

Empiric trial or diagnostic tests for Bile Acid Diarrhea? That is the question!

Ginevra BERTI, Francesco RETTURA, Christian LAMBIASE, Massimo BELLINI*.

Department of New Technologies and Translational Research in Medicine and Surgery,
Gastroenterology Unit, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy

*Corresponding author

Department of New Technologies and Translational Research in Medicine and Surgery,
Gastroenterology Unit, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy

mbellini@med.unipi.it

050997394

Diagnosis of bile acid diarrhea.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/1751-2980.13044](https://doi.org/10.1111/1751-2980.13044)

This article is protected by copyright. All rights reserved.

Empiric trial or diagnostic tests for Bile Acid Diarrhea? That is the question!

Ginevra BERTI, Francesco RETTURA, Christian LAMBIASE, Massimo BELLINI*.

Department of New Technologies and Translational Research in Medicine and Surgery,
Gastroenterology Unit, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy

*Corresponding author

Department of New Technologies and Translational Research in Medicine and Surgery,
Gastroenterology Unit, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy

mbellini@med.unipi.it

050997394

Diagnosis of bile acid diarrhea.

To the editor,

We read with great interest the paper by Costa S. et al. "Prevalence and clinical features of bile acid diarrhea in patients with chronic diarrhea"(1). Bile acid malabsorption (BAM) and bile acid diarrhea (BAD) are not rare findings, but they are rather overlooked diagnoses. Indeed, about 25-30% of patients complaining of functional diarrhea (FD) and/or irritable bowel syndrome with diarrhea (IBS-D) could have BAM (2, 3) and the lack or the delay of diagnosis is highly cost-effective for both patients and the society, leading to pointless and/or expensive prescription of tests

and drugs(4, 5). So, in our opinion, the study by Costa et al. has the great merit of highlighting the need to evaluate the prevalence of BAD in patients with chronic diarrhea and discussing the way to reach an effective diagnosis.

Indeed, different methods, serological, fecal and scintigraphic, have been suggested (6) but, at present, they are rarely carried out, or are completely unavailable in many countries.

Therefore, it is not surprising, as the authors report, that empiric testing with cholestyramine, a bile acid sequestrant (BAS), is used in everyday clinical practice to diagnose BAM. In fact, it is less expensive and immediately available everywhere. Unfortunately, this is not supported by any quantitative data, because there is no consensus about the right dosage (from 4 to 36 gr/day are reported in the literature) and the adequate duration (10 days? 4 weeks?) of such a trial (6).

Finding the adequate dosage is not simple, especially in patients taking many drugs e.g. elderly patients, because cholestyramine, and generally all BASs may lead to malabsorption of fats and liposoluble vitamins (A, D, and K), increasing the risk of osteoporosis and coagulation abnormalities, and can interact with different types of drugs, thus decreasing their efficacy (6).

So, the risk of both overtreatment or undertreatment are not negligible (7).

Moreover, it is also important to clearly establish the degree of symptom improvement considered sufficient in order to judge the empiric test positive and which is the time period, after cholestyramine is stopped, to be considered adequate (6).

Furthermore, evaluating only the clinical response to BASs could give false positive results due to a placebo effect, which is not uncommon when treating patients with functional digestive disorders. Or the false positive could also be on account of the lack of specificity of cholestyramine, which may inactivate some diarrhea etiological agents such as the *Clostridium difficile* toxin (6, 8, 9). This could lead to an inappropriate, prolonged, sometimes lifelong, prescription of a drug which is not very easy to manage (8).

On the other hand, false negative results for poor compliance with the drug are not to be neglected (6). Indeed, cholestyramine has a very poor palatability, so, even if it is effective, some patients autonomously decide to stop the intake or, at least, decrease its dosage, even only a few weeks after starting the therapy (10). Unfortunately, in most countries, e.g. Italy, cholestyramine is the only BAS available, and colesevelam, more expensive but more palatable because marketed in tablets, is not available (11).

For these reasons different guidelines (4, 7, 12) report insufficient evidence to recommend use of an empirical trial with BASs, rather than making a positive diagnosis using determination of serum 7α -hydroxy-4 cholesten-3-one (C4) or Fibroblastic Growth Factor 19 (FGF-19) levels, or the 75-selenium homocholic acid taurine (SeHCAT) test.

Even if specificity and sensitivity of these tests need to be further improved and the normal values of C4 and FGF 19 are not yet universally shared (7, 12), a recent systematic review (13) showed an association between the severity of BAM, evaluated by SeHCAT, and response to cholestyramine. Moreover, a quantitative BAM evaluation could make doctors more confident in increasing the dosage of a drug not

devoid of adverse events and, on the other hand, a confirmed, instrumental, diagnosis could encourage the patients to start and to stay on a poorly palatable therapy like BASs, motivating them to adhere more strictly to the treatment (7).

Unfortunately, in most countries BAM diagnostic tests are usually available only at tertiary referral centers, due to their costs or to the relatively poor awareness of gastroenterologists regarding the importance of this disturbance. Therefore, a blind empirical test often remains the first diagnostic choice suggested to most patients.

It is hoped that gastroenterologists, nuclear doctors and laboratory doctors can strongly work together to better detect normal and shared values of serological tests and compare them with the SeHCAT test, which is, currently, the “gold standard” for BAM diagnosis.

So, the diagnostic tests could be increasingly widespread and made accessible to all patients with suspicion of BAM and/or diarrheic symptoms who need the clearest diagnosis possible.

References

1. Costa S, Gattoni S, Nicolardi ML, et al. Prevalence and clinical features of bile acid diarrhea in patients with chronic diarrhea. *J Dig Dis.* 2021;22(2):108-12.
2. 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(12):1951-9.
3. Camilleri M. Bile Acid diarrhea: prevalence, pathogenesis, and therapy. *Gut Liver.* 2015;9(3):332-9.
4. Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut.* 2018;67(8):1380-99.
5. Turner JM, Pattni SS, Appleby RN, Walters JR. A positive SeHCAT test results in fewer subsequent investigations in patients with chronic diarrhoea. *Frontline Gastroenterol.* 2017;8(4):279-83.

6. Fani B, Bertani L, Paglianiti I, et al. Pros and Cons of the SeHCAT Test in Bile Acid Diarrhea: A More Appropriate Use of an Old Nuclear Medicine Technique. *Gastroenterol Res Pract*. 2018;2018:2097359.
7. Sadowski DC, Camilleri M, Chey WD, et al. Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea. *J Can Assoc Gastroenterol*. 2020;3(1):e10-e27.
8. Puri BK, Hakkarainen-Smith JS, Monro JA. The potential use of cholestyramine to reduce the risk of developing *Clostridium difficile*-associated diarrhoea in patients receiving long-term intravenous ceftriaxone. *Med Hypotheses*. 2015;84(1):78-80.
9. McCoy RM, Klick A, Hill S, Dull RB. Luminal Toxin-Binding Agents for *Clostridium difficile* Infection. *J Pharm Pract*. 2016;29(4):361-7.
10. Bellini M, Pancetti A, Ciranni F, et al. Mo1555 BILE ACID MALABSORPTION: AN OVERLOOKED DIAGNOSIS? *Gastroenterology*. 2020;158:S-893.
11. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother*. 2001;35(7-8):898-907.
12. Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). *Gastroenterology*. 2019;157(3):851-4.
13. Ruiz-Campos L, Gisbert JP, Ysamat M, et al. Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy. *Aliment Pharmacol Ther*. 2019;49(3):242-50.