Bile acid Diarrhea(BAD)

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Digestive Healthy Day 2026



Chronic Diarrhea; Don’t Flush Signs away

Introduction:

- **BAD** : **dysregulated recycling** of bile acids within the enterohepatic circulation
- **BAD**, sometimes also known as **bile acid malabsorption** or **bile salt malabsorption**
- **characterized by:**
  - ✓ excessive biosynthesis
  - ✓ excessive secretion
  - ✓ malabsorption of bile acids by the ileum

The presence of unabsorbed bile acids in the colon induce diarrhea

Int. J. Mol. Sci. 2024, 25, 1544.

➢ **Prevalence of BAD is relatively high.**

- **25%** of chronic diarrhea are diagnosed with BAD.
- Patients with **IBS**, around **30%** have an underlying condition of **BAD**

➢ **The mechanisms of diarrhea:**

✓ stimulation of fluid, mucus, or sodium secretion

✓ enhancement of gastrointestinal motility

✓ mucosal damage

✓ promotion of defecation

Korean J Gastroenterol. 2024 Apr 25;83(4):133-142.
Int. J. Mol. Sci. 2024, 25, 1544; Frontline Gastroenterology 2021;12:500–507.

- The pathophysiology of BAD is dependent on an excess passage of bile acids (**BA**s) from the small bowel to the colon

1) Overproduction of BAs

a)Decreased feedback inhibition of BAs synthesis

- i. Impaired ileal fibroblast growth factor (FGF)19 production
- ii. Hepatic resistance to FGF19 effect

b) Associated with hypertriglyceridemia

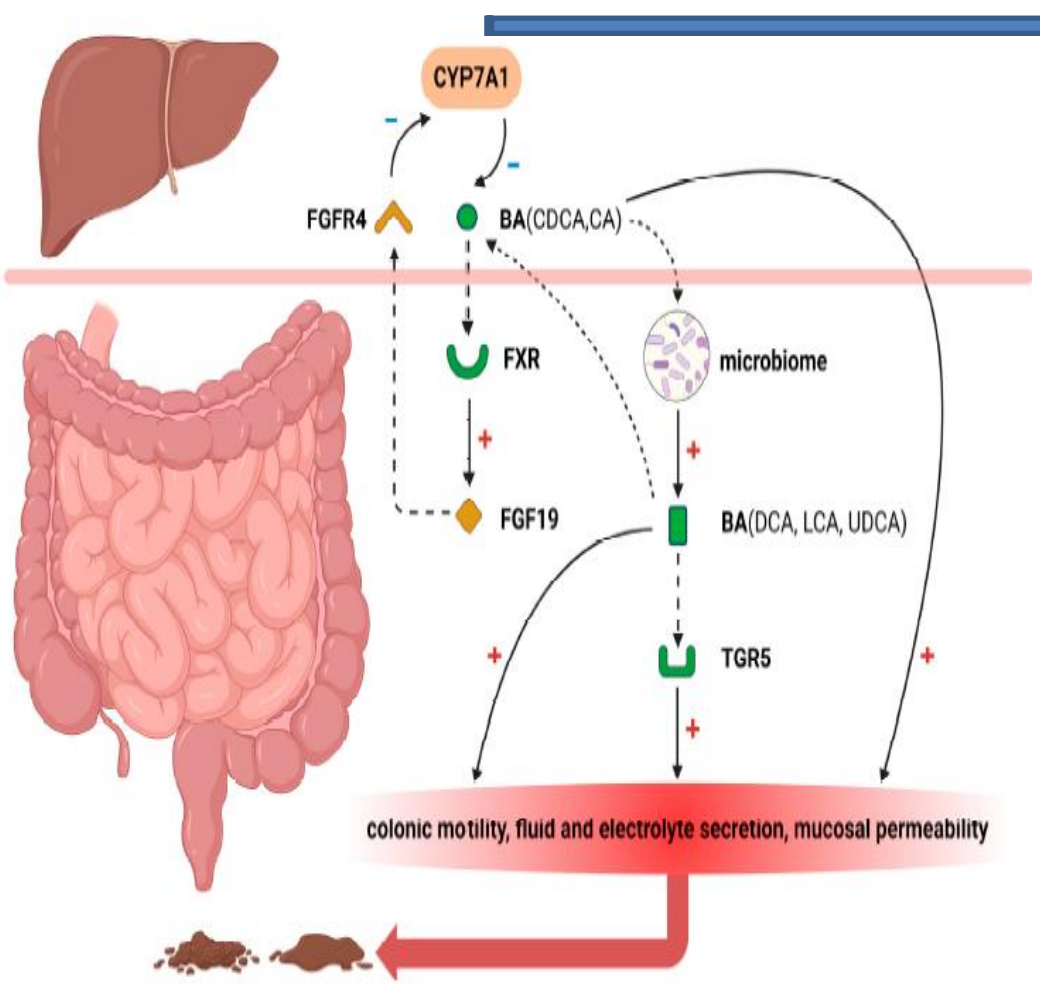
2) Impaired reabsorption of BAs

a. ileal disease /resection

b. other intestinal disorders

pathophysiologic mechanisms

due to the influence of bile acids in the colon



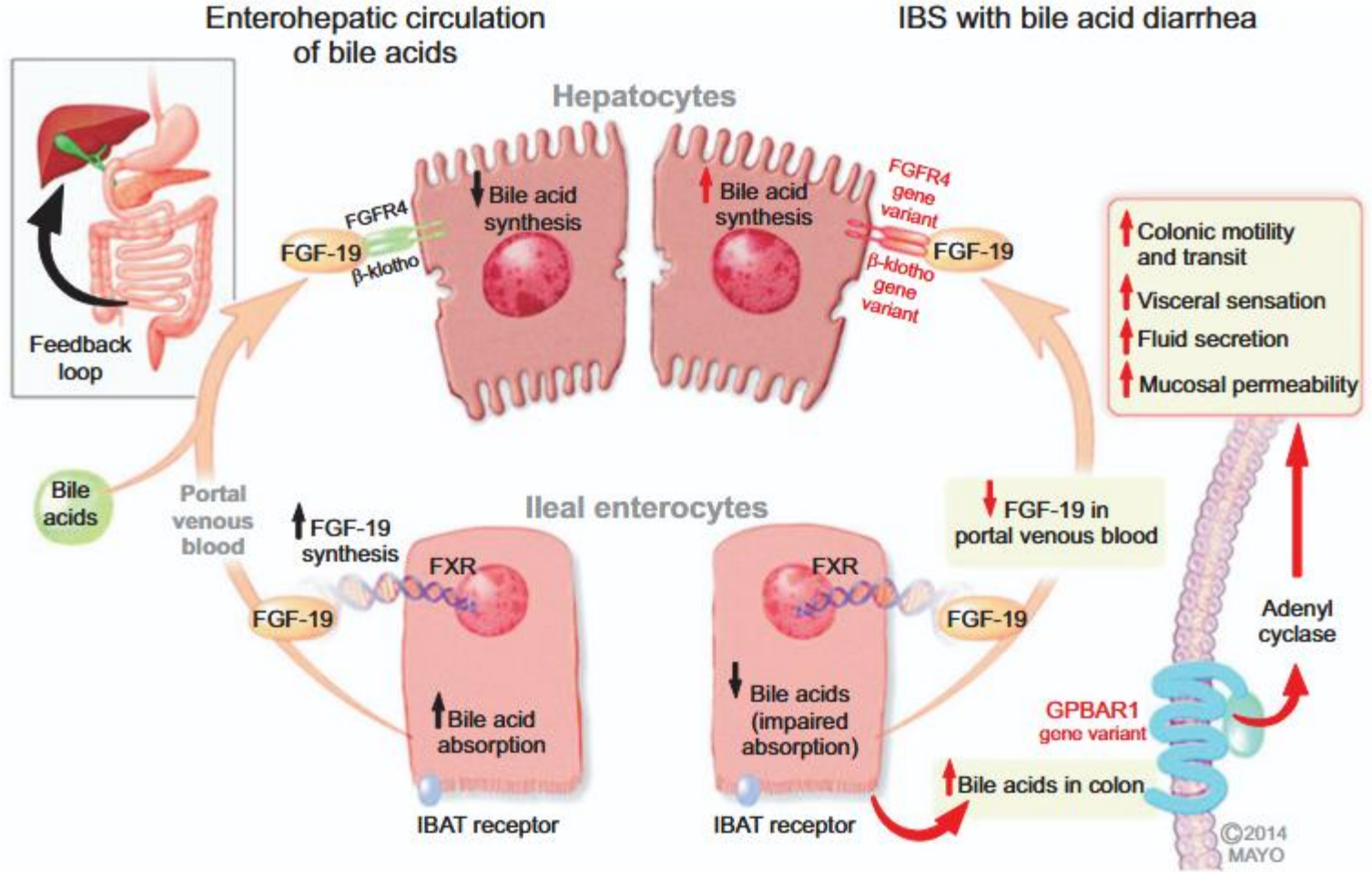
- bile acids activate the farnesoid X receptor(FXR)

It cause production of fibroblast growth factor 19 (FGF19)

It bind to FGF receptor 4

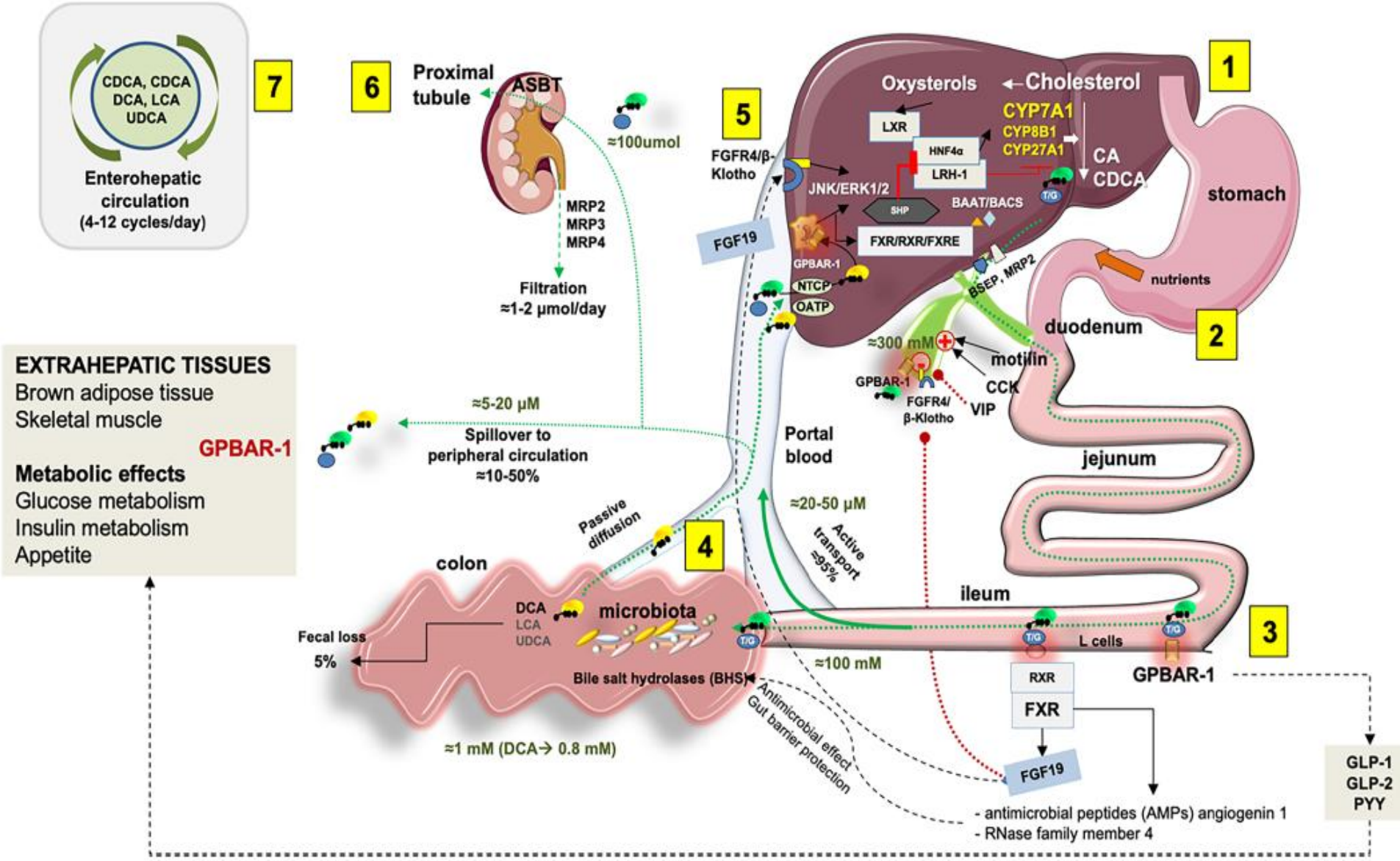
That influence on cholesterol 7α hydroxylase and eventually BAs synthesis in hepatocytes

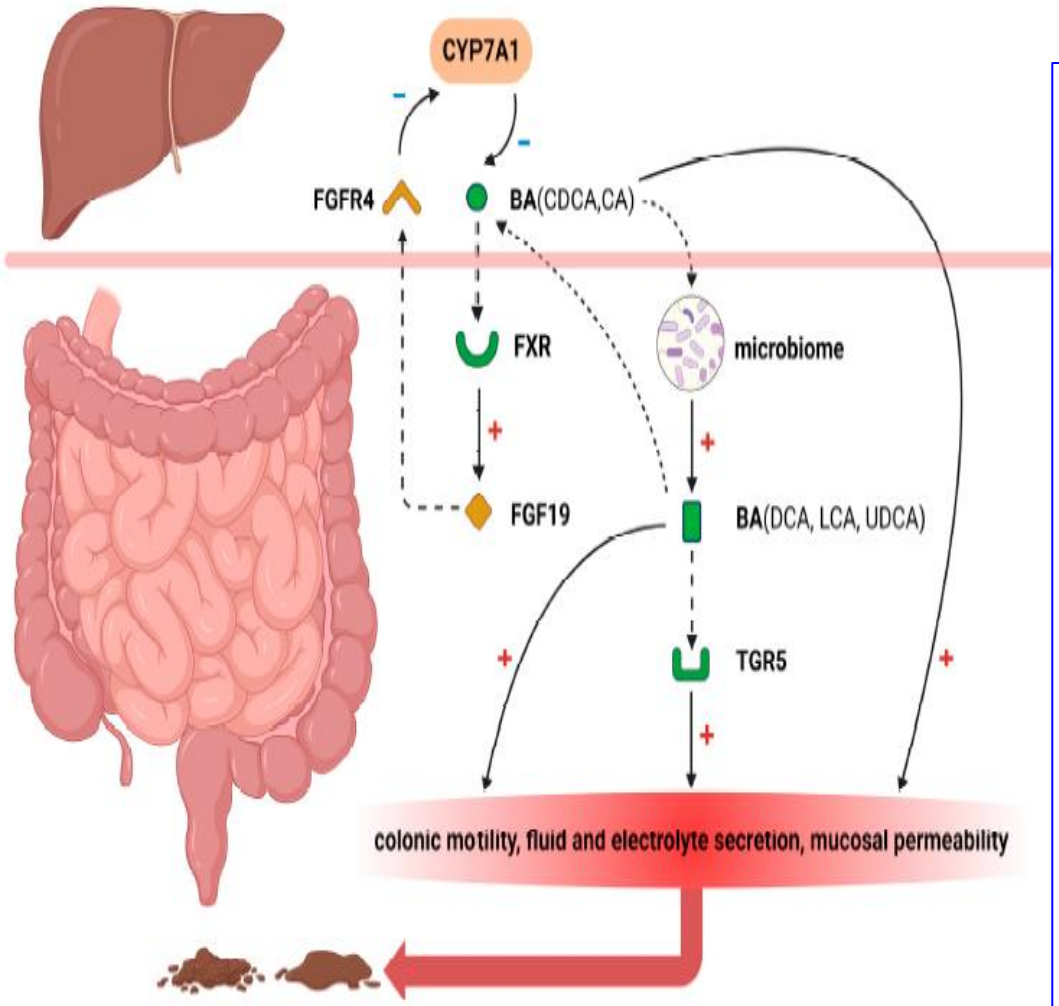
Int. J. Mol. Sci. 2024, 25, 1544



Mechanisms of bile acid (BA)-related bowel dysfunction in IBS with diarrhea (IBS-D) or idiopathic BA diarrhea

Bile acid (BA) biosynthesis, enterohepatic circulation and function through their receptors and enterohormones in the liver and intestine.





Bile released into the gut,
1-primary bile acids can be converted into secondary bile acids
2-secondary bile acids are passively absorbed and subsequently recycled back to the liver
3-they may interact with Takeda G proteincoupled receptor 5(TGR5).
4-the excessive **accumulation** of diverse **bile acid**s in the **gut** can also **stimulate** colonic **motility**, **fluid, and electrolyte secretion**, and enhance mucosal **permeability**, ultimately leading to **diarrhea**—a cardinal manifestation of **BAD**

Fibroblast growth factor 19 (FGF19) is a bile acid–farnesoid X receptor (FXR)-dependent hormone produced in the ileum

FXR promotes increases in FGF19 expression and concentration in the blood

BA overproduction due to impaired feedback inhibition by FGF19 might be the cause of the primary disorder

Therapeutic strategies to increase FGF19 expression and concentration are a new approach to treat BAD

1) **Liver:** primary BAs are mainly synthesized from cholesterol
2) **Gallbladder:** bile is stored, concentrated and periodically secreted in the duodenum during gallbladder contraction
3) **Terminal ileum:** BAs activate FXR and increase the transcription of the enterokine FGF19 in humans which enters the portal circulation and regulates both gallbladder and liver effects BAs
4) **Terminal ileum-colon:** BAs are efficiently (i.e., >95%) reabsorbed in the terminal ileum. The remaining BAs enter the colon, undergo biotransformation to the secondary BAs by the resident gut microbiota, and undergo passive diffusion and reabsorption.
5) **Kidney:** BAs also undergo renal uptake by the apical sodium/dependent BA transporter (ASBT) in the proximal tubule. Glomerular filtration of BAs is regulated by MRP 2, 3, 4 transporters
7) **Enterohepatic circulation of BAs:** consists of 4-12 cycles daily of both primary, secondary, and tertiary conjugated and unconjugated

Types and Classification

BAD, classified into four subtypes:

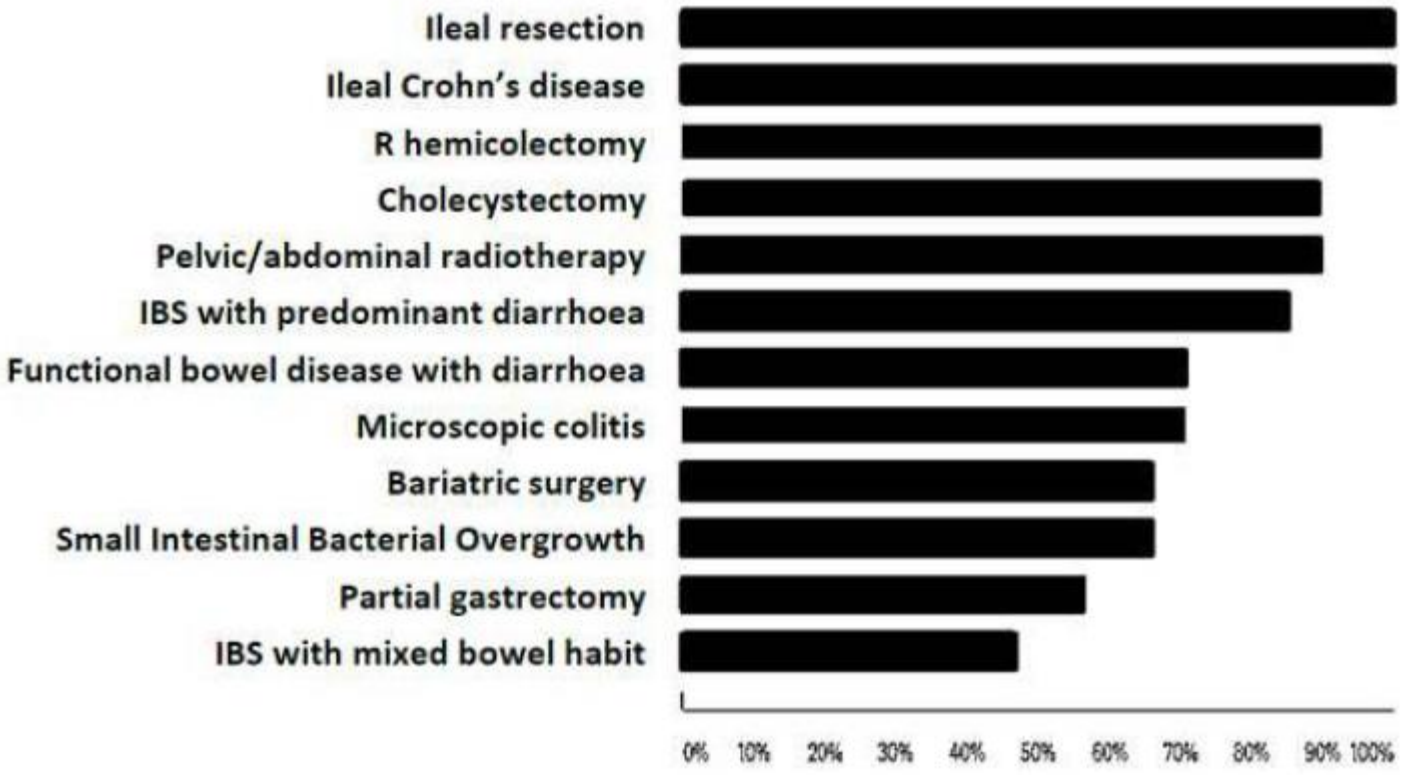
Type 1:malabsorption of BAs due to conditions that prevent the reabsorption of BAs in the ileum ,such as: CD , extensive surgical resection of the ileum, and abdominal radiation therapy
Patients develop **osmotic diarrhea** or true **steatorrhea** due to the consequent malabsorption of fats

Type2:called idiopathic and is associated with primary BAD or IBS- D or Functional Diarrhea (FD)
reduced microbial biotransformation of primary to secondary BAs also some genetic variants, gut microbiota dysbiosis, associated to the greater bioavailability of primary BAs

Type 3: This category includes malabsorption or gut dysmotility , due to biliary-pancreatic diseases, celiac disease, or post- cholecystectomy outcomes and microscopic colitis

Type 4: Type 4 BAD depends on excessive BA synthesis and essentially occurs in hyper TG and antidiabetic therapy with metformin

Conditions with a higher incidence of bile acid diarrhea.



Frontline Gastroenterology 2020;

BAD clinical manifestations

- Patients commonly complain of frequent, watery bowel movements, with urgency, abdominal pain, bloating, and fecal incontinence
- Systemic symptoms including **fatigue**, **dizziness**, and feeling of **fainting** are also frequently reported
- Patients with unexplained diarrhea or IBS-D who have increased fecal BAs excretion typically have **higher BMI**, **increased stool weight and fat**, and **accelerated colonic transit** compared to patients without increased fecal BAs excretion



Digestive and Liver Disease 57 (2025) 680–687

Symptoms routinely leading to consideration

Symptoms	% of respondents
Always having loose stools	86
Frequency of bowel movements >6×/day	86
Frequency of bowel movements 3–6×/day	81
Intermittent loose stools	76
Faecal urgency at least weekly	67
Faecal incontinence at least weekly	62

Gastroenterology 2019;156:1233–8
Frontline Gastroenterology 2020;**11**:358–363

- Symptoms that the majority **did not** routinely consider BAD included

weight gain or loss combined with loose stools,
variable loose and hard stools, anal faecal soiling, frequency between 1 and 3 times/day,
bdominal pain associated with or relieved by defaecation or specific yellow or green coloured stools.

Diagnostic tests:

1-Selenium HomotauroCholic Acid Test (SeHCAT):

As the **gold standard** administering radiolabeled taurocholic acid followed by measuring the excretion rate of the radiolabeled isotope after 7 days

2-48 h Fecal Bile Acid Test:

high-performance liquid chromatography (HPLC) or mass spectrometry is employed to measure fecal bile acids

- It is recommended to combine the measurement of primary bile acids with total fecal bile acid content to make a more accurate judgment

3-Diagnostic Therapy

such as cholestyramine or colesevelam are selected for diagnostic therapy based on the patient's clinical symptoms and medical history

➢ Existing Diagnostic Methods

4- Molecular Biomarkers Detection

high-level C4 or low-level FGF19 can indicate the presence of BAD
Provide a the direct assessment of hepatic synthesis, secretion, and intestinal absorption of bile acids

Other Potential Molecular Biomarkers Detection

The binding of bile acids to TGR5 and **FXR** represents a potential diagnostic approach for BAD.

Urine: volatile organic compounds(VOC) detection of *2-propanol* and *acetamide* as markers of BAD,

J. Pharm. Pharmacol. 2021,73, 855–861. Gels **2023**, 9, 500.; Liver Physiol. **2020**, 318, G554–G573; Cell Metab. **2021**, 33, 791–803.e7.

75Selenium HomotauroCholic Acid Test (75SeHCAT)

For the assessment of BAs retention in the body

severe malabsorption : 7-day whole-body retention of 75SeHCAT <5%

severe and moderate malabsorption: <10%

mild to moderate malabsorption: <15%

SeHCAT for BAD: Sensitivity (80-94%) Specificity (70-100%)

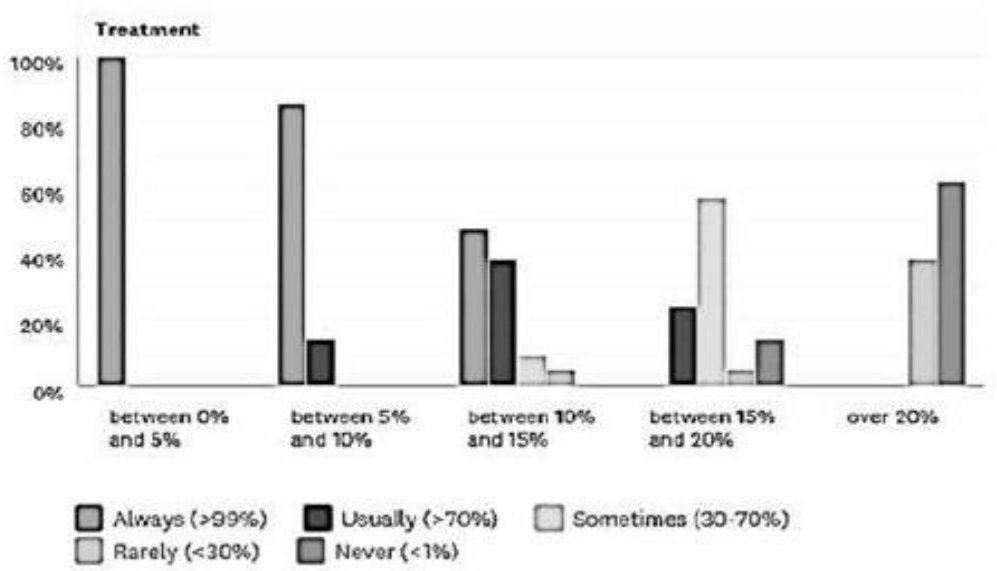
Disadvantages:

Relatively expensive

Needs nuclear department

It is nor for exclusion of other etiology

Likelihood of treatment according to SeHCAT result



Rev Esp Med Nucl Imagen Mol . 2017 Jan-Feb;36(1):37-47.

Frontline Gastroenterology 2020;**11**:358–363

Current BAD diagnostic tests

Potential treatment methods are based on the underlying mechanisms of diagnostic tests

Diagnostic Test	^{75}SeHCAT	48 h Fecal Bile Acid Test	BAS Diagnostic Therapy	Serum C4	Serum FGF19
Molecular mechanism	Radionuclide-labeled reagents; Simulate bile acid metabolism	Dietary manipulation replicates bile acid metabolism.	Drugs chelate excess bile acids.	C4 is a rate-limiting enzyme in the synthesis of bile acids.	FGF19, FXR, FGFR4 facilitate endogenous bile acid synthesis.
Diagnostic criteria	<5% (severe) <10% (moderate) <15% (mild)	Total fecal Bas ≥ 2337 μmol/48 h; OR Primary BA > 4% + total fecal BA > 1000 μmol/48 h OR Primary BA> 10%	Based on the patient's clinical symptoms	>52.5 ng/mL	<61.7 pg/mL
Advantage	Reliable; High Sensitivity and Specificity	Quantitative assessment of BAs; No radiation	Non-invasive test; widely used; No radiation	relatively simple; No radiation	No radiation; commercial ELISA assay
Disadvantage	Expensive; Not be widely available; Radiation exposure	Collection Challenges; Interpretation Complexity	No clear diagnosis; Potential Side Effects; Poor compliance	Non-specificity; Variation; Confirmation required	Confirmation required
Potential treatment method	Reduce the generation and excretion of bile acids in the body			FXR agonists; Anti-C4 drugs	FXR agonists; FGF19 analog

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Test	Diagnostic accuracy	Notes
Fecal BA content	• 45% sensitivity, 63% specificity of detecting ^{75}SeHCAT <15% with primary BAs >10%; • - total fecal BAs alone >2337 μmol/48 h: similar diagnostic accuracy than elevated primary BAs alone or in combination with total fecal BAs >1000 μmol/48 h in patients with BAD [10,36]	• It is advisable to combine the measurement of total fecal BAs content with percentage of primary fecal bile acids to increase the diagnostic accuracy [7].
Selenium HomotauroCholic Acid Test (^{75}SeHCAT)	• 94% sensitivity, 100%, specificity in diagnosing chronic diarrhoea *vs* healthy subjects [147]. • 87.32% sensitivity, 93.2% specificity when compared to sensitivity and specificity of serum levels of 7α-hydroxy-4-cholesten-3-one (85.2% and 71.1%, respectively) [148].	• The test with the highest accuracy [31] • The diagnostic accuracy for BAM increases with ^{75}SeHCAT retention rate <10% [31]

Fasting Serum 7α-hydroxy-4-cholesten-3-one (C4)	• 82.6% sensitivity, 84.3% specificity for detecting BAM [31,41]. • fasting serum C4 > 48.4 ng/mL: 90% sensitivity, 79% specificity, as compared to ^{75}SeHCAT retention value of < 10% [43] • NPV 98%, PPV 74%, as compared with ^{75}SeHCAT test [46]	• Combination of C4 detection with ≥1.1 daily watery (Bristol type 6-7) stools: 70% sensitivity, 95% specificity. • Combining C4, the sum of measured stool BAs, and daily watery stools increased the sensitivity to 77%, with 93% specificity [52].
Fasting Serum Fibroblast Growth Factor 19 (FGF19)	• Fasting serum FGF19 < 145 pg/mL: 58% sensitivity, 84% specificity [44]; • FGF19 <60 ng/L: 80% sensitivity, 68% specificity in chronic diarrhoea from Crohn's ileitis [149].	• Biohumoral diagnosis of BAM possible with decreased FGF19 and elevated C4 levels [48].

Comparison of diagnostic methods of bile acid diarrhea

Diagnostic method	Favourable points	Limitations
^{75}SeHCAT	Well established Predicts response to treatment	Involves radiation Limited availability in certain countries for example, unavailable in USA
C4	No radiation Simple	Diurnal variation Fasting sample Not widely available (in the UK as a research tool)
FGF19	No radiation Simple Commercial assay available	Diurnal variation Requires further validation
Faecal bile acids/faecal metabolomics	No radiation	Cumbersome 48 hours sample collection versus spot test Not widely available Poor patient compliance
Urine	Easy collection	Experimental Not widely available
Therapeutic trial	Easily available	Unreliable Poor response does not exclude diagnosis of BAD Not cost-effective Delays diagnosis and affects patients quality of life.

Therapy of bile acid-induced diarrhea

The optimal therapeutic approach including understanding the underlying pathophysiological mechanisms that lead to excessive BA entering the colon , treatment option includes:

1. **Dietary modifications**
2. **BA sequestrant therapy (BAST)**
3. **Farnesoid X Receptors (FXR) agonists**
4. **FGF19 analogues**
5. **Glucagon-like peptide-1 (GLP-1) receptor agonists**

Dietary modifications

low-fat diet with <20% of daily energy intake derived from fat (i.e., <30 g per day) can improve :

- ✓ Nocturnal defecation
- ✓ Urgency
- ✓ Abdominal pain, flatulence
- ✓ Stool consistency and frequency

Clin Med (Lond) 2017;17:412–
*European Journal of Internal Medicine 128 (2024) 10–19*8.

BA sequestrant therapy (BAST)

BA sequestrants include cholestyramine, colestipol , and colesevelam are able to improve :

- abdominal symptoms
- stool frequency, and
- stool consistency

BAST can improve symptoms in about 50% of patients

- Among who have undergone **ileal resection**, it is recommended to initiate **empirical BAST**
- Their **side effects** influence on patients compliance

side effects: constipation, bloating, abdominal pain, fullness, nausea, flatulence

Colesevelam has a strong binding affinity to BAs 4–6 times greater than cholestyramine.
it is associated with increased patient adherence,
reduced occurrence of adverse effects such as constipation, dyspepsia, and nausea

Among IBS-D, colesevelam increased total fecal BA excretion, Stool consistency improved along with a reduction in the frequency of bowel movements per week

Other BAS treatments

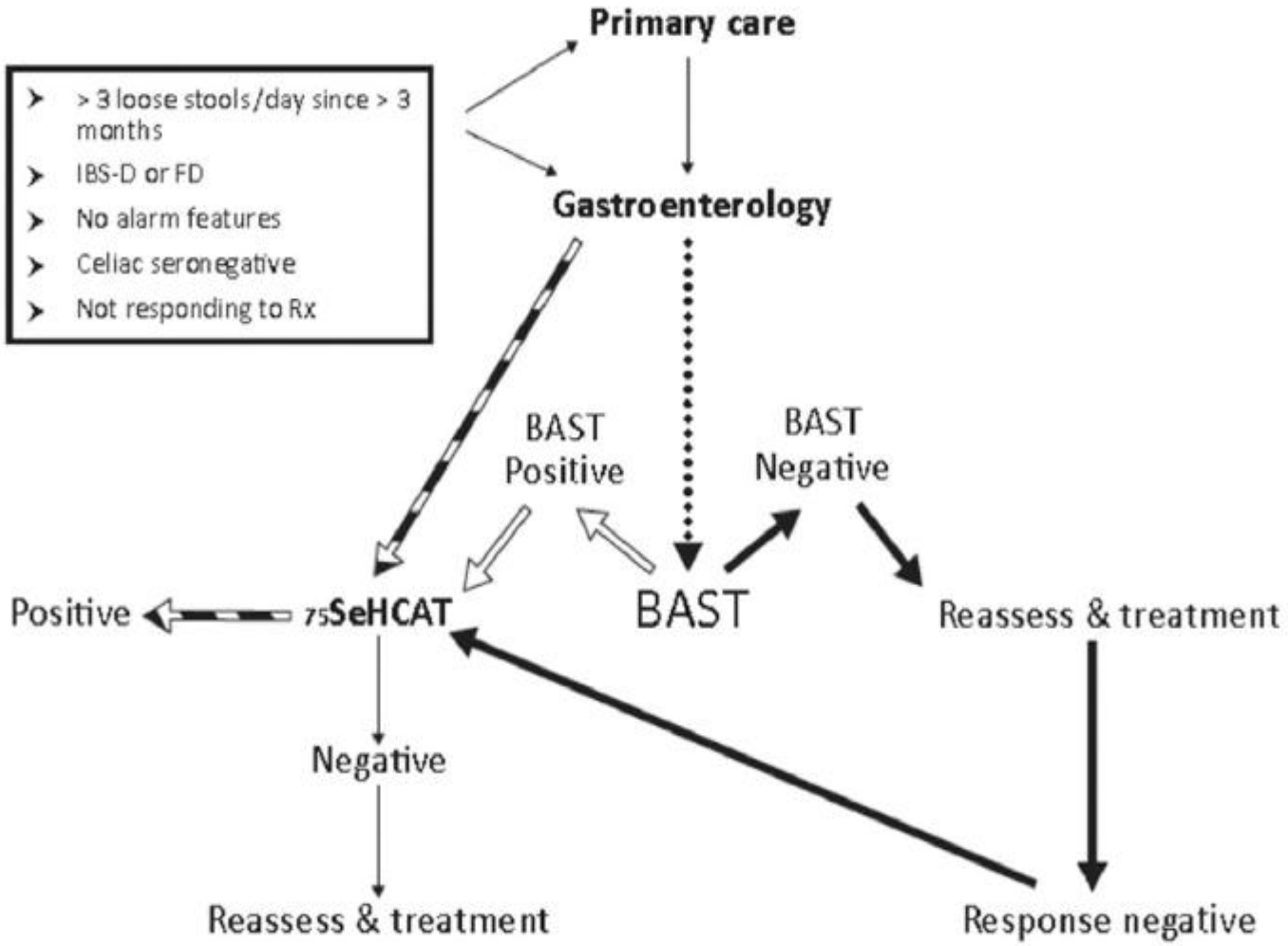
Farnesoid X receptor agonists: decrease chloride secretion in the intestinal epithelium in response to Cal. and cAMP-dependent agonists.
Obeticholic acid: is a potent activator of the FXR pathway, administering 25 mg daily; in both primary and secondary BAD, but not in IBS-D without BAD, obeticholic acid improved stool form and stool index.

Tropifexor: inhibit BAs synthesis and colonic transit was the most effective treatment in raising the FGF19 levels and in reducing C4 levels

Aldafermin: recombinant human FGF19, with high treatment-related adverse events

Glucagon-like peptide-1 (GLP-1) receptor agonists
Liraglutide compared to colesevelam and placebo more efficiently decreased fecal BA concentration reduction in daily stool frequency by 25% or more after 6 weeks of treatment

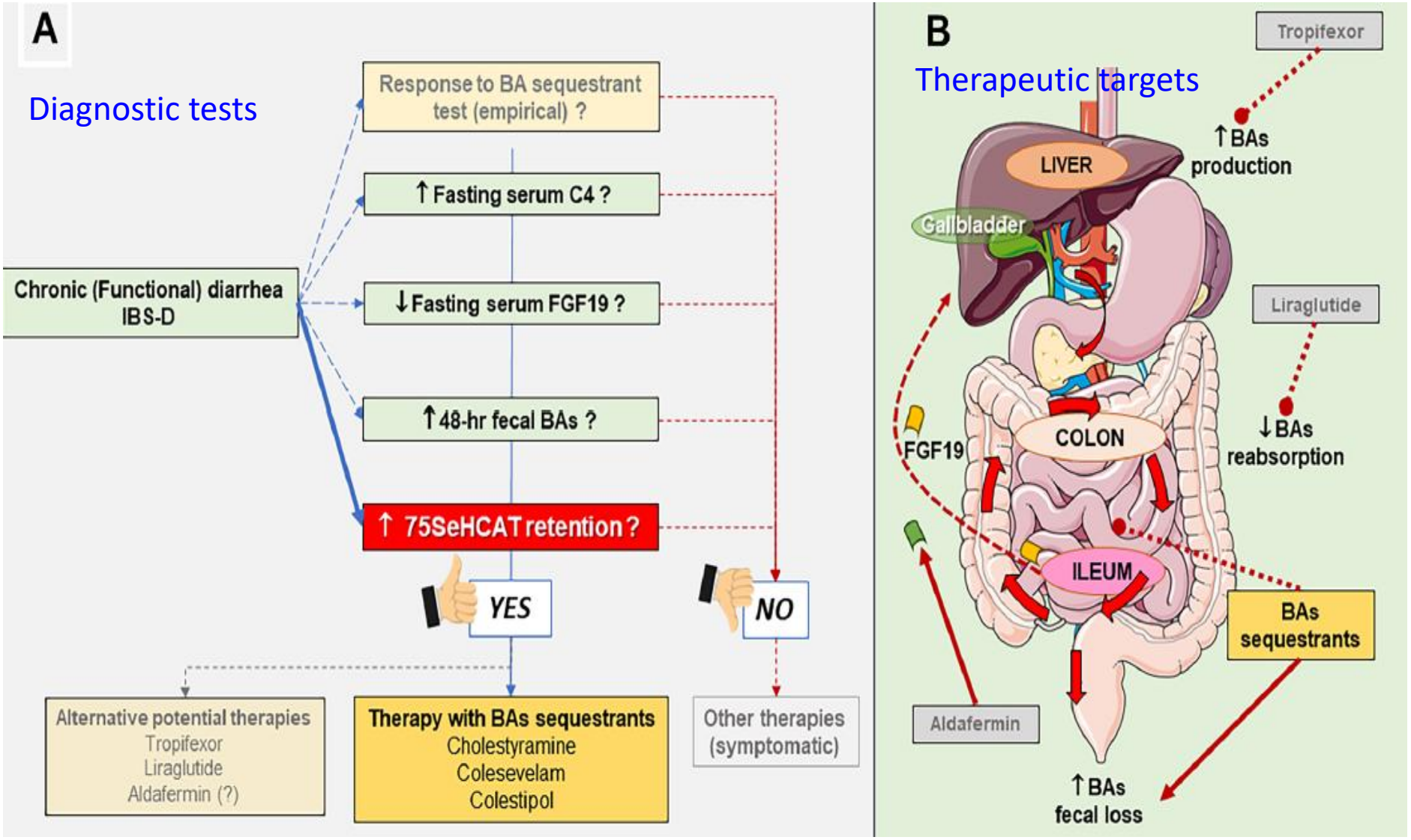
Simple algorithm for BAD diagnosis



BAST: Bile Acid Sequestrant Treatment

Colonoscopy with multiple biopsies > 50years

Diagnosis and management of bile acid diarrhea and malabsorption .



European Journal of Internal Medicine 128 (2024) 10–19

North America Recommendations for the Diagnosis and Management of BAD

Statement 1. we recommend using risk factors (history of terminal ileal resection, cholecystectomy, or abdominal radiotherapy) as the initial assessment to identify patients with possible BAD.

Statement 2. we suggest against using symptom presentation as the initial assessment to identify patients with possible BAD.

Statement 3. among IBS-D and functional diarrhea, we suggest SeHCAT testing to identify patients with BAD.

Statement 4. In patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea, we suggest SeHCAT testing.

Statement 5. In patients with chronic diarrhea including IBS-D and functional diarrhea, we suggest using a C4 assay to identify possible BAD

North America Recommendations for the Diagnosis and Management of BAD: Induction therapy

Statement 6. In patients with suspected BAD, we suggest against initiating empiric BAST over performing SeHCAT to establish a diagnosis of 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

Statement 8. In patients with BAD, we suggest using cholestyramine over other BASTs as initial therapy for induction of clinical response.

Statement 9. In patients with BAD who are unable to tolerate cholestyramine, we suggest using an alternate BAST for induction of clinical response

Statement 10. In patients with BAD receiving empiric BAST, gradual daily dose titration should be used to minimize side effects.

Statement 11. In patients with BAD who respond to BAST, we suggest that intermittent, on-demand dosing be tried.

