Cohort study n = 87 | Serious[f] | Not serious | Serious[g] | Serious[e] | None | ⊕⊖⊖⊖ VERY LOW | | 49 / 87 (56.3%) Cholestyramine as first-line treatment | NA | NA | NA |
| **Safety (Adverse events)** | | | | | | | | | | | |
| 1 RCT n = 26 | Not serious | Not serious | Very serious[a] | Serious[b] | None | ⊕⊖⊖⊖ VERY LOW | | 2/ 13 (15.4%) drug-related | 2 / 13 (15.4%) drug-related | 1.00 (0.12 to 8.42) | 0 fewer per 1000 (from 135 fewer to 1000 more) |
| 1 SRs of Observational Studies (Cohort studies) n = 801 | Serious[c] | Not serious | Serious[d] | Serious[e] | None | ⊕⊖⊖⊖ VERY LOW | | 11% Range: 0% to 46% Cholestyramine intolerable due to unpalatability or side effects | NA | NA | NA |

a. Not a direct comparison of treatment for cholestyramine vs. other BAST. The comparator was hydroxypropyl cellulose (possible active drug). All patients had SeHCAT 7-d retention ≤ 20%, but not all patients had BAD (SeHCAT 7-d retention < 10%).
b. Small sample size and low event rates. Optimal information size not met.
c. High risk for selection bias, incomplete follow-up, performance bias, and outcome detection bias. Lack of reporting of adverse effects in many studies.
d. Not a direct comparison of treatment for cholestyramine vs. other BAST. All studies used cholestyramine as first-line treatment. A few studies other BAST as second line treatments.
e. Small sample size and low event rates.

**Overall QoE for PICO 8 & 9:**

**Efficacy:**

There are no RCTs comparing cholestyramine vs. other BAST in patients with BAD.

1 RCT included patients with chronic watery diarrhea / IBS-D with 7d SeHCAT < 20% (69% had SeHCAT < 10%), compared cholestyramine vs. hydroxypropyl cellulose which may be an active drug, and showed no difference in clinical remission (a mean of 3 or fewer stools per day during the week before visit with less than 1 watery stool per day). However, there was a significant reduction in daily watery stool number with cholestyramine than with hydroxypropyl cellulose. The evidence was downgraded for imprecision and indirectness (as not a direct comparison for cholestyramine vs. other BAST). Also, not all patients had BAD (SeHCAT 7-day < 10%).

There are 1 SRs of observational cohort studies and 1 cohort study published after the SR. Cholestyramine was used as first line therapy in all studies, other BASTs were offered as second line therapy in a few studies. Among these cohort studies, there was large variation in study designs, patient populations, inclusion / exclusion criteria, diagnostic testing used for BAD and cut-off values, treatment dose and timing of administration, and definition of clinical response. Overall, about 70% of patients responded to cholestyramine as first line treatment (range 63 – 100%). The evidence was downgraded for risk of bias, imprecision, and indirectness (not a direct comparison of treatment for cholestyramine vs. other BAST).

Overall, there is **VERY LOW** quality evidence supporting the use of cholestyramine over no treatment in patients with BAD. There is, however, no direct evidence that cholestyramine is more effective than other BAST.

**Safety:**
1 RCT found that the rate of drug-related adverse events did not differ between cholestyramine and hydroxypropyl cellulose. In 1 SR of observational cohort studies, there was lack of reporting of adverse effects in most studies. **Overall, 11% of patients found cholestyramine intolerable due to unpalatability or side effects. The reported rates of adverse events range from 0 to 46% with no control group for comparison.** It is also uncertain whether these adverse events were drug related. There is no direct evidence that Cholestyramine is associated with more side effects than other BAST.

Adverse events of BAST in non-GI conditions:
In a large RCT of pravastatin vs. pravastatin + **cholestyramine**[6] in patients at increased risk for cardiovascular disease (dyslipidemia and/or additional risk factors), the rates of GI adverse events were significantly higher with the addition of cholestyramine (269/492, 54.7% cholestyramine + pravastatin vs. 172/1049, 16.4% pravastatin), mainly **constipation**. **The compliance rates were also significantly lower with the addition of cholestyramine** (261/492, 53% vs. 812/1049, 77%).

In a Cochrane SR[7] of 6 RCTs (n = 1450 participants) in patients with T2DM and dyslipidemia comparing **colesevelam** vs. placebo (+/- antidiabetic agents), the rates of adverse events were similar in both the colesevelam and placebo groups (RR 1.06, 95% CI 0.97-1.15), and most AEs were minor. Colesevelam was well tolerated. The most common drug-related AEs with colesevelam were gastrointestinal in nature (mainly **constipation,** dyspepsia and nausea) and were mild in nature.

**Other factors** that should influence the strength (or direction) of recommendation:
**Balance between benefits and harms**: In the SR of cohort studies, **the overall response rate was 69.8% (range 63 – 100%)**. The safety of short term use of cholestyramine has also been demonstrated in a RCT and observational studies with minor AEs (bloating

and pain, dyspepsia, nausea and vomiting, flatulence, borborygmi, distension, constipation and diarrhea) and unpalatability. Of the 23 cohort studies in 1 SR (Wilcox 2014[2]), 30% reported treatment failure with first line cholestyramine therapy and did not continue with treatment due to ineffectiveness / side effects / unpalatability (**11% found cholestyramine intolerable due to unpalatability or side effects**, 16% found therapy ineffective, 0.12% was noncompliant with treatment regime, 2% unclear reasons).
**Patient values and preferences**: unknown if patient values more the reduction in diarrhea vs. side effects / unpalatability of Cholestyramine. Also, Cholestyramine administered as granules and powders, less convenient, and less palatable? Need to time with administration of other medications.
**Cost:** lower cost compared to other BASTs

Data from Canadian Drug Expert Committee (CDEC 2012 Common Drug Review):
Cholestyramine - $1.32 to 7.90; 4g to 24g
Colesevelam - $4.40 to $7.70; 2.5g to 4.5g
Colestipol - $0.91 to $5.46; 5 g to 30g
Uncertainty regarding the dose equivalence of colesevelam vs. cholestyramine and colestipol.

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

**Borghede EJIM 2011 (**Borghede MK, Schlutter JM, Agnholt JS, et al. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med 2011;22:e137-40): Retrospective cohort study included in the SR by Wilcox 2014.

**Fernandez-Banares AJG 2007** (Fernandez-Banares F, Esteve M, Salas A, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol 2007;102:2520-8): Prospective cohort study included in the SR by Wilcox 2014.

**Westergaard CTOG 2007** (Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33): Review article.

**Wildt SJG 2003** (Wildt S, Norby Rasmussen S, Lysgard Madsen J, et al. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. Scand J Gastroenterol 2003;38:826-30): Retrospective cohort study included in the SR by Wilcox 2014.

**Sinha APT 1998** (Sinha L, Liston R, Testa HJ, et al. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. Aliment Pharmacol Ther 1998;12:839-44): Prospective cohort study included in the SR by Wilcox 2014.

**Niaz JRCPL 1997** (Niaz SK, Sandrasegaran K, Renny FH, et al. Postinfective diarrhoea and bile acid malabsorption. J R Coll Physicians Lond 1997;31:53-6): Retrospective cohort study included in the SR by Wilcox 2014.

**Rudberg AR 1996** (Rudberg U, Nylander B. Radiological bile acid absorption test 75SeHCAT in patients with diarrhoea of unknown cause. Acta Radiol 1996;37:672-5): Prospective cohort study included in the SR by Wilcox 2014.

**Luman EJGH 1995** (Luman W, Williams AJ, Merrick MV, et al. Idiopathic bile acid malabsorption: long-term outcome. Eur J Gastroenterol Hepatol 1995;7:641-5): Case series of 23 patients with IBAM who all responded to bile acid chelator (cholestyramine / aluminum hydroxide) follow-up data.

**Eusufzai Gut 1993** (Eusufzai S, Axelson M, Angelin B, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. Gut 1993;34:698-701): Prospective cohort study included in the SR by Wilcox 2014.

**Ford PM 1992** (Ford GA, Preece JD, Davies IH, et al. Use of the SeHCAT test in the investigation of diarrhoea. Postgrad Med J 1992;68:272-6): Retrospective cohort study included in the SR by Wilcox 2014.

**Galatola EJGH 1992** (Galatola G, Ferraris R, Pellerito R, et al. The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine: An uncontrolled open multicentre study. Eur J Gastroenterol Hepatol 1992;4:533-7): Prospective cohort study included in the SR by Wilcox 2014.

## Evidence to Decision framework (management question)

## PICO 8: In patients with BAD, should we use cholestyramine over no treatment for induction of clinical response?

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |

| | |
|---|---|
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



**Evidence to Decision framework (management question)**

**PICO 9: In patients with BAD, should we use cholestyramine over other BASTs as initial therapy for induction of clinical response?**

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large |

| | |
|---|---|
| | ○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No |

| | |
|---|---|
| | ○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 8 & 9*


1. Fernandez-Banares F, Rosinach M, Piqueras M, et al. Randomised clinical trial: colestyramine vs. hydroxypropyl cellulose in patients with functional chronic watery diarrhoea. Aliment Pharmacol Ther 2015;41:1132-40.
2. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther 2014;39:923-39.
3. Wedlake L, A'Hern R, Russell D, et al. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2009;30:707-17.
4. Lin S, Sanders DS, Gleeson JT, et al. Long-term outcomes in patients diagnosed with bile-acid diarrhoea. Eur J Gastroenterol Hepatol 2016;28:240-5.
5. Orekoya O, McLaughlin J, Leitao E, et al. Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clin Med (Lond) 2015;15:252-7.
6. Eriksson M, Hadell K, Holme I, et al. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med 1998;243:373-80.
7. Ooi CP, Loke SC. Colesevelam for type 2 diabetes mellitus. Cochrane Database Syst Rev 2012;12:CD009361.


**PICO 10: In patients with BAD who are unable to tolerate cholestyramine, should an alternate BAST be used for induction of clinical response?**

| **RCTs** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Study | Adequate sequence generation | Allocation concealment | Blinding | Incomplete outcome data addressed | Free of selective reporting | Free of other bias | Comments |
| Beigel 2014[1] | OK | OK | OK | OK | OK | Inflammatory disease cannot be completely | • 26 patients with **CD in remission with BAM** (cholestenone > 50ng/mL) randomized to **COV** 3 x 2 tablets 625mg (3750mg) vs. placebo x 4 wks |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | excluded as remission was based on CRP ≤ 1 and CDAI ≤ 150. | • Primary endpt (proportion of pts with > 30% reduction of liquid stools /d) 69.7% vs. 27.3% (ns ITT, 0.036 PP).<br>• Secondary endpts: **significant reduction of liquid stools and improvement of stool consistency with COV**<br>• **No difference in mild AEs** (constipation, bloating and nausea) |
| Odunsi-Shiyanbade 2010[2] | OK | Unclear | OK | OK | OK | OK | • 24 patients with IBS-D randomized to COV 1.875g bid vs. placebo x 12-14 d. **Only 4/24 patients had BAM by serum C4.** Excluded<br>• COV had no effect on # of BM/d, but trend to improve stool consistency (P = 0.12) and ease stool passage (P= 0.048). Did not subgroup data based on BAM + /-<br>• **No difference in mild AEs** (headache, nausea, flatulence, green colored stools, cramps) |

| **SR of Observational Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Wilcox 2014[3] | No | No | No | No<br>High risk for performance bias, selection bias, recall bias, ascertainment bias, co-interventions etc | • SR of 1 cohort study (Ung 2000) of 12 patients with BAM treated with cholestyraine as 1st line, and due to poor taste, **one patient** switched to **colestipol** with improvement in diarrhea < 1 week that was maintained after 2 mos<br>• SR of 1 RCT and **4 cohort studies (n = 90) treated with Colesevelam.**<br>  • RCT (Odunsi-Shiyanbade 2010[2]) of COV vs. placebo (n = 24): COV -> greater ease of stool passage (p=0.048) and firmer stool consistency (ns).<br>  • 3 retrospective cohort studies used **COV as 2nd line**: 36/63, **57% found tx effective.**<br>  • 1 retrospective cohort study (Wedlake 2009[4]) on cancer patients with BAM (SeHCAT < 10%), COV as 1st line: 13/15, 87% effective; **COV as 2nd line:** 17/30, **57% effective.**<br>  • 19% found tx ineffective, **9% found tx intolerable due to unpalatability or side effects (bloating, constipation, flatulence, N/V)**<br>• Variation in diagnostic testing used for BAM and cut-off value, treatment dose and timing of administration, and definition of clinical response<br>• No quality assessment of included studies |

| **Cohort Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Camilleri 2015[5] | Unclear | OK | OK | No<br>High risk for selection bias, performance bias, outcome detection bias etc | • Prospective cohort study of 12 patients with IBS-D and "evidence of increased BA synthesis / fecal excretion" treated with colesevelam 1875 mg bid x 10 d<br>• Colesevelam resulted in significant decrease in the average score of stool consistency from 4.8+/-0.3 to 4.4 +/-0.3 (Bristol Stool Form) and numerical reductions in # of BMs (ns). **No dichotomous outcome**<br>• No report of side effects |
| Lin 2016[6] | No | OK | No<br>54% of BAD | No<br>High risk for | • Retrospective cohort study (107/207 patients diagnosed with Type 1 – 3 BAD with 10% SeHCAT and started on BAS, only 58 were contactable and had f/u data (median f/u was 6.8 yrs) |

| | | | | | |
|---|---|---|---|---|---|
| | | | patients who were started on BAS were contactable and agreed to f/u | selection bias, performance bias, etc | • Only 38% of patients were still on BAS during f/u (17 cholestyramine / **4 colestipol / 1 colesevelam**) with decreased median bowel freq (6 vs 3). **Did not provide subgroup data on cholestyramine vs. other BAST**<br>• 28% used alternative tx (loperamide, diet, octreotide) had decreased median bowel freq (7.5 vs. 3)<br>• 34% d/c tx (poor tolerability) had no change in stool freq (6 vs. 5) |
| Orekoya 2015[7] | No | No<br>Subjective report of symptom improvement or improved QoL | No | No<br>High risk for selection bias, outcome detection bias, performance bias etc | • Retrospective cohort study of 92 patients with BAM (SeHCAT < 15%) treated with BAS with f/u data available<br>• Subjective improvement in frequency, consistency, QOL<br>• Cholestyramine as 1st line (49/87, 56%) had successful response<br>• **Only 45% of cholestyramine non-responders were offered colesevelam as 2nd line treatment.** Colesevelam as 1st line (2/5, 40%) had successful response, as 2nd line (7/15, 47%) had successful response<br>• **No patient reported colesevelam intolerance.** |

## GRADE report

| Quality Assessment | | | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | No of patients | | Effect | |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Alternative BAST | Comparator | Relative (95% CI) | Absolute (95% CI) |
| **Efficacy (subjective / objective clinical response – highly variable definitions among studies)** | | | | | | | | | | | |
| 1 RCT<br>n = 26 | Not serious | Not serious | Serious[a] | Serious[b] | Diagnostic tests used for BAD (cholestenone > 50ng/mL) | ⊕⊕⊖⊖<br>LOW | ⊕⊕⊖⊖<br>LOW | 10/15 (66.7%) Colesevelam as first-line treatment | 3/11 (27.3%) Placebo | RR 6.67 (1.24 to 35.71) | 1000 more per 1000 (from 65 more to 1000 more) |
| 1 SR of Observational Studies (4 Cohort studies)<br>n = 63 | Serious[c] | Not serious | Not serious | Serious[d] | Variation in diagnostic testing used for BAD and cut-off values, treatment dose and timing of administration, and definition of clinical response | ⊕⊖⊖⊖<br>VERY LOW | | 36 / 63 (57%) range 42 – 100% Colesevelam as second-line treatment after failure of Cholestyramine | NA | NA | NA |
| 1 Cohort Study<br>n = 15 | Serious[c] | Not serious | Not serious | Serious[d] | Variation in diagnostic testing used | ⊕⊖⊖⊖<br>VERY LOW | | 7/15 (46.7%) Colesevelam as | NA | NA | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | for BAD and cut-off values, treatment dose and timing of administration, and definition of clinical response | | | second-line treatment after failure of Cholestyramine | | | |
| **Safety (Adverse events)** | | | | | | | | | | | |
| 1 RCT (n = 26) | Not serious | Not serious | Serious[a] | Serious[b] | None | ⊕⊕⊖⊖ LOW | | 6 / 15 (40.0%) | 4 / 11 (36.4%) | RR 1.17 (0.34 to 5.81) | 62 more per 1000 (from 280 fewer to 1000 more) |
| 1 SR of Observational Studies (Cohort) n = 90 | Serious[c] | Not serious | Not serious | Serious[d] | None | ⊕⊖⊖⊖ VERY LOW | | 8/90 (9%) Colesevelam intolerable due to unpalatability or side effects | NA | NA | NA |

a. Alternative BAST was used as first line therapy, and not in patients who were unable to tolerate cholestyramine. 1 RCT (Beigel 2014) may have included patients with active Crohn's disease.
b. Small sample size and low event rates. Optimal information size not met.
c. High risk for selection bias, incomplete follow-up, recall bias, and outcome detection bias.
d. Small sample size and low event rates.

**Overall QoE for PICO 10:**

**Efficacy:**

There are no RCTs comparing alternative BASTS to other treatments / placebo in patients with BAD who are unable to tolerate cholestyramine.

1 RCT (Beigel 2014[1]) assessed Colesevelam as first line treatment vs. placebo in patients with BAD (cholestenone > 50ng/mL) and Crohn's disease in remission, and found colesevelam to be more effective than placebo. The study may have included patients with active Crohn's as remission was defined as CDAI ≤ 150 points and CRP ≤ 1mg/dL. Clinical response was defined as proportion of pts with > 30% reduction of liquid stools /d (RR 6.67, 95% CI 1.24 to 35.71). 1 RCT (Odunsi-Shiyanbade 2010[2]) was excluded as the majority of patients 20/24 (83%) did not have BAD (Serum 7αC4 < 61ng/mL), and the results were not reported based on BAD +/-. The evidence was downgraded for imprecision and indirectness (alternative BAST was used as first line therapy).

There is 1 SR of 4 observational cohort studies and 1 cohort study published after the SR. colesevelam was used as second-line therapy after failing cholestyramine. Among these cohort studies, there was large variation in study designs, patient populations, inclusion / exclusion criteria, diagnostic testing used for BAD and cut-off values, treatment dose and timing of administration, and definition of clinical response. Overall, about 57% of patients responded to colesevelam as second line treatment (range 42 – 100%). However, with no control group, we cannot exclude a higher likelihood of placebo response, as there may be great expectation associated with second line colesevelam. The evidence was downgraded for risk of bias and imprecision.

Overall, there is **LOW** quality evidence supporting the use of **colesevelam** over no treatment in patients with BAD who are unable to tolerate Cholestyramine.

For **colestipol**, there is very limited evidence of its use as second-line treatment after failing cholestyramine. 1 cohort study (Ung 2000) of 12 patients with BAD and collageneous colitis treated with cholestyramine as 1st line, and due to poor taste, 1 patient switched to colestipol with improvement in diarrhea < 1 week that was maintained after 2 months.

**Safety:**
1 RCT found that the rate of drug-related adverse events did not differ between colesevelam vs. placebo. All drug-related adverse events were mild (constipation). In 1 SR of observational cohort studies (Wilcox 2014[3]), 19% patients found colesevelam ineffective; **9% found therapy intolerable due to unpalatability or side effects**; 3% felt the treatment regime was too difficult to follow. Side effects included bloating, constipation, flatulence, nausea and vomiting. There is no direct evidence that colesevelam is associated with more/ less side effects than cholestyramine or other BAST.

Adverse events of BAST in non-GI conditions:
In a large RCT of pravastatin vs. pravastatin + **cholestyramine**[8] in patients at increased risk for cardiovascular disease (dyslipidemia and/or additional risk factors), the rates of GI adverse events were significantly higher with the addition of cholestyramine (269/492, 54.7% cholestyramine + pravastatin vs. 172/1049, 16.4% pravastatin), mainly **constipation**. **The compliance rates were also significantly lower with the addition of cholestyramine** (261/492, 53% vs. 812/1049, 77%).

In a Cochrane SR[9] of 6 RCTs (n = 1450 participants) in patients with T2DM and dyslipidemia comparing **colesevelam** vs. placebo (+/- antidiabetic agents), the rates of adverse events were similar in both the colesevelam and placebo groups (RR 1.06, 95% CI 0.97-1.15), and most AEs were minor. Colesevelam was well tolerated. The most common drug-related AEs with colesevelam were gastrointestinal in nature (mainly **constipation,** dyspepsia and nausea) and were mild in nature.

**Other factors** that should influence the strength (or direction) of recommendation:
**Balance between benefits and risks**: In the SR of cohort studies, **the overall response rate of colesevelam as a second-line treatment was 57% (range 42 – 100%)**. The safety of short term use of alternative BASTS (Colesevelam) has been demonstrated in RCTs with minor AEs (bloating, nausea, and constipation). Of the 4 cohort studies in 1 SR, 9% found colesevelam intolerable due to unpalatability or side effects, 19% found therapy ineffective. No significant AEs was found in RCTs.
**Patient values and preferences**: Administered more easily (tablet rather than granules and powders) and more convenient than cholestyramine. Apparent lack of effect on the bioavailability of co-administered drugs based on pharmacokinetics study (see PICO 17). May increase compliance, particularly in patients who require the use of multiple medications.
**Cost:** higher cost with colesevelam compared to cholestyramine (7x). Lower cost with Colestipol compared to cholestyramine.

Data from Canadian Drug Expert Committee (CDEC 2012 Common Drug Review):
Cholestyramine - $1.32 to 7.90; 4g to 24g
Colesevelam - $4.40 to $7.70; 2.5g to 4.5g (most studies used close to 4g dose)
Colestipol - $0.91 to $5.46; 5 g to 30g
Uncertainty regarding the dose equivalence of colesevelam vs. cholestyramine and colestipol.

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Wedlake Clin Ther 2009 (**Wedlake L, Thomas K, Lalji A, et al. Effectiveness and tolerability of colesevelam hydrochloride for bile-acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire. Clin Ther 2009;31:2549-58): Retrospective cohort study included in the SR by Wilcox 2014.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Camilleri Gut Liver 2015** (Camilleri M. Bile acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver 2015;9:332-9). Review article.

**Camilleri ERGH 2014** (Camilleri M. Advances in understanding of bile acid diarrhea. Expert Rev Gastroenterol Hepatol 2014;8:49-61): Review article.

**Arnold AJSP 2014** (Arnold MA, Swanson BJ, Crowder CD, et al. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. Am J Surg Pathol 2014;38:1530-7): BAS resins (morphologic description of colesevelam, colestipol and cholestyramine) in biopsy specimens.

**Tziomalos CPD 2013** (Tziomalos K, Karagiannis A, Mikhailidis DP, et al. Colesevelam: a new and improved bile acid sequestrant? Curr Pharm Des 2013;19:3115-23): Review article on Colesevelam in cardiovascular prevention strategies.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

**Evidence to Decision framework (management question)**

**PICO 10: In patients with BAD who are unable to tolerate cholestyramine, should an alternate BAST be used for induction of clinical response?**

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies |

| | |
|---|---|
| | ○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 10*


1. Beigel F, Teich N, Howaldt S, et al. Colesevelam for the treatment of bile acid malabsorption-associated diarrhea in patients with Crohn's disease: a randomized, double-blind, placebo-controlled study. J Crohns Colitis 2014;8:1471-9.
2. Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, et al. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Clin Gastroenterol Hepatol 2010;8:159-65.
3. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther 2014;39:923-39.
4. Wedlake L, Thomas K, Lalji A, et al. Effectiveness and tolerability of colesevelam hydrochloride for bile-acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire. Clin Ther 2009;31:2549-58.
5. Camilleri M, Acosta A, Busciglio I, et al. Effect of colesevelam on faecal bile acids and bowel functions in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2015;41:438-48.
6. Lin S, Sanders DS, Gleeson JT, et al. Long-term outcomes in patients diagnosed with bile-acid diarrhoea. Eur J Gastroenterol Hepatol 2016;28:240-5.
7. Orekoya O, McLaughlin J, Leitao E, et al. Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clin Med (Lond) 2015;15:252-7.
8. Eriksson M, Hadell K, Holme I, et al. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med 1998;243:373-80.
9. Ooi CP, Loke SC. Colesevelam for type 2 diabetes mellitus. Cochrane Database Syst Rev 2012;12:CD009361.

**PICO 11: In patients with BAD receiving empiric BAST, should gradual daily dose titration vs. no titration be used to minimize side effects?**

| SR of Observational Studies | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Wilcox 2014[1] | No | No | Unclear | No<br>High risk for performance bias, selection bias etc | • SR of 23 cohort studies (n = 801) of BAM patients treated with cholestyramine, 1 RCT and 4 cohort studies of colesevelam, 1 cohort study (1 patient) switched to colestipol after failing cholestyramine.<br>• Treatment dose and timing of administration not standardized and were highly variable among studies.<br>• **Cholestyramine: generally started at low dose 2-4 g/d and titrated to response (no mention of dose titration in some studies)**<br>• **Colesevelam / colestipol: no mention of dose titration**<br>• **11% patients found cholestyramine intolerable due to unpalatability or side effects**<br>• **9% patients found colesevelam intolerable due to unpalatability or side effects** |

| Cohort Studies | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Orekoya 2015[2] | No | No<br>Subjective report of symptom improvement or improved QoL | No | No<br>High risk for selection bias, outcome detection bias, performance bias etc | • Retrospective cohort study of 92 patients with BAM (SeHCAT < 15%) treated with BAS with f/u data available<br>• Subjective improvement in frequency, consistency, QOL<br>• Cholestyramine: practice varied, but generally prescribed low dose (2-4 g/d) and titrated dose based on response (max 4-24g/d)<br>• **Cholestyramine as 1st line (49/87, 56%) had successful response. 20% of patients had Intolerance to cholestyramine**<br>• **Only 45% of cholestyramine non-responders were offered colesevelam as 2nd line treatment.** Colesevelam as 1st line (2/5, 40%) had successful response, as 2nd line (7/15, 47%) had successful response. **No patient reported colesevelam intolerance.** |

## GRADE report

| Quality Assessment |
|---|

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
|---|---|---|---|---|---|---|---|
| **Safety** | | | | | | | ⊕⊖⊖⊖ VERY LOW |
| 1 SR of Observational Studies (Cohort) n = 1241 | Serious[a] | Not serious | Not serious | Serious[b] | Variation in diagnostic testing used for BAD and cut-off values, treatment dose and timing of administration, definition of clinical response, and assessment of adverse events | ⊕⊖⊖⊖ VERY LOW | |
| 1 Cohort Study n = 92 | Serious[a] | Not serious | Not serious | Serious[b] | Dose and timing of administration, as well as practice of titration highly variable (not standardized) | ⊕⊖⊖⊖ VERY LOW | |

a. High risk for selection bias, incomplete follow-up, performance bias, and outcome detection bias.
b. Small sample size and low event rates.

**Overall QoE for PICO 11:**
There are no RCTs or observational studies that have directly compared dose titration vs. no dose titration of BAST in patients with BAD.

In general, most cohort studies reported gradual dose titration for cholestyramine to clinical response. There was, however, no mention of dose titration of colesevelam or colestipol. For any medication that alleviates symptoms but does not alter the natural history of the disease, it is intuitive to gradually titrate the medication to minimize symptoms / side effects. This is particularly relevant with BAST due to the high frequency of side effects and intolerance. It is conceivable that gradual dose titration may reduce the risks of side effects, increase compliance, and potentially less costly. Does the panel believe that in patients with BAD, gradual dose titration to minimize symptoms represents good practice? If so, this statement can be considered a **good practice statement.**

This statement can be considered an ungraded **good practice statement**. The unstated alternative of no dose titration when starting patients on BAST be absurd given the side effects and poor tolerability of BAST.

Checklist for good practice statements:
1. Is the statement clear and actionable?
2. Is the message really necessary in regard to actual health care practice?

3. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences? Need to consider benefits are large and harm very small; certainty of benefits and harms are great; the values and preferences are clear; the intervention is cost saving; and the intervention is clearly acceptable, feasible, and promotes equity.
4. Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy?
5. Is there a well-documented clear and explicit rationale connecting the indirect evidence?

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Camilleri APT 2015** (Camilleri M, Acosta A, Busciglio I, et al. Effect of colesevelam on faecal bile acids and bowel functions in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2015;41:438-48): Cohort study of colesevelam in 12 patients with IBS-D. No titration of dose. All took 1875mg BID x 10 days.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Camilleri ERGH 2014** (Camilleri M. Advances in understanding of bile acid diarrhea. Expert Rev Gastroenterol Hepatol 2014;8:49-61): Review article.

**Fernandez-Banares AJG 2007** (Fernandez-Banares F, Esteve M, Salas A, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol 2007;102:2520-8): Prospective cohort study included in the SR by Wilcox 2014. Starting Cholestyramine 8g/d, titrated to clinical response (range 2 – 12 g/d).

**Wildt SJG 2003** (Wildt S, Norby Rasmussen S, Lysgard Madsen J, et al. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. Scand J Gastroenterol 2003;38:826-30): Retrospective cohort study included in the SR by Wilcox 2014.

**Rossel SJG 1999** (Rossel P, Sortsoe Jensen H, Qvist P, et al. Prognosis of adult-onset idiopathic bile acid malabsorption. Scand J Gastroenterol 1999;34:587-90): Retrospective cohort study of patients with IBAM treated with cholestyramine. No mention of how the drug was dosed / titrated.

**Ford PM 1992** (Ford GA, Preece JD, Davies IH, et al. Use of the SeHCAT test in the investigation of diarrhoea. Postgrad Med J 1992;68:272-6): Retrospective cohort study included in the SR by Wilcox 2014.

**Sciarretta AJG 1992** (Sciarretta G, Furno A, Mazzoni M, et al. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. Am J Gastroenterol 1992;87:1852-4): Prospective cohort study included in the SR by Wilcox 2014.

**Galatola EJGH 1992** (Galatola G, Ferraris R, Pellerito R, et al. The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine: An uncontrolled open multicentre study. Eur J Gastroenterol Hepatol 1992;4:533-7): Prospective cohort study included in the SR by Wilcox 2014.

**Williams Gut 1991** (Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut 1991;32:1004-6): Prospective cohort study included in the SR by Wilcox 2014.

**Evidence to Decision framework (management question)**

**PICO 11: In patients with BAD receiving empiric BAST, should gradual daily dose titration vs. no titration be used to minimize patient-reported symptoms (interpreted as side effects)?**

DESIGNATED A GOOD PRACTICE STATEMENT

*References for PICO 11*

1. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther 2014;39:923-39.
2. Orekoya O, McLaughlin J, Leitao E, et al. Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clin Med (Lond) 2015;15:252-7.

**PICO 12: In patients with Crohn's disease with extensive ileal involvement or resection, should we use BAST vs. no BAST?**

| **Cohort Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Hofmann 1972[1] (Not tagged) | No | OK | OK | High risk for selection bias | • Experimental design on patients with ileal resection<br>• 4 randomized periods: LCT, LCT + cholestyramine, MCT, MCT + cholestyramine<br>• Measured fecal fat, total fecal BA excretion, stearrohea, diarrhea, fecal lyte<br>• **3 patients severe steatorrhea** (**ileal resection >100cm, steatorrhea > 20g/d**): cholestyramine leads to small decrease in diarrhea with no symptomatic benefit, but increase in steatorrhea causing significant caloric loss<br>• **6 patients Mild steatorrhea (ileal resection < 100cm, steatorrhea < 20g/d)**: Cholestyramine significantly decreased diarrhea of symptomatic benefit, but increase in steatorrhea with no caloric significance. |
| Poley 1976[2] (Not tagged) (same patients as Hofmann 1972) | No | ok | ok | High risk for selection bias | • Fat digestion after two sequential test meals +/- cholestyramine in 8 patients with ileal resection (5 with "small" resection, BAD and steatorrhea < 20g/d; 3 with "large" resection, fatty acid diarrhea and steatorrhea > 20g/d) and 4 controls<br>• Cholestyramine decreased the aqueous phase bile acid concentrations in all patients. The degree of fat maldigestion in patients with small resections (and normal control) became similar to that in patients with large resections. |

## GRADE report

| **Quality Assessment** |
|---|

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
|---|---|---|---|---|---|---|---|
| **Safety** | | | | | | | ⊕⊖⊖⊖ VERY LOW |
| 1 Cohort Study n = 3 with ileal resection > 100cm, steatorrhea > 20g/d | Serious[a] | Not serious | Not serious | Very serious[b] | Patients were divided into 2 groups < 100cm vs. > 100cm ileal resection. | ⊕⊖⊖⊖ VERY LOW | |

a. High risk for selection bias.
b. Small sample size.

**Overall QoE for PICO 12:**
Based on 1 experimental cohort study (**3 patients with ileal resection > 100cm**), there is **VERY LOW** quality evidence against the use of BAST in patients with Crohn's disease with extensive ileal disease or resection (**but not > 50cm**). In these 3 patients, cholestyramine leads to small decrease in diarrhea with no symptomatic benefit, but increase in steatorrhea causing significant caloric loss.

**Other factors** that should influence the strength (or direction) of recommendation:
**Balance between benefits and risks**: There is no long term study assessing the safety of cholestyramine especially in patients with extensive ileal resection. Based on the small cohort study with increase in steatorrhea in patients with extensive ileal resection > 100cm, the potential long term effects of this medication could be very harmful.
**Patient values and preferences**: ?
**Cost: ?**

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Ford PM 1992** (Ford GA, Preece JD, Davies IH, et al. Use of the SeHCAT test in the investigation of diarrhoea. Postgrad Med J 1992;68:272-6): Small cohort study of 28 patients with Type 1 BAD (7 ileal resection). SeHCAT was < 10% in all patients with ileal resection. All patients were treated with cholestyramine. They all responded to cholestyramine. Did not specify how much ileum was resected.

**Nyhlin Gut 1994** (Nyhlin H, Merrick MV, Eastwood MA. Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. Gut 1994;35:90-3): Small cohort study of 53 patients with Crohn's disease and tested for SeHCAT. Some patients were treated with cholestyramine with relief in symptoms. Did not specify how much ileum was resected.

**Westergaard CTOG 2007** (Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33): Review article.

**Worobetz CJGH 1993** (Worobetz L, Wilkinson A, Chmielowiec C, et al. Evaluation of SeHCAT test in determining ileal involvement and dysfunction in Crohn's disease. Can J Gastroenterol Hepatol 1993;7:597-601): Small cohort study of 22 patients with Crohn's limited to small bowel underwent SeHCAT testing (14 had ileal resection). No correlation between clinical response to cholestyramine vs. length of TI disease / resection (35.3+/-5.4 cm in responder vs. 46.4cm +/-6.1 cm in non-responders) – Most patients had ileal disease / resection < 50cm.

**Valdes Olmos EJGH 1993** (Valdés Olmos RA, Taal BG, Hoefnagel CA, et al. 75SeHCAT in the assessment of improved bile acid absorption in patients with ileal damage by delaying bowel motility with loperamide. Eur J Gastroenterol Hepatol 1993;5:941-946): Small cohort study (13/19 patients who had ileocolonic resection, all had cancer) ha improvement / normalization of SeHCAT retention with loperamide

## Evidence to Decision framework (management question)

## PICO 12: In patients with Crohn's disease with extensive ileal involvement or resection, should we use BAST vs. no BAST?

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability |

| | |
|---|---|
| | ○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



*References for PICO 12*

1. Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. Gastroenterology 1972;62:918-34.
2. Poley JR, Hofmann AF. Role of fat maldigestion in pathogenesis of steatorrhea in ileal resection. Fat digestion after two sequential test meals with and without cholestyramine. Gastroenterology 1976;71:38-44.

## Role of BAST in the maintenance treatment of BAD

### PICO 13: In patients with BAD who respond to BAST, should intermittent, on demand dosing be tried?

| Cohort Studies | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Sciarretta 1992[1] | No | No | OK | No<br>High risk for performance / co-intervention bias, selection bias, etc | • Prospective cohort study assessing the prevalence of bile acid malabsorption (7d SeHCAT<8%) patients with diarrhea post choly (25/26)<br>• Cholestyramine was effective 23/26 patients, recurrent diarrhea in 9/23 patients when tx was withdrawn. 14 patients **(61%)** remained normal and only took the drug occasionally **(no demand)** in the event of slight diarrhea. |
| Galatola 1992[2] | | No | No | No<br>High risk for performance / co-intervention bias, selection bias, etc | • Prospective cohort study assessing the prevalence of bile acid malabsorption (7d SeHCAT < 11.7%) in patients with IBS-D (56/98, 57%)<br>• Cholestyramine was effective in 39/42 patients, recurrent diarrhea in 33/35 (94%) patients when tx was withdrawn. 2 (6%) patients did not have recurrent diarrhea and stopped tx. |

### GRADE report

| Quality Assessment | | | | | | | |
|---|---|---|---|---|---|---|---|
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence |
| **Safety** | | | | | | | ⊕⊖⊖⊖<br>VERY LOW |
| 2 Cohort Studies | Serious[a] | Not serious | Not serious | Serious[b] | None | ⊕⊖⊖⊖<br>VERY LOW | |

a. High risk for selection bias, performance bias, and outcome detection bias.
b. Small sample size.

### Overall QoE for PICO 13:

There are no RCTs or observational studies that have directly compared regular daily dosing vs. intermittent, on-demand therapy in patients with BAD who respond to BAST.

There are 2 small cohort studies suggesting that in some patients with BAD, their symptoms could be controlled with on-demand therapy or no therapy at all. In a cohort study (Sciarretta 1992[1]) of patients with BAD post cholecystectomy, recurrent diarrhea occurred only in 9/23 (39%) of patients when cholestyramine was withdrawn, and 61% remained normal and took the drug on demand in the event of slight diarrhea. In another small cohort study (Galatola 1992[2]) of patients with BAD and IBS-D, recurrent diarrhea occurred in 33/35 (94%) of patients when Cholestyramine was withdrawn, only 6% of patients did not have recurrent diarrhea and stopped treatment. In those with recurrent diarrhea, they were advised to continue treatment at the dose that controlled their symptoms (unclear if regular daily vs. on demand).

The dose or frequency of BAST required to control symptoms may be dependent on severity of symptoms, underlying cause of BAD, any other associated GI conditions, concurrent illness (e.g. gastroenteritis, c. diff infection), or concurrent medication use (eg. medications that cause constipation may reduce the use of cholestyramine and medications that cause diarrhea may increase the use of cholestyramine).

Overall, there is **VERY LOW** quality of evidence suggesting that some patients with BAD will need regular daily dosing, while some may be able to come off therapy or use on-demand therapy to minimize symptoms.

**Other factors** that should influence the strength (or direction) of recommendation:

**Balance between benefits and risks**: Side effects, uncertainty of long term harms with BAST - malabsorption of fat / fat soluble vitamins, and unpalatability
**Patient values and preferences**: ? compliance. Patients may use on demand after achieving an initial response to minimize side effects.
**Cost:** on-demand therapy is less costly than regular use

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Torbicki TDTMV 2015** (Torbicki E, Oh J, Mishra S, et al. Interventions for post-infectious irritable bowel syndrome: a systematic review of treatment efficacy. Trop Dis Travel Med Vaccines 2015;1:1): 2 retrospective cohort studies on cholestyramine were included in this SR. Patients took different doses of cholestyramine and for different lengths of time. No comparison between daily vs. on demand therapy.

**Riemsma HTA 2013** (Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236): Systematic review and cost effectiveness analysis of SeHCAT for bile acid malabsorption. Irrelevant to the PICO.

**Wedlake 2009 (**Wedlake L, Thomas K, Lalji A, et al. Effectiveness and tolerability of colesevelam hydrochloride for bile-acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire. Clin Ther 2009;31:2549-58): Retrospective cohort study of colesevelam in patients with bile acid malabsorption and cancer. Did not assess daily vs. on demand therapy.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Camilleri Gut Liver 2015** (Camilleri M. Bile acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver 2015;9:332-9): Review article.

**Arnold AJSP 2014** (Arnold MA, Swanson BJ, Crowder CD, et al. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. Am J Surg Pathol 2014;38:1530-7): Coleveselam and Colestipol resins in the GI tract. Irrelevant to the PICO.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

**Borghede EJIM 2011 (**Borghede MK, Schlutter JM, Agnholt JS, et al. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med 2011;22:e137-40): Retrospective cohort study of patients with bile acid malabsorption by SeHCAT and response to Cholestyramine. Did not assess daily vs. on demand therapy.

**Westergaard CTOG 2007** (Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33): Review article.

**Rossel SJG 1999** (Rossel P, Sortsoe Jensen H, Qvist P, et al. Prognosis of adult-onset idiopathic bile acid malabsorption. Scand J Gastroenterol 1999;34:587-90): Retrospective cohort study of patients with I-BAM and their response to Cholestyramine. Did not assess daily vs. on demand therapy.

**Sinha APT 1998** (Sinha L, Liston R, Testa HJ, et al. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. Aliment Pharmacol Ther 1998;12:839-44): Retrospective cohort study of patients with I-BAM and their response to Cholestyramine. Did not assess daily vs. on demand therapy.

**Niaz JRCPL 1997** (Niaz SK, Sandrasegaran K, Renny FH, et al. Postinfective diarrhoea and bile acid malabsorption. J R Coll Physicians Lond 1997;31:53-6): Retrospective cohort study of patients with PI-IBS and bile acid malabsorption and their response to Cholestyramine. Did not assess daily vs. on demand therapy.

**RuDusky Angiol 1997** (RuDusky BM. Cholestyramine therapy for quinidine-induced diarrhea. Case reports. Angiology 1997;48:173-6**):** Case reports of Cholestyramine therapy for Quinidine-induced diarrhea. Irrelevant to the PICO.

**Luman EJGH 1995** (Luman W, Williams AJ, Merrick MV, et al. Idiopathic bile acid malabsorption: long-term outcome. Eur J Gastroenterol Hepatol 1995;7:641-5): Long term outcome of I-BAM and response to Cholestyramine. Did not assess daily vs. on demand therapy.

**Eusufzai Gut 1993** (Eusufzai S, Axelson M, Angelin B, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. Gut 1993;34:698-701): Prevalence of bile acid malabsorption in patients with chronic diarrhea and response to cholestyramine. Did not assess daily vs. on demand therapy.

**Williams Gut 1991** (Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut 1991;32:1004-6): Prevalence of bile acid malabsorption in patients with chronic diarrhea and their response to cholestyramine. Did not assess daily vs. on demand therapy.

## Evidence to Decision framework (management question)

## PICO 13: In patients with BAD who respond to BAST, should intermittent, on demand dosing be tried?

| Judgement |
|---|

| | |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes |

| | |
|---|---|
| | ○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO 13*


1. Sciarretta G, Furno A, Mazzoni M, et al. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. Am J Gastroenterol 1992;87:1852-4.
2. Galatola G, Ferraris R, Pellerito R, et al. The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine: An uncontrolled open multicentre study. Eur J Gastroenterol Hepatol 1992;4:533-7.


**PICO 14: In patients with BAD who are unable to tolerate BAST, should alternative anti-diarrheal agents vs. no treatment be used for long-term symptomatic therapy?**

| **RCTs** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Study | Adequate sequence generation | Allocation concealment | Blinding | Incomplete outcome data addressed | Free of selective reporting | Free of other bias | Comments |
| Fernandez-Banares 2015[1] | OK | OK | OK | OK | OK | OK | • 26 patients with chronic functional watery diarrhea or IBS-D (SeHCAT 7-d retention ≤ 20%) randomized to **cholestyramine 4g bid vs. hydroxypropyl cellulose** x 8 wks.<br>• Clinical remission: < 3 BMs/d x 1 wk before visit (< 1 watery stool/d). **No difference in clinical remission (53.8% vs. 38.4%; P = 0.43; ITT). Higher mean % decrease in watery stool number with cholestyramine** (-92.4+/- 3.5% vs. -75.8+/-7.1%; P = 0.048).<br>• **No difference in adverse events**<br>• Presence of BAM (SeHCAT < 10%) was not a prerequisite for inclusion |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | (77% vs. 54%).<br>• Hydroxypropyl cellulose may be an active drug (bulking effect) – no placebo group for comparison. |
| Yeoh 1993[2] | Probably OK | Probably OK | OK | OK | OK | OK | • 18 patients with diarrhea caused by chronic radiation enteritis.<br>• Double-blind randomized **cross-over** order loperamide (3mg bid) and placebo x 14 days (washout period of 14 days).<br>• Mean 7d SeHCAT % 3.3% during placebo phase and 20.5% during loperamide phase<br>• Reduced frequency of BMs during loperamide phase (mean BMs/ week 13.5 vs. 19) |

| **SR of Observational Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Wilcox 2014[3] | No | No | No<br>Outcome available in 96/304 patients | No<br>High risk for performance bias, selection bias etc | • 1 prospective cohort study (Smith 2000) assessed "conventional" anti-diarrheal therapies in 96 patients with BAM (7d SeHCAT < 10%). CD with ileal resection, Unoperated CD, Vagotomy & pylorplasty +/- choly, IBS-D<br>• Did not specify response to individual medications, stating only that patients **received first line treatment with codeine, loperamide, or prednisolone** (not considered a conventional anti-diarrheal agent).<br>• Patient's perception of improvement in symptoms: 28% of patients<br>• If conventional therapies failed, BAST were used. |

| **Cohort Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Valdes 1993[4] | No | OK | OK | No<br>Selection, performance bias, co-intervention bias | • Prospective cohort study of 19 patients with chronic diarrhea due to ileal irradiation and/or resection.<br>• Measured SeHCAT before and during administration of loperamide<br>• 7d SeHCAT normalized or improved in 13 patients (7 with resection 20-50cm, 6 no resection) with symptomatic relief during loperamide (subjective outcome)<br>• 7d SeHCAT remained abnormal in 6 patients (resection > 80cm) during loperamide. 3 patients with slight relief. (subjective outcome) |

## GRADE report

| **Quality Assessment** | **Summary of Findings** | |
|---|---|---|
| | No of patients | Effect |

| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Alternative anti-diarrheal agents | Comparator | Relative (95% CI) | Absolute (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Efficacy (subjective / objective clinical response – highly variable definitions among studies)** | | | | | | | ⊕⊖⊖⊖ VERY LOW | | | | |
| 1 RCT n = 26 | Not serious | Not serious | Very serious[a] | Serious[b] | First line treatment with hydroxypropyl cellulose | ⊕⊖⊖⊖ VERY LOW | | 5/13 (38.5%) Hydroxypropyl cellulose (possible active drug) | 7/13 (53.8%) Cholestyramine | RR 0.54 (0.11 to 2.55) | 248 fewer per 1000 (from 479 fewer to 835 more) |
| 1 RCT n = 18 | Not serious | Not serious | Very serious[c] | Very serious[d] | First line treatment with loperamide | ⊕⊖⊖⊖ VERY LOW | | NA | NA | NA | NA |
| 1 SR of Observational Studies (1 Cohort study) n = 96 | Serious[c] | Not serious | Serious[d] | Serious[e] | First line treatment with codeine, loperamide, or prednisolone | ⊕⊖⊖⊖ VERY LOW | | 27/96 (28.1%) Conventional anti-diarrheal agents (codeine, loperamide, or prednisolone) | NA | NA | NA |
| 2 Cohort studies n = 37 (only 1 Cohort study had dichotomous outcome) | Serious[f] | Not serious | Serious[g] | Serious[e] | First line treatment with loperamide | ⊕⊖⊖⊖ VERY LOW | | 13/16 no resection or ilea resection 20-50cm (81.3%)<br><br>3/6 ileal resection > 80cm (50%)<br><br>Loperamide | NA | NA | NA |

a. Not in patients who are unable to tolerate BAST. All patients had SeHCAT 7-d retention ≤ 20%, but not all patients had BAD (SeHCAT 7-d retention < 10%).
b. Small sample size and low event rates. Optimal information size not met.
c. High risk for selection bias, incomplete follow-up, and outcome detection bias.
d. Not in patients who are unable to tolerate BAST. Anti-diarrheal agents were used as first-line treatments.
e. Small sample size and low event rates.
f. High risk for selection bias, performance bias, and outcome detection bias.
g. Not in patients who are unable to tolerate BAST.

## Overall QoE for PICO 14:

There are no RCTs or observational studies that have systematically assessed the effectiveness of other anti-diarrheal agents in patients with BAD who are unable to tolerate BAST.

There is 1 RCT (Fernandez-Banares 2015[1]) comparing cholestyramine vs. hydroxypropyl cellulose as first-line treatment in patients with functional chronic watery diarrhea and bile acid malabsorption (7d SeHCAT $\leq$ 20%) suggesting that there was no difference between the 2 medications in clinical remission. Another cross-over RCT patients with chronic diarrhea due to chronic radiation enteritis ileal irradiation and/or resection compared loperamide and placebo. Both RCTs have indirectness and imprecision. There are 2 cohort studies assessing Loperamide as first-line treatment in patients with BAD. The effectiveness of loperamide in these cohort studies is difficult to estimate due to differences in patient populations, study designs, and outcome measurements (mostly subjective improvement of symptoms). Overall, there is **VERY LOW** quality evidence supporting the use of alternative anti-diarrheal agents in patients with BAD who are unable to tolerate BAST.

**Other factors** that should influence the strength (or direction) of recommendation:
**Balance between benefits and harms:** Alternative anti-diarrheal agents (loperamide, diphenoxylate, hydroxypropyl cellulose) are generally safe agents to use over the long term.
**Patient values and preferences**: value controlling diarrhea with alternative agents than no treatment
**Cost:** Inexpensive

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Lacy Gastro 2016 (**Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393-1407. e5): Review article.

**Torbicki TDTMV 2015** (Torbicki E, Oh J, Mishra S, et al. Interventions for post-infectious irritable bowel syndrome: a systematic review of treatment efficacy. Trop Dis Travel Med Vaccines 2015;1:1): Systematic review of interventions for PI-IBS. 2 retrospective studies on cholestyramine. No report on alternative anti-diarrheal agents.

**Nee EOP 2015** (Nee J, Zakari M, Lembo AJ. Current and emerging drug options in the treatment of diarrhea predominant irritable bowel syndrome. Expert Opin Pharmacother 2015;16:2781-92): Review article.

**Wadhwa CGR 2015** (Wadhwa A, Camilleri M, Grover M. New and investigational agents for irritable bowel syndrome. Curr Gastroenterol Rep 2015;17:46.): Review article.

**Camilleri EOP 2013** (Camilleri M. Current and future pharmacological treatments for diarrhea-predominant irritable bowel syndrome. Expert Opin Pharmacother 2013;14:1151-60): Review article.

**Li BPRCG 2012** (Li Z, Vaziri H. Treatment of chronic diarrhoea. Best Pract Res Clin Gastroenterol 2012;26:677-87): Review article.

**Manabe CGR 2010** (Manabe N, Rao AS, Wong BS, et al. Emerging pharmacologic therapies for irritable bowel syndrome. Curr Gastroenterol Rep 2010;12:408-16.): Review article.

**Chande CDBSR 2008** (Chande N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis. Cochrane Database Syst Rev 2008:CD003575): SR of 10 RCTs comparing various therapies to either placebo or active comparator in patients with collagenous or microscopic colitis. Most trials did not specify if patients also had BAD. 1 RCT (Munck 2003) excluded patients with BAD.

**Shah RGD 2007** (Shah SB, Hanauer SB. Treatment of diarrhea in patients with inflammatory bowel disease: concepts and cautions. Rev Gastroenterol Disord 2007;7 Suppl 3:S3-10): Review article.

**Nyhlin APT 2006** (Nyhlin N, Bohr J, Eriksson S, et al. Systematic review: microscopic colitis. Aliment Pharmacol Ther 2006;23:1525-34): Review article.

**Thomas Gut 2003 (**Thomas PD, Forbes A, Green J, et al. Guidelines for the investigation of chronic diarrhoea, 2nd edition. Gut 2003;52 Suppl 5:v1-15): Guidelines for investigation of chronic diarrhea.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

## Evidence to Decision framework (management question)

## PICO 14: In patients with BAD who are unable to tolerate BAST, should alternative anti-diarrheal agents vs. no treatment be used for long-term symptomatic therapy?

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low |

| | |
|---|---|
| | ○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies<br>○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |



*References for PICO 14*

1. Fernandez-Banares F, Rosinach M, Piqueras M, et al. Randomised clinical trial: colestyramine vs. hydroxypropyl cellulose in patients with functional chronic watery diarrhoea. Aliment Pharmacol Ther 2015;41:1132-40.
2. Yeoh EK, Horowitz M, Russo A, et al. Gastrointestinal function in chronic radiation enteritis--effects of loperamide-N-oxide. Gut 1993;34:476-82.

3. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther 2014;39:923-39.
4. Valdés Olmos RA, Taal BG, Hoefnagel CA, et al. 75SeHCAT in the assessment of improved bile acid absorption in patients with ileal damage by delaying bowel motility with loperamide. Eur J Gastroenterol Hepatol 1993;5:941-946.

**PICO 15: In patients with BAD receiving BAST, should maintenance therapy be used at the lowest dose needed to maintain symptom response vs. no dose titration?**

| **SR of Observational Studies** | | | | | |
|---|---|---|---|---|---|
| Study | Similar for prognostic factors | Outcome detection similar | Follow-up complete | Free of other bias | Comments |
| Torbicki 2015[1] | No | OK<br>Frequency of diarrhea | No | No<br>High risk for performance bias, co-interventions, selection bias etc | • SR of interventions for PI-IBS.<br>• ½ retrospective study (menon et al) reported long term outcome of 25 patients with PI-IBS and bile acid malabsorption (SeHCAT) treated with **cholestyramine.** 18 had significant decrease in frequency of BM with sustained response for over 1 year. Patients were **allowed to titrate** their own dose of cholestyramine, varying between 2- 16g/d |
| Wilcox 2014[2] (not tagged) | No | No | Unclear | No<br>High risk for performance bias, selection bias etc | • SR of 23 cohort studies (n = 801) of BAM patients treated with cholestyramine.<br>• Most studies did not specify duration of treatment. Treatment for 6 – 12 months (Rudberg 1996, Fernandez-Banares 2007, Ung 2000).<br>• **Cholestyramine: generally started at low dose 2-4 g/d and titrated to response (no mention of dose titration in some studies)**<br>• **Colesevelam / Colestipol: no mention of dose titration**<br>• Variation in diagnostic testing used for BAM and cut-off value, treatment dose and timing of administration, and definition of clinical response<br>• No quality assessment of included studies |

**GRADE report**

**Overall QoE for PICO 15:**

There are no RCTs or observational studies that have directly compared dose titration vs. no dose titration of BAST in patients with BAD.

In general, most cohort studies reported gradual dose titration for cholestyramine to clinical response. There was, however, no mention of dose titration of colesevelam or colestipol. For any medication that alleviates symptoms but does not alter the natural history of the disease, it is intuitive to gradually titrate the medication to minimize symptoms / side effects. This is particularly relevant with BAST due to the high frequency of side effects and intolerance. It is conceivable that gradual dose titration may reduce the risks of side effects, increase compliance, and potentially less costly. Does the panel believe that in patients with BAD, gradual dose titration to minimize symptoms represents good practice? If so, this statement can be considered a **good practice statement.**

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Beigel JCC 2014** (Beigel F, Teich N, Howaldt S, et al. Colesevelam for the treatment of bile acid malabsorption-associated diarrhea in patients with Crohn's disease: a randomized, double-blind, placebo-controlled study. J Crohns Colitis 2014;8:1471-9): RCT of Colesevelam for bile acid malabsorption associated diarrhea in Crohn's disease. 4-week endpoint. Not a maintenance trial.

**Wong DDS 2012** (Wong BS, Camilleri M, Carlson PJ, et al. Pharmacogenetics of the effects of colesevelam on colonic transit in irritable bowel syndrome with diarrhea. Dig Dis Sci 2012;57:1222-6): Cohort study of the pharmacogenetics of the effects of Colesevelam on colonic transit in IBS-D. Not specifically on patients with BAD.

**Islam PG 2012** (Islam RS, DiBaise JK. Bile acids: an underrecognized and underappreciated cause of chronic diarrhea. Pract Gastroenterol 2012;36:32-44): Review article.

**Walters ERGH 2010** (Walters JR. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. Expert Rev Gastroenterol Hepatol 2010;4:561-7): Review article.

**Odunsi-Shiyanbade CGH 2010** (Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, et al. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Clin Gastroenterol Hepatol 2010;8:159-65): RCT of Colesevelam for 12 – 14 days in patients with IBS-D. Outcomes were colonic transit time, daily bowel frequency and consistency and permeability. Only 4/24 patients had abnormal 7αC4 levels (BAD). Not a maintenance trial.

**Wedlake 2009 (**Wedlake L, Thomas K, Lalji A, et al. Effectiveness and tolerability of colesevelam hydrochloride for bile-acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire. Clin Ther 2009;31:2549-58): Retrospective cohort study of patients with cancer and bile acid malabsorption who were prescribed colesevelam. No mention of dose titration.

**DeMeo AJG 1998** (DeMeo M, Kolli S, Keshavarzian A, et al. Beneficial effect of a bile acid resin binder on enteral feeding induced diarrhea. Am J Gastroenterol 1998;93:967-71): RCT of Colestid on enteral feeding induced diarrhea x 7 days. Not a maintenance trial. No mention of dose titration.

**Peleman CGH 2017 (**Peleman C, Camilleri M, Busciglio I, et al. Colonic transit and bile acid synthesis or excretion in patients with irritable bowel syndrome-diarrhea without bile acid malabsorption. Clin Gastroenterol Hepatol 2017;15:720-727 e1): Cohort study assessing colonic transit and bile acid synthesis or excretion in patients with IBS-D without bile acid malabsorption. BAST was not assessed.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Camilleri Gut Liver 2015** (Camilleri M. Bile acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver 2015;9:332-9): Review article.

**Camilleri ERGH 2014** (Camilleri M. Advances in understanding of bile acid diarrhea. Expert Rev Gastroenterol Hepatol 2014;8:49-61): Review article.

**Appleby NGM 2014** (Appleby RN, Walters JR. The role of bile acids in functional GI disorders. Neurogastroenterol Motil 2014;26:1057-69): Review article.

**Arnold AJSP 2014** (Arnold MA, Swanson BJ, Crowder CD, et al. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. Am J Surg Pathol 2014;38:1530-7): Morphologic description of bile acid sequestrants.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

**Borghede EJIM 2011 (**Borghede MK, Schlutter JM, Agnholt JS, et al. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med 2011;22:e137-40): Retrospective cohort study of patients with chronic watery diarrhea and their response to cholestyramine. No mention of duration of treatment or titration of doses.

**Westergaard CTOG 2007** (Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33): Review article.

**Baert ACB 2004** (Baert D, Coppens M, Burvenich P, et al. Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. Acta Clin Belg 2004;59:258-62): case series of 20 patients with microscopic colitis treated with cholestyramine. Did not specify if patients also had BAD.

**Wildt SJG 2003** (Wildt S, Norby Rasmussen S, Lysgard Madsen J, et al. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. Scand J Gastroenterol 2003;38:826-30): Retrospective cohort study of patients with chronic diarrhea and bile acid malabsorption. Response to cholestyramine reported. Dosage was titrated to response, but unclear duration of cholestyramine.

**Ung EJGH 2000** (Ung KA, Kilander AF, Lindgren A, et al. Impact of bile acid malabsorption on steatorrhoea and symptoms in patients with chronic diarrhoea. Eur J Gastroenterol Hepatol 2000;12:541-7): Prospective cohort study included in Wilcox 2014.

**Rossel SJG 1999** (Rossel P, Sortsoe Jensen H, Qvist P, et al. Prognosis of adult-onset idiopathic bile acid malabsorption. Scand J Gastroenterol 1999;34:587-90): Retrospective cohort study of patients with IBAM treated with cholestyramine. No mention of how the drug was dosed / titrated.

**Sinha APT 1998** (Sinha L, Liston R, Testa HJ, et al. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. Aliment Pharmacol Ther 1998;12:839-44): Retrospective cohort study included in Wilcox 2014.

**Niaz JRCPL 1997** (Niaz SK, Sandrasegaran K, Renny FH, et al. Postinfective diarrhoea and bile acid malabsorption. J R Coll Physicians Lond 1997;31:53-6): Retrospective cohort study included in Wilcox 2014. Outcome assessed only over 2 weeks.

**Luman EJGH 1995** (Luman W, Williams AJ, Merrick MV, et al. Idiopathic bile acid malabsorption: long-term outcome. Eur J Gastroenterol Hepatol 1995;7:641-5): Case series of 23 patients with IBAM who all responded to bile acid chelator (cholestyramine / aluminum hydroxide) follow-up data. No mention of dose titration.

**Nyhlin Gut 1994** (Nyhlin H, Merrick MV, Eastwood MA. Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. Gut 1994;35:90-3): case series of 51 patients with CD who had failed to respond to conventional treatment tested for BAM with SeHCAT. A small subgroup of patients was given cholestyramine with good response (19/22). No mention of dose titration.

**Sciarretta AJG 1994** (Sciarretta G, Bonazzi L, Monti M, et al. Bile acid malabsorption in AIDS-associated chronic diarrhea: a prospective 1-year study. Am J Gastroenterol 1994;89:379-81). Case control study of patients with AIDS associated chronic diarrhea and AIDS controls for bile acid malabsorption. No mention of BAST.

**Eusufzai Gut 1993** (Eusufzai S, Axelson M, Angelin B, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. Gut 1993;34:698-701): Prospective cohort study included in the SR by Wilcox 2014. Dose was titrated to symptoms. But unclear duration of treatment.

**Ford PM 1992** (Ford GA, Preece JD, Davies IH, et al. Use of the SeHCAT test in the investigation of diarrhoea. Postgrad Med J 1992;68:272-6): Retrospective cohort study included in the SR by Wilcox 2014. Dose was titrated to symptoms. Duration only 1 month

**Sciarretta AJG 1992** (Sciarretta G, Furno A, Mazzoni M, et al. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. Am J Gastroenterol 1992;87:1852-4): Prospective cohort study already included in the SR by Wilcox 2014. Did not mention dose titration.

**Galatola EJGH 1992** (Galatola G, Ferraris R, Pellerito R, et al. The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine: An uncontrolled open multicentre study. Eur J Gastroenterol Hepatol 1992;4:533-7): Prospective cohort study included in the SR by Wilcox 2014. Dose titrated to symptoms. Unclear duration of treatment. Follow-up was 1 – 24 months.

**Williams Gut 1991** (Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut 1991;32:1004-6): Prospective cohort study included in the SR by Wilcox 2014. Did not mention dose titration.

**Evidence to Decision framework (management question)**

**PICO 15: In patients with BAD receiving BAST, should maintenance therapy be used at the lowest dose needed to maintain symptom response vs. no dose titration?**

DESIGNATED A GOOD PRACTICE STATEMENT

*References for PICO 15*

1. Torbicki E, Oh J, Mishra S, et al. Interventions for post-infectious irritable bowel syndrome: a systematic review of treatment efficacy. Trop Dis Travel Med Vaccines 2015;1:1.
2. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Aliment Pharmacol Ther 2014;39:923-39.

**PICO 16: In patients with BAD and recurrent or worsening symptoms despite stable BAST, should diagnostic re-evaluation or dose escalation be used?**

The underlying PICO question is that in patients with BAD and recurrent or worsening symptoms despite stable BAST, what is the probability / likelihood that another condition is causing the symptoms that warrants re-evaluation? Unfortunately, the tagged studies did not address this question. Most of the included studies evaluated the diagnostic utility of different tests for BAD and the response to BAST based on the test results. We found **no evidence** relevant to this PICO.

The PICO is somewhat vague and/or unclear. First, it is unclear what type of evaluations the patients had prior to the diagnosis of BAD and how the diagnosis of BAD was made (therapeutic trial with BAST, SeHCAT or other tests). Second, it is also unclear what type of BAD this question relates to – Type 1/2/3 as the decision to re-evaluate may differ depending on the underlying GI condition.

Third, it is unclear what type of re-evaluations the PICO is referring to (repeat SeHCAT test, stool studies, colonoscopy, etc). Fourth, the severity of symptoms may play a role in the decision making for re-evaluation or dose escalation. We will need to discuss whether it is worth splitting the PICOs based on Type 1 / 2 / 3.

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

**Scheurlen Dig 1986** (Scheurlen C, Kruis W, Bull U, et al. Comparison of 75SeHCAT retention half-life and fecal content of individual bile acids in patients with chronic diarrheal disorders. Digestion 1986;35:102-8): Comparison of SeHCAT retention half-life and fecal content of individual bile acids in patients with chronic diarrheal disorders. Irrelevant to the PICO.

**Valentin Gut 2016 (**Valentin N, Camilleri M, Altayar O, et al. Biomarkers for bile acid diarrhoea in functional bowel disorder with diarrhoea: a systematic review and meta-analysis. Gut 2016;65:1951-1959): Systematic review of the diagnostic yield of biomarkers of bie acid diarrhea. Irrelevant to the PICO.

**Riemsma HTA 2013** (Riemsma R, Al M, Corro Ramos I, et al. SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis. Health Technol Assess 2013;17:1-236): Systematic review and cost-effectiveness analysis of SeHCAT for the investigation of bile acid malabsorption and measurement of bile acid pool loss. Irrelevant to the PICO.

**Wong DDS 2012** (Wong BS, Camilleri M, Carlson PJ, et al. Pharmacogenetics of the effects of colesevelam on colonic transit in irritable bowel syndrome with diarrhea. Dig Dis Sci 2012;57:1222-6): Pharmacogenetics of the effects of Colesevelam on colonic transit in IBS-D. Irrelevant to the PICO.

**Walters ERGH 2010** (Walters JR. Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. Expert Rev Gastroenterol Hepatol 2010;4:561-7): Review article.

**Odunsi-Shiyanbade CGH 2010** (Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, et al. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Clin Gastroenterol Hepatol 2010;8:159-65): Effects of Chenodeoxycholate and a bile acid sequestrant, Colesevelam, on intestinal transit and bowel function. Irrelevant to the PICO.

**Vijayvargiya APT 2017** (Vijayvargiya P, Camilleri M, Carlson P, et al. Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. Aliment Pharmacol Ther 2017;46:581-588): Performance characteristics of serum C4 and FGF19 in identifying BAD in patients with IBS-D or functional diarrhea (compared to 48 hour fecal bile acids). Irrelevant to the PICO.

**Peleman CGH 2017 (**Peleman C, Camilleri M, Busciglio I, et al. Colonic transit and bile acid synthesis or excretion in patients with irritable bowel syndrome-diarrhea without bile acid malabsorption. Clin Gastroenterol Hepatol 2017;15:720-727 e1): Associations among BA in stool and colonic transit in IBS-D without BAM patients. Irrelevant to the PICO.

**Mottacki APT 2016** (Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea - pathogenesis, diagnosis and management. Aliment Pharmacol Ther 2016;43:884-898): Review article.

**Johnston AJG 2016** (Johnston IM, Nolan JD, Pattni SS, et al. Characterizing factors associated with differences in FGF19 blood levels and synthesis in patients with primary bile acid diarrhea. Am J Gastroenterol 2016;111:423-32): Exploratory studies of functional variants in candidate genes for patients with primary bile acid diarrhea. Irrelevant to the PICO.

**Camilleri Gut Liver 2015** (Camilleri M. Bile acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver 2015;9:332-9): Review article.

**Camilleri ERGH 2014** (Camilleri M. Advances in understanding of bile acid diarrhea. Expert Rev Gastroenterol Hepatol 2014;8:49-61): Review article.

**Gothe JCC 2014** (Gothe F, Beigel F, Rust C, et al. Bile acid malabsorption assessed by 7 alpha-hydroxy-4-cholesten-3-one in pediatric inflammatory bowel disease: correlation to clinical and laboratory findings. J Crohns Colitis 2014;8:1072-8): Correlation between C4 and symptoms and laboratory findings in pediatric patients with IBD. Irrelevant to the PICO.

**Appleby NGM 2014** (Appleby RN, Walters JR. The role of bile acids in functional GI disorders. Neurogastroenterol Motil 2014;26:1057-69): Review article.

**Camilleri NGM 2014 (**Camilleri M, Shin A, Busciglio I, et al. Validating biomarkers of treatable mechanisms in irritable bowel syndrome. Neurogastroenterol Motil 2014;26:1677-85)**:** Associations between biomarkers and colonic transit and fecal bile acids in patients with IBS. Irrelevant to the PICO.

**Vijayvargiya CGH 2013 (**Vijayvargiya P, Camilleri M, Shin A, et al. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol 2013;11:1232-9): Review article.

**Barkun CJG 2013** (Barkun AN, Love J, Gould M, et al. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol 2013;27:653-9): Review article.

**Pattni APT 2013** (Pattni SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. Aliment Pharmacol Ther 2013;38:967-76): Correlation between FGF19 and C4 values in patients with chronic diarrhea. Irrelevant to the PICO.

**Gracie NGM 2012** (Gracie DJ, Kane JS, Mumtaz S, et al. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. Neurogastroenterol Motil 2012;24:983-e538): Prevalence of bile acid malabsorption in patients with chronic diarrhea. Irrelevant to the PICO.

**Pattni CTG 2012 (**Pattni SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 and 7alpha-hydroxy-4-cholesten-3-one in the diagnosis of patients with possible bile acid diarrhea. Clin Transl Gastroenterol 2012;3:e18): Fibroblast growth factor 19 and 7 alpha-hydroxy-4-cholesten-3-one in the diagnosis of patients with possible bile acid diarrhea. Irrelevant to the PICO.

**Borghede EJIM 2011 (**Borghede MK, Schlutter JM, Agnholt JS, et al. Bile acid malabsorption investigated by selenium-75-homocholic acid taurine ((75)SeHCAT) scans: causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea. Eur J Intern Med 2011;22:e137-40): Prevalence of bile acid malabsorption in patients with chronic diarrhea by SeHCAT and response to cholestyramine. Irrelevant to the PICO.

**Brydon CGH 2011 (**Brydon WG, Culbert P, Kingstone K, et al. An evaluation of the use of serum 7-alpha-hydroxycholestenone as a diagnostic test of bile acid malabsorption causing watery diarrhea. Can J Gastroenterol 2011;25:319-23)**:** Evaluation of 7-alpha-hydroxycholestenone as a diagnostic test of bile acid malabsorption in patients with chronic diarrhea. Irrelevant to the PICO.

**Camilleri NGM 2011** (Camilleri M, Vazquez-Roque MI, Carlson P, et al. Association of bile acid receptor TGR5 variation and transit in health and lower functional gastrointestinal disorders. Neurogastroenterol Motil 2011;23:995-9, e458): Association of genetic variation in TGR5 and small bowel transit and colonic transit in patients with IBS. Irrelevant to the PICO.

**Fernandez-Banares AJG 2007** (Fernandez-Banares F, Esteve M, Salas A, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol 2007;102:2520-8): Prevalence of gluten-sensitive enteropathy, bile acid malabsorption, and sugar malabsorption in patients with chronic watery diarrhea. Irrelevant to the PICO.

**Westergaard CTOG 2007** (Westergaard H. Bile acid malabsorption. Curr Treat Options Gastroenterol 2007;10:28-33): Review article.

**Montagnani WJG 2006** (Montagnani M, Abrahamsson A, Galman C, et al. Analysis of ileal sodium/bile acid cotransporter and related nuclear receptor genes in a family with multiple cases of idiopathic bile acid malabsorption. World J Gastroenterol 2006;12:7710-4): Analysis of ileal sodium / bile acid cotransporter and related nuclear receptor genes in a family with multiple cases if IBAM. Irrelevant to the PICO.

**Wildt SJG 2003** (Wildt S, Norby Rasmussen S, Lysgard Madsen J, et al. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. Scand J Gastroenterol 2003;38:826-30): Prevalence of bile acid malabsorption in patients with chronic diarrhea and response to cholestyramine. Irrelevant to the PICO.

**Montagnani SJG 2001** (Montagnani M, Love MW, Rossel P, et al. Absence of dysfunctional ileal sodium-bile acid cotransporter gene mutations in patients with adult-onset idiopathic bile acid malabsorption. Scand J Gastroenterol 2001;36:1077-80): Mutations in the ileal sodium bile acid cotransporter gene in patients with IBAM. Irrelevant to the PICO.

**Sauter DDS 1999** (Sauter GH, Munzing W, von Ritter C, et al. Bile acid malabsorption as a cause of chronic diarrhea: diagnostic value of 7alpha-hydroxy-4-cholesten-3-one in serum. Dig Dis Sci 1999;44:14-9): Diagnostic value of serum HCO for bile acid malabsorption in patients with positive SeHCAT. Irrelevant to the PICO.

**Rudberg AR 1996** (Rudberg U, Nylander B. Radiological bile acid absorption test 75SeHCAT in patients with diarrhoea of unknown cause. Acta Radiol 1996;37:672-5): Prevalence of bile acid malabsorption (SeHCAT) in patients with chronic diarrhea and their response to cholestyramine. Irrelevant to the PICO.

**Nyhlin Gut 1994** (Nyhlin H, Merrick MV, Eastwood MA. Bile acid malabsorption in Crohn's disease and indications for its assessment using SeHCAT. Gut 1994;35:90-3): Prevalence of bile acid malabsorption in Crohn's disease not responding to conventional treatment. Irrelevant to the PICO.

**Valdes Olmos EJGH 1993** (Valdés Olmos RA, Taal BG, Hoefnagel CA, et al. 75SeHCAT in the assessment of improved bile acid absorption in patients with ileal damage by delaying bowel motility with loperamide. Eur J Gastroenterol Hepatol 1993;5:941-946): Bile acid absorption in patients with ileal damage in response to loperamide. Irrelevant to the PICO.

**Worobetz CJGH 1993** (Worobetz L, Wilkinson A, Chmielowiec C, et al. Evaluation of SeHCAT test in determining ileal involvement and dysfunction in Crohn's disease. Can J Gastroenterol Hepatol 1993;7:597-601): Correlation of SeHCAT with Crohn's disease activity, extent, diarrhea, and response to cholestyramine. Irrelevant to the PICO.

**Eusufzai Gut 1993** (Eusufzai S, Axelson M, Angelin B, et al. Serum 7 alpha-hydroxy-4-cholesten-3-one concentrations in the evaluation of bile acid malabsorption in patients with diarrhoea: correlation to SeHCAT test. Gut 1993;34:698-701): Prevalence of bile acid malabsorption in patients with chronic diarrhea and response to cholestyramine. Irrelevant to the PICO.

**Ford PM 1992** (Ford GA, Preece JD, Davies IH, et al. Use of the SeHCAT test in the investigation of diarrhoea. Postgrad Med J 1992;68:272-6): Prevalence of bile acid malabsorption by SeHCAT test in patients with chronic diarrhea and response to cholestyramine. Irrelevant to the PICO.

**Sciarretta AJG 1992** (Sciarretta G, Furno A, Mazzoni M, et al. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. Am J Gastroenterol 1992;87:1852-4): Prevalence of bile acid malabsorption by SeHCAT test in post-cholecystectomy patients and their response to cholestyramine. Irrelevant to the PICO.

**Ferraris DDS 1992** (Ferraris R, Galatola G, Barlotta A, et al. Measurement of bile acid half-life using [75Se]HCAT in health and intestinal diseases. Comparison with [75Se]HCAT abdominal retention methods. Dig Dis Sci 1992;37:225-32): Measurement of bile acid half-life using SeHCAT. Irrelevant to the PICO.

**Williams Gut 1991** (Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut 1991;32:1004-6): Prevalence of bile acid malabsorption in patients with chronic diarrhea and their response to cholestyramine. Irrelevant to the PICO.

## Evidence to Decision framework (management question)

## PICO 16: In patients with BAD and recurrent or worsening symptoms despite stable BAST, should diagnostic re-evaluation or dose escalation be used?

DESIGNATED A GOOD PRACTICE STATEMENT

### *References for PICO 16*

Not applicable

**PICO 17: In patients being considered for BAST, should concurrent medications be reviewed to minimize the potential for drug interactions?**

This statement can be considered an ungraded **good practice statement**. It is generally considered good practice to check for potential drug interactions when patients are started on new medications. The unstated alternative of not checking for potential drug interactions is absurd.

BAST is known to bind other medications and this necessitates spaced administration. For example, cholestyramine has been shown to reduce the bioavailability of fluvastatin, ezetimibe, glipizide, furosemide, hydrochlorothiazide, digoxin and valproic acid when administered at the same time with the latter. In some pharmacokinetics studies, Colesevelam appears to interact less with some medications (eg, lovastatin, ezetimibe, fenofibrate, digoxin, warfarin, verapamil, metoprolol, quinidine and valproic acid), but in other studies, Colesevelam was found to reduce the absorption of other medications (e.g. glyburide, levothyroxine). Would the panel consider a good practice to always check for medication interactions when patients are started on new medications?

Checklist for good practice statements:

6. Is the statement clear and actionable?
7. Is the message really necessary in regard to actual health care practice?
8. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences? Need to consider benefits are large and harm very small; certainty of benefits and harms are great; the values and preferences are clear; the intervention is cost saving; and the intervention is clearly acceptable, feasible, and promotes equity.
9. Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy? It is possible to collect all the case reports of the adverse consequences of not checking for potential drug interactions. We could also collect and summarize the benefits of checking for potential drug interactions. We can then link the bodies of evidence to make the case for checking for potential drug interactions. This makes the case for a good practice statement rather than a GRADEd recommendation as it is poor use of time in collecting and summarizing the relevant evidence.
10. Is there a well-documented clear and explicit rationale connecting the indirect evidence?
    - The panel believes that in patients being considered for BAST, a review of concurrent medications to minimize the potential drug interactions represents good practice?

- BAST is known to bind other medications and this necessitates spaced administration. For example, cholestyramine has been shown to reduce the bioavailability of fluvastatin, ezetimibe, glipizide, furosemide, hydrochlorothiazide, digoxin and valproic acid when administered at the same time with the latter. In some pharmacokinetics studies, Colesevelam appears to interact less with some medications (eg, lovastatin, ezetimibe, fenofibrate, digoxin, warfarin, verapamil, metoprolol, quinidine and valproic acid), but in other studies, Colesevelam was found to reduce the absorption of other medications (eg, glyburide, levothyroxine).

**Articles that were initially tagged as potentially eligible, but did not directly contribute to the GRADE assessment of the quality of evidence for this PICO**

Donovan JM, Kisicki JC, Stiles MR, Tracewell WG, Burke SK. Effect of colesevelam on lovastatin pharmacokinetics. Ann Pharmacother. 2002;36:392-7.

Jones MR1, Baker BA, Mathew P. Effect of colesevelam HCl on single-dose fenofibrate pharmacokinetics. Clin Pharmacokinet. 2004;43:943-50.

Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. Cardiovasc Drugs Ther. 2000;14:681-90.

Brown KS, Armstrong IC, Wang A, et al. Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. J Clin Pharmacol. 2010;50:554-65.

Weitzman SP, Ginsburg KC, Carlson HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. Thyroid. 2009;19:77-9.

Brown DD, Juhl RP, Warner SL. Decreased bioavailability of digoxin due to hypocholesterolemic interventions. Circulation. 1978;58:164-72.

Brown DD, Schmid J, Long RA, Hull JH. A steady-state evaluation of the effects of propantheline bromide and cholestyramine on the bioavailability of digoxin when administered as tablets or capsules. J Clin Pharmacol. 1985;25:360-4.

Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet. 2005;44:467-94. Review.

Malloy MJ, Ravis WR, Pennell AT, Diskin CJ. Effect of cholestyramine resin on single dose valproate pharmacokinetics. Int J Clin Pharmacol Ther. 1996;34:208-11.

Smith HT, Jokubaitis LA, Troendle AJ, Hwang DS, Robinson WT. Pharmacokinetics of fluvastatin and specific drug interactions. Am J Hypertens. 1993;6:375S-382S.

Kivistö KT, Neuvonen PJ. The effect of cholestyramine and activated charcoal on glipizide absorption. Br J Clin Pharmacol. 1990;30:733-6.

Neuvonen PJ, Kivistö K, Hirvisalo EL. Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide. Br J Clin Pharmacol. 1988;25:229-33.

Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. Clin Pharmacol Ther. 1986;39:329-34.

Hunninghake DB, King S, LaCroix K. The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. Int J Clin Pharmacol Ther Toxicol. 1982;20:151-4.

**Evidence to Decision framework (management question)**

**PICO 17: In patients being considered for BAST, should concurrent medications be reviewed to minimize the potential for drug interactions?**

DESIGNATED A GOOD PRACTICE STATEMENT

*References for PICO 17*
Not applicable

**PICO B (no recommendation): In patients receiving long-term maintenance therapy with BAST, should fat-soluble vitamin levels be measured at baseline and annually, thereafter?**

The literature search failed to identify any relevant article assessing fat-soluble vitamin levels before and after initiation of long-term maintenance therapy with BAST.

It has been long known that in theory the use of BAST can cause coagulopathy due to reduced absorption of vitamin K, only **a few case reports of coagulopathy and bleeding due to vitamin K deficiency** with cholestyramine use have been reported.[1-5] In patients with BAD on long-term maintenance therapy with BAST, the risks for malabsorption of fat-soluble vitamin levels may be even higher.

In a case report (Gross 1970[1]), a woman on chronic cholestyramine therapy for diarrhea due to extensive distal ileal post-radiation changes (cholerheic enteropathy) developed bleeding with gross hematuria, gastrointestinal bleeding, and hypotension with prolongation of prothrombin time that was reversed with vitamin K. She had normal prothrombin time before cholestyramine therapy. “It is likely that despite a reduced enterohepatic circulation before cholestyramine was maintained at a level above the critical micellar concentration by increased hepatic bile-salt synthesis. Addition of cholestyramine further interfered with the enterohepatic circulation beyond the compensatory capacity of the liver and probably reduced jejunal bile-salt concentration critically, resulting in vitamin K malabsorption and hemorrhage secondary to hypoprothrombinemia.”

In one case report (West 1975[5]), long term use of cholestyramine led to reduced absorption of vitamin A and E.

Overall, there is **VERY LOW** quality evidence supporting the assessment of fat-soluble vitamin levels at baseline and annually, thereafter, in patients receiving long term therapy with BAST. **Panel to provide other applicable evidence during meeting.**

**Evidence to Decision framework (management question)**

**PICO B (no recommendation): In patients receiving long-term maintenance therapy with BAST, should fat-soluble vitamin levels be measured at baseline and annually, thereafter?**

| | **Judgement** |
|---|---|
| Desirable Effects | **How substantial are the desirable anticipated effects?**<br>○ Trivial<br>○ Small<br>○ Moderate<br>○ Large<br><br>○ Varies<br>○ Don't know |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**<br>○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br><br>○ Varies<br>○ Don't know |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**<br>○ Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>○ No included studies |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**<br>○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br><br>○ Varies |

| | |
|---|---|
| | ○ Don't know |
| Acceptability | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |
| Feasibility | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br><br>○ Varies<br>○ Don't know |

*References for PICO B*


1. Gross L, Brotman M. Hypoprothrombinemia and hemorrhage associated with cholestyramine therapy. Ann Intern Med 1970;72:95-6.
2. Vroonhof K, van Rijn HJ, van Hattum J. Vitamin K deficiency and bleeding after long-term use of cholestyramine. Neth J Med 2003;61:19-21.
3. Shojania AM, Grewar D. Hypoprothrombinemic hemorrhage due to cholestyramine therapy. CMAJ 1986;134:609-10.
4. Sadler LC, Lane M, North R. Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 1995;102:169-70.
5. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. Gut 1975;16:93-8.


**PICO III (no vote): In patients with BAD, should BAST be taken once daily to minimize interaction with other medications?**

The literature search failed to identify any relevant article assessing whether BAST should be taken once daily or more than once daily to minimize interaction with other medications.

A paper by Camilleri 2016[1] reviewed the functions of the stomach and the kinetics of emptying at different food forms or formulations. He concluded a window of 3 hours would be expected to allow a median of at least 80% of a resin-like or other medication with particle size < 1mm to empty from the stomach and, hence to avoid potential interactions such as binding within the stomach. However, there is no clinical study or physiologic study that compared once daily vs. more than once daily administration in terms of drug interactions. Theoretically, the more frequent the dosing of BAST, the more likely there will be interactions with other medications and compliance will decrease. It is uncertain whether frequency of dosing has any impact on efficacy of BAST.

Overall, there is **no evidence found** to support BAST be taken once daily to minimize interaction with other medications. There is **VERY LOW** quality evidence supporting the practice of spacing out timing of BAST from other medications by at least 3 hours. **Panel to provide other applicable evidence during meeting.**

**Evidence to Decision framework (management question)**
**PICO III (no vote): In patients with BAD, should BAST be taken once daily to minimize interaction with other medications?**

The EtD framework was not completed, there was no vote, and no additional recommendation statement was developed because “drug interactions” are included in PICO 17.

*References for PICO III*

1. Camilleri M. Drug-resin drug interactions in patients with delayed gastric emptying: What is optimal time window for drug administration? Neurogastroenterol Motil 2016;28:1268-71.

**PICO IV (no vote): In patients with BAD, should BAST be taken AM (or PM/ HS)?**

The literature search failed to identify any relevant article assessing whether BAST should be AM (or PM/HS).
There is **no evidence found** to support BAST be taken AM (or PM/HS). **Panel to provide other applicable evidence during meeting.**

**Evidence to Decision framework (management question)**
**PICO IV (no vote): In patients with BAD, should BAST be taken AM (or PM/ HS)?**

The EtD framework was not completed, there was no vote, and no recommendation statement was developed because there were no data to inform this issue, which is discussed in terms of future research needs

*References for PICO IV*

Not applicable