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SeHCAT test and Bile Acid Diarrhea

BAD is a chronic watery diarrhea requiring long-term therapy

About 1% of the general population is affected by BAD

(Walters, JR 2010)

About a third of patients labelled with **IBS-D** and **F**D actually suffer from bile acid diarrhoea

(Bannaga A, 2017)
(Valentin N, 2016)
(Fernandes DCR, 2018)

BAM is as common as *coeliac disease*, twice as common as *IBD* and five times as common as *microscopic colitis*

(Walters, JR 2010)
(Mottacki N, 2015)

-BAM is an overlooked diagnosis due to a lack of clinician awareness and access to appropriate investigations: a late consideration in the investigation of chronic diarrhoea
-About 50% with BAM/BAD wait for >5 years to be diagnosed.
-Likely <1 % of BAD pts. are currently diagnosed. ***(Walters, JR 2010)***

-Diagnosis and management remain suboptimal ***(Mottacki N, 2015)***

Pros and Cons of the SeHCAT Test in Bile Acid Diarrhea: A More Appropriate Use of an Old Nuclear Medicine Technique

Bernardo Fani,[1] Lorenzo Bertani,[1] Italia Paglianiti,[2] Lorenzo Fantechi,[2] Nicola De Bortoli,[1] Francesco Costa,[3] Duccio Volterrani,[2] Santino Marchi,[1] and Massimo Bellini[1]

Gastroenterology Research and Practice
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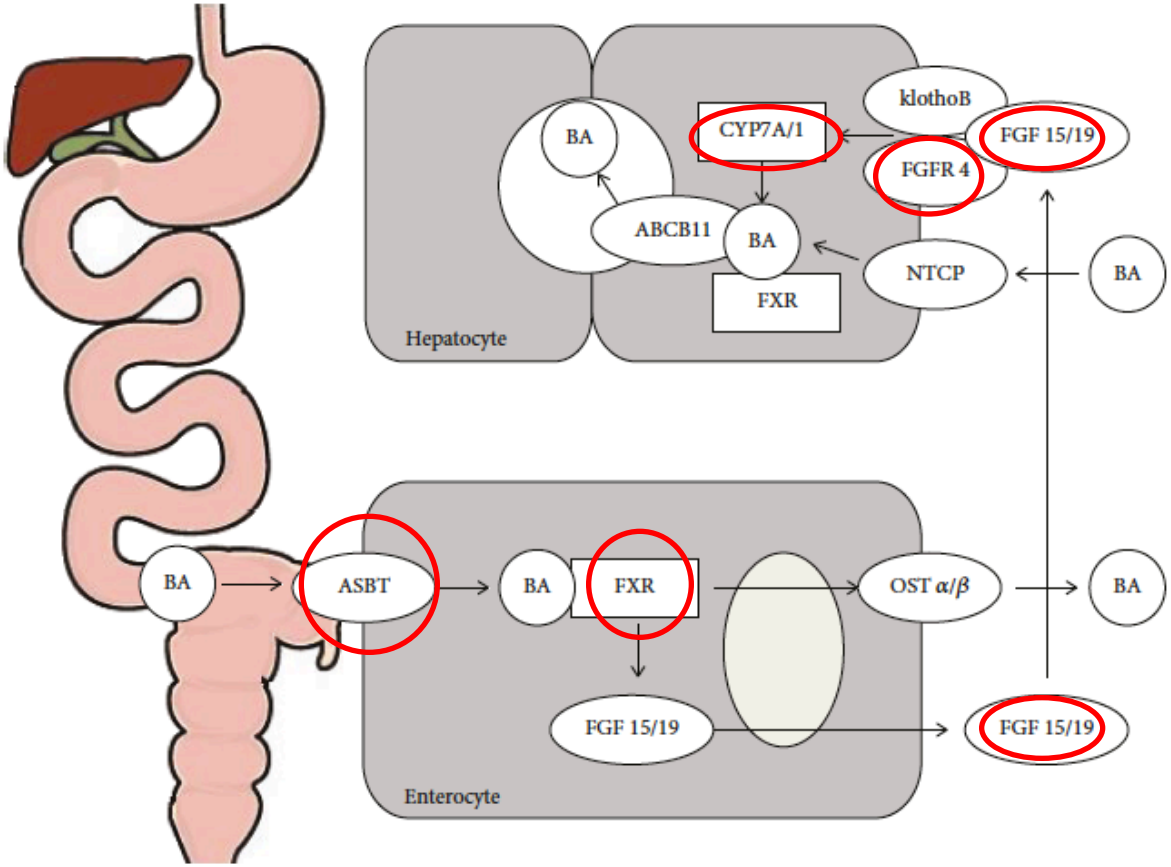

FIGURE 2: Pathophysiology of enterohepatic circulation: bile acids (BAs) excreted in the intestinal lumen are mainly reabsorbed in the ileum through the apical sodium-dependent bile acid transporter (ASBT) and return to the liver through the portal vessels. Stimulation of the farnesoid X receptor (FXR) initiates the production of fibroblastic growth factor 15/19 (FGF-15/19) that interacts in the hepatocytes with cholesterol 7 alpha-hydroxylase (CYP7A/1) and reduces BA synthesis, with a negative feedback mechanism. Mutations in ASBT and klothoB have been demonstrated to be a cause of bile acid malabsorption (BAM).

BAM: defective absorption in the terminal ileum due to ileal disease, mucosal dysfunction or surgical resection.

BAD: due to impaired FGF19 feedback inhibition by a non-diseased, intact ileum > excessive bile acid synthesis by the liver, overwhelming ileal absorptive capacity > excessive bile salts reaching the colon

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-**Type I:** secondary to ileal dysfunction i.e. failure of reabsorption of bile acids in the ileum because of resection, bypass or Crohn's disease.

-**Type II:** primary idiopathic condition. Decreased plasma levels of ileal fibroblast growth factor 19 (FGF-19) (produced by ileal enterocytes as a response to excess bile acids in the terminal ileum) > impaired negative feedback loop on hepatic bile acid synthesis through the farnesoid X receptor > excessive BA synthesis

-**Type III:** GI conditions interfering with the bile acid reabsorption
(cholecistectomy, chronic pancreatitis, SIBO, colitis, celiac disease, radiation-induced enteritis, diabetes mellitus)*

-Type IV: excessive hepatic BA synthesis: i.e. metformin

*BAD Postcholecistectomy: transient or chronic condition?
Real prevalence? (9%- 36%)

(Sciarretta G, 1992)
(Lin S, 2016)
(Slattery 2015)

MECHANISMS

(Camilleri M, 2017)
(Camilleri M, 2015)

-increased mucosal permeability;

-colonocyte water and chloryde secretion (through activation of CFTR via adenylate cyclase and inhibition of apical Cl/OH exchange);

-lubrication by increased mucus secretion (a direct effect on goblet cells);

-acceleration of colonic motility, likely via TGR5 stimulation of myenteric ganglionic neurons and enteroendocrine cells > 5HT. BAs induce colonic HAPCs)

Rapid intestinal transit may reduce the possibility for intestinal microbiota to convert primary bile acids, leading to BAD

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Empirical trial

Not supported by any quantitative data but only by the presence or the absence of a clinical improvement referred by the patients.

False positive for a placebo effect > patients labelled as suffering a chronic condition requiring long-term treatment
False negative for poor compliance with the therapy (or low dose).

Furthermore, the lack of specificity (cholestyramine may inactivate some diarrhea etiological agents such as the Cl. difficile toxin), the possible adverse events associated with BASs (e.g., drug interactions), and the difficulty in determining the effective dosage are not to be neglected.

Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition

Ramesh P Arasaradnam,[1,2,3] Steven Brown,[4] Alastair Forbes,[5] Mark R Fox,[6,7] Pali Hungin,[8] Lawrence Kelman,[9] Giles Major,[10] Michelle O'Connor,[9] Dave S Sanders,[4] Rakesh Sinha,[11] Stephen Charles Smith,[12] Paul Thomas,[13] Julian R F Walters[14]

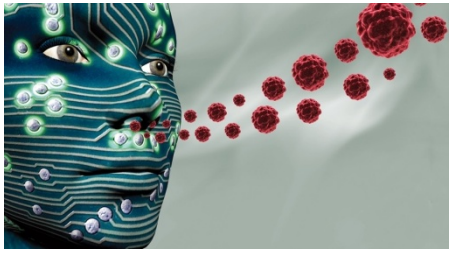
Gut 2018;**0**:1–20. doi:10.1136/gutjnl-2017-315909

Insufficient evidence to recommend use of an empirical trial of treatment for bile acid diarrhoea rather than making a positive diagnosis *(5, strong).*

Five methods can establish the diagnosis of BAM: ***(Mena Bares LM, 2017)***

a) Determination of *bile acids in fecal* material obtained over 24 h: this is a tedious method that is only available in some laboratories.
b) The *14C-glycocholic acid breath test (*limited clinical utility).
c) *Serum C4* levels by liquid chromatography; the greater the synthesis of bile acids the higher the C4 level. False positive results: liver disease; statins. C4 levels may be altered according to the circadian rhythm.
d) *Serum FGF 19* levels by ELISA. Values are inversely related to C4: they are reduced in the presence of BAM.
e) Scintigraphy with *75SeHCAT*: measures abdominal retention (AR) of synthetich omocholic bile acid conjugated with taurine and labeled with 75Se. Widely validated method; good correlation with the loss of bile acids in stools and very low levels of radiation.

Electronic nose to detect Volatile Organic Compounds in the urine: BAD: increased 2-propanol and acetamide compared to healthy controls. ***(Covington JA, 2013)***



SeHCAT®

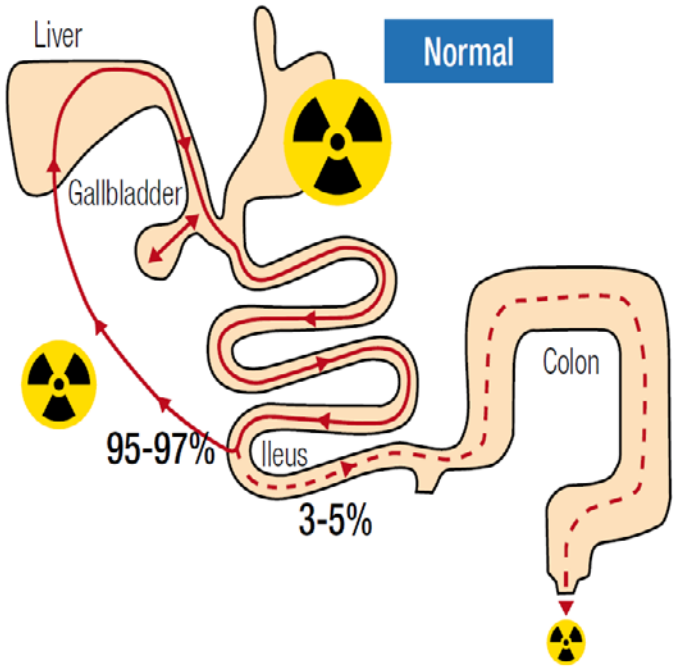
1981 Malcolm Merrick:
Compound G

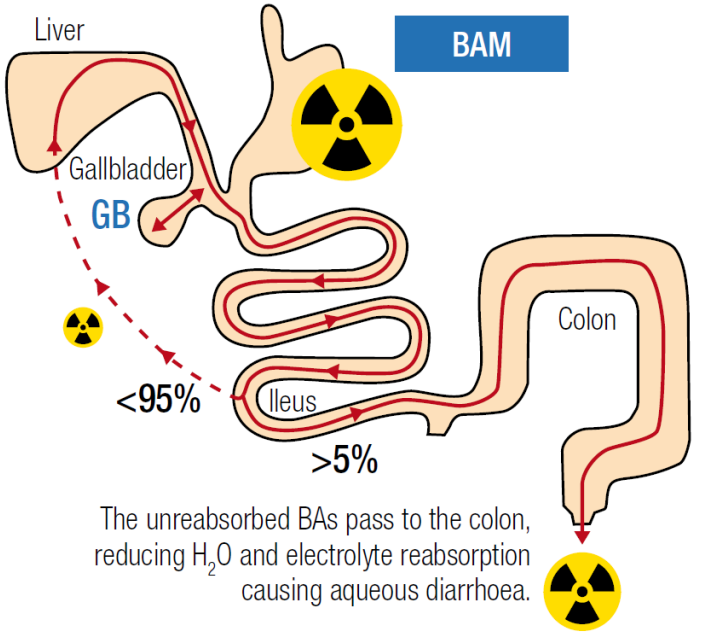
Capsula da 370 kBq (10 µCi)

^{75}Se: T1/2 118 gg
emissione gamma 136 e 265 KeV
SeHCAT: T1/2 biologico 3 gg

(GE Healthcare)

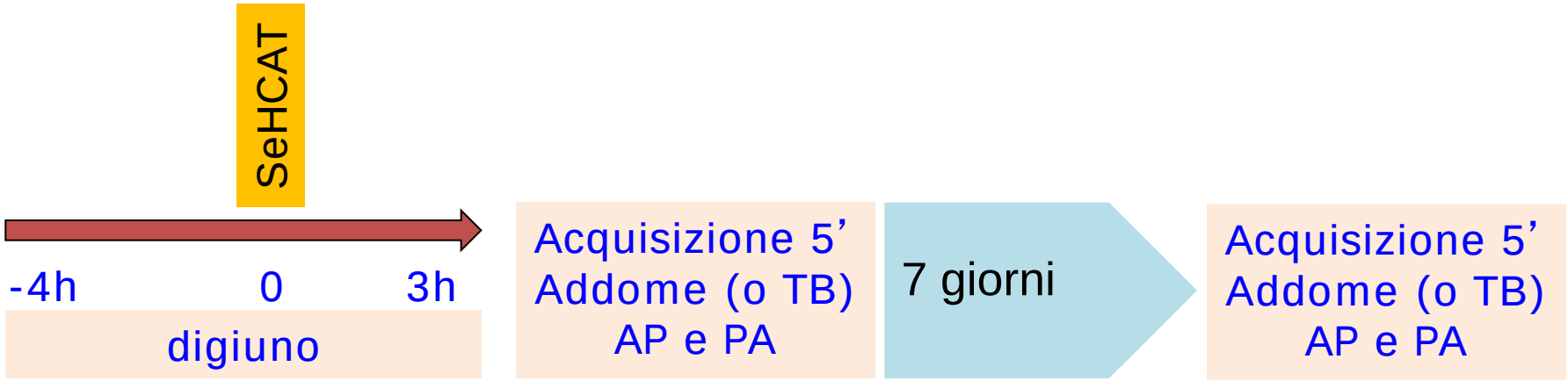
SeHCAT: razionale





L’acido Tauroselcolico non subisce degradazione batterica nel colon e non è sottoposto a diffusione passiva

SeHCAT: protocollo di acquisizione



- **Terapia medica**: **è consigliabile la sospensione**

  sequestranti gli AB (sospensione da 1 a 7 gg)

  lassativi (se possibile durante la settimana dello studio perché teoricamente possono interferire con la misura del test)

***Colonscopia**: attendere almeno 7 gg dall'esecuzione*

SeHCAT: protocollo di acquisizione

$$\frac{DCF \times \sqrt{\{(_{Day7}AP\ Count - {}_{Day7}BG) \times (_{Day7}PA\ Count - {}_{Day7}BG)\}} \times 100}{\sqrt{\{(_{Day0}AP\ Count - {}_{Day0}BG) \times (_{Day0}PA\ Count - {}_{Day0}BG)\}}}$$

Camera settings

Collimator: None (see previous reference to collimated acquisitions)

Energy window: ^{75}Se 137 and 264KeV (20% window)
(Possibly exclude lower window to avoid interference from ^{99m}Tc sources)

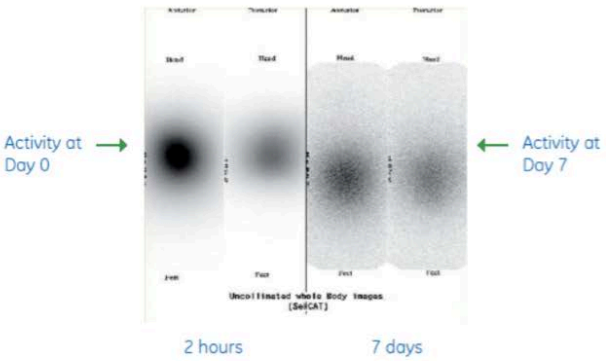
Matrix: Irrelevant

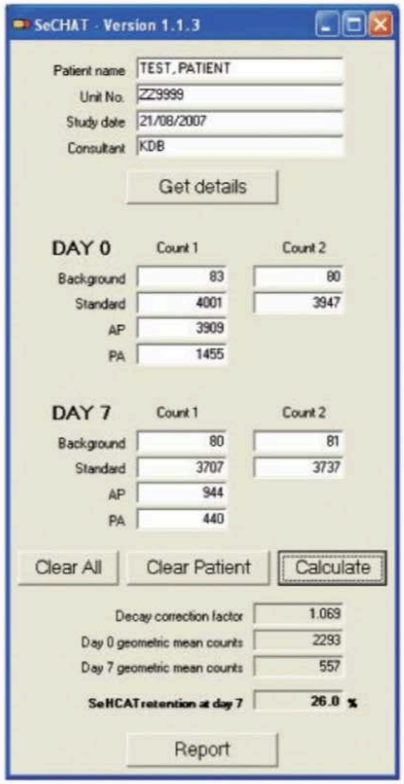
Examples of times of acquisition: Anterior and posterior 300 seconds or 3 minute whole body acquisition head to thigh acquiring anterior and posterior simultaneously.

Detectors: At maximum radius

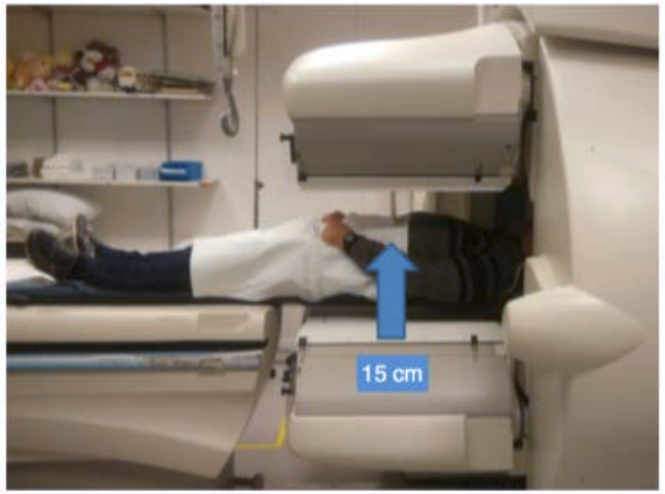
Patient position: Ideally supine or prone.
All acquisitions should be performed with identical parameters.

Results





Less than 10-15% retention at day 7 is abnormal.



SeHCAT

A retention of **10–15%** at 7 days is usually defined as **mild BA loss**, **5–10%** as **moderate** and **0–5%** as **severe**. These values predict response to therapy with BA sequestrants.

Wedlake L, 2009

Dosimetria: dose efficace

SeHCAT

- SeHCAT *0.26 mSv*
- TC Addome *15-25 mSv*
- Scintigrafia ossea *4 mSv*
- PET *7-10 mSv*

"Efficacia" diagnostica

Valori di Sehcat	<5%	<10%	<15%	Totali
n. di studi	5	17	7	18
n. di pazienti	429	1073	618	1223
n. di valori anormali	43	339	163	
% patologici	10%	32%	26%	
% risposta alla colestiramina	96%	80%	70%	

Wedlake et al. Aliment Pharmacol Ther,2009

Special collaboration

^{75}SeHCAT scan in bile acid malabsorption in chronic diarrhea☆

L.M. Mena Bares[a,*], E. Carmona Asenjo[a], M.V. García Sánchez[b], E. Moreno Ortega[a], F.R. Maza Muret[a], M.V. Guiote Moreno[a], A.M. Santos Bueno[a], E. Iglesias Flores[b], J.M. Benítez Cantero[b], J.A. Vallejo Casas[a]

(Mena Bares LM, 2017)

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

Walters JR, et al. *Therap Adv Gastroenterol*. 2010
Wilcox C, et al. *Aliment Pharmacol Ther*. 2014
Mottacki N, et al. *Aliment Pharmacol Ther*. 2016
Sciarretta G, et al. Gastroenterology. 1986
Pattni S et al. Clin Transl Gastroenterol. 2012

On analyzing the diagnostic methods the gold standard is considered to be the ^{75}SeHCAT test based on its sensitivity and specificity (^{75}SeHCAT: 80–94% and 70–100%; C4 levels: 90–97% and 74–77%; FGF19 levels: 58–74% and 72–79%, respectively),[13,17,18]

SeHCAT is the most recommended diagnostic test in Europe for diagnosing BAM as it presents the highest values of sensitivity and specificity. It has a significant cost-benefit ratio, making it the test with the highest degree of recommendation. *However, it is still not possible to use it in a recognised way as a gold standard due to the lack of studies that provide conclusive data that allow consensus.*

(Baena Garcia A, 2019)

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SeHCAT

Advantages

Gold standard for the diagnosis of BAM with high sensitivity and specificity

Simple, safe and well tolerated

Quantitative evaluation of BAM predicts the response to therapy with BASs

More rational use of BASs in relation to possible side effects

Disadvantages

Relatively expensive and usually only available only at third-level centres

SeHCAT does not exclude other causes of organic diarrhoea

Establishing a diagnosis is of great value to motivating compliance and tailoring the patient's therapy at follow-up ***(Mottacki N, 2015)***

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

Treatment	Advantages	Disadvantages	Dosage range and schedule
Colestyramine	Most studied and established treatment Appears to be effective in high proportion of patients	Can be poorly tolerated due to unpalatability and abdominal side effects (come in powders) May reduce the bioavailability of co-administered agents and fat-soluble vitamins (levels therefore need to be monitored and supplemented where necessary)	4 g daily initially, increased by 4 g at weekly intervals (in 1–4 divided doses) to max. 36 g daily. Other drugs should be taken 1 h before or 4–6 h after
Colestipol	May be an effective alternative in those who cannot tolerate taste of colestyramine	Not traditionally indicated and no large-scale studies to date Can be poorly tolerated due to unpalatability (come in granules) and abdominal side effects May reduce the bioavailability of co-administered agents and fat-soluble vitamins (levels therefore need to be monitored and supplemented where necessary)	5 g daily initially, increased in 5 g increments every 1 month to max. 30 g daily Other drugs should be taken 1 h before or 4–6 h after
Colesevelam	Available in tablet form May have improved tolerability Apparent lack of effect on the	Not licensed for BAM No large-scale studies to date Tablets are large in size	3.75 g daily in 1–2 divided doses; max. 4.375 g daily

Efficacy of colestyramine is very high: response rate of around 70% (63-100%) Of the remaining 30% of pts: 16% do not achieve a response because of the lack of efficacy of the drug and 11% due to drug intolerance

(Ruiz-Campos L, 2018)

Long-term effect of medical treatment of diarrhoea in 594 patients with SeHCAT scan diagnosed bile acid malabsorption from 2003 to 2016; a retrospective study

B. Damsgaard[1] | H. R. Dalby[1] | K. Krogh[1] | S. M. D. Jørgensen[1] | A. K. Arveschough[2] | J. Agnholt[1] | J. F. Dahlerup[1] | S. P. Jørgensen[1]

The **severity of symptoms** was significantly associated with **low retention fractions** of SeHCAT. This further supports the clinical use of the test.

SeHCAT: BAM severity and response to colestyramine

Table 2. Summary of studies reporting abnormal SeHCAT values in patients with diarrhoea-predominant IBS [Wedlake *et al.* 2009a].

Reported SeHCAT value	<5%	<10%	<15%	Total
Number of studies reporting	5	17	7	18
Total number of patients	429	1073	618	1223
Number abnormal	43	339	163	
Percentage abnormal [95% confidence intervals]	10% [7–13]	32% [29–35]	26% [23–30]	
Percentage response to colestyramine	96%	80%	70%	

Response to BAS was strongly correlated with whether the SeHCAT scan was positive or not ($p<.001$).

(Murray IA, 2017)

Good or partial response was seen in 15% of those with normal SeHCAT, 65% mild BAD, 73% moderate BAD,and 75% with severe BAD

Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy

Laura Ruiz-Campos[1] | Javier P. Gisbert[2,3] | Montserrat Ysamat[4] | Beatriz Arau[1] | Carme Loras[1,3] | Maria Esteve[1,3] | Fernando Fernández-Bañares[1,3]

Aliment Pharmacol Ther. 2019;49:242–250.

Severe disease (SeHCAT <5%) significant higher short-term response rate to colestyramine than non severe disease (SeHCAT 5%-10%) (62/77 [81%] vs 22/36 [61%], respectively, p = 0.026).

74% BAD pts treated with colestyramine responded to treatment.

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

Aliment Pharmacol Ther 2014; **39**: 923-939

C. Wilcox*, J. Turner† & J. Green†

Colestyramine successful in 559 (70%) patients

"….may not be an association between the severity of BAM and response to colestyramine" *(…but cut-off retention value defined as 'abnormal' and definition of a "response to treatment" varied between the studies)*

42 pz. diarrea cronica: 19 SeHCAT + (45%)

- **Grado Lieve (15-10%):** 9 pz (media: 12,10%)
- **Grado Intermedio (10-5%):** 2 pz. (media 9.60%)
- **Grado Severo (<5%):** 8 pz (media 2.05%)

Colestiramina **4-8 gr/die**

Mancata/sospesa assunzione

2 pz grado lieve: per scarsa compliance
2 pz. grado lieve per patologia organica (etp colon; colite microscopica)
1 pz. grado lieve e 1 pz. grado intermedio (miglioramento con LFD)

Follow up: 9.2 months

Miglioramento sintomatologico globale (0-10)**: 6,1**

-Pazienti con forma lieve (4/9): **3.45** (1-8)
-Pazienti con forma intermedia (1/2): **0**
-Pazienti con forma severa (8/8): **6.85** (4-9)

Long-term effect of medical treatment of diarrhoea in 594 patients with SeHCAT scan diagnosed bile acid malabsorption from 2003 to 2016; a retrospective study

Aliment Pharmacol Ther. 2018;1–7.

B. Damsgaard[1] | H. R. Dalby[1] | K. Krogh[1] | S. M. D. Jørgensen[1] |
A. K. Arveschough[2] | J. Agnholt[1] | J. F. Dahlerup[1] | S. P. Jørgensen[1]

377 BAD pts. (2003-2016)

Retrospective analysis
Follow up duration unspecified

At follow-up

-184 (50%), reported improvement of diarrhoea.
-273 (74%) still reported diarrhoea
-234 (62%) regularly used anti-diarrhoeal medications.
-235 (64%) considered reduced quality of life by diarrhoea

The majority of patients with BAD continued to have bothersome diarrhoea in spite of correct diagnosis by SeHCAT and appropriate initial treatment

This calls for long-term follow-up with **adjustment of treatment** and also for **new treatment principles** for BAD

Long-term response to **colestyramine** was clearly lower than the initial response, which may in part be due to failure to adhere to treatment.

Bad taste; Poor Tolerance: Previous studies reported that >50% of the patients treated with colestyramine, either for dyslipidaemia or for IBS-D, discontinued treatment during the first year.

Interactions may occur with drugs such as glyburide, glimepiride, glipizide, tetracycline, penicillin G, levothyroxine, cyclosporine, olmesartan, phenobarbital, warfarin, digitalis, fat-soluble vitamins and oral contraceptives containing ethinyl estradiol and norethindrone
Patients should generally be advised to take medications either 1 h before or 4 h to 6 h after the bile acid sequestering agent ***(Barkun A, 2013)***

Colesevelam is better tolerated (available in tablet), does not affect the bioavailability of coadministered drugs and may be a good option but, its higher cost limits its use, requiring a bile acid diarrhoea confirmation test

Challenging current views on bile acid diarrhoea and malabsorption

Matthew Kurien,[1] Elizabeth Thurgar,[2] Ashley Davies,[2] Ron Akehurst,[2] Jervoise Andreyev[3]

Frontline Gastroenterology 2017;**0**:1–6. doi:10.1136/flgastro-2017-100808

BAD/BAM are being increasingly described in patients ***during and after cancer treatment***: evidence shows that cancer treatment is a common cause of diarrhoea-with chemotherapy, biological treatments after many forms of GI surgery and pelvic radiotherapy (during and after) *compromising* these peoples' opportunity to receive curative *therapy* and enormously *increasing the cost of cancer care* delivery

Economic evaluation needs to be reconsidered as the impact of not making a positive diagnosis leads to repeat (unnecessary) testing with additional cost to the NHS.

Making a positive diagnosis of BAM (using SeHCAT) was economically beneficial as those who had negative SeHCAT tests underwent significantly more investigations (1.8x more), especially cross-sectional imaging (13x more likely), although those with a positive SeHCAT had more clinical appointments.

A positive diagnosis of bile acid diarrhoea, made by a SeHCAT test, resulted in reduced use of diagnostic investigations **(CT and MRI)** over the subsequent 5 years.

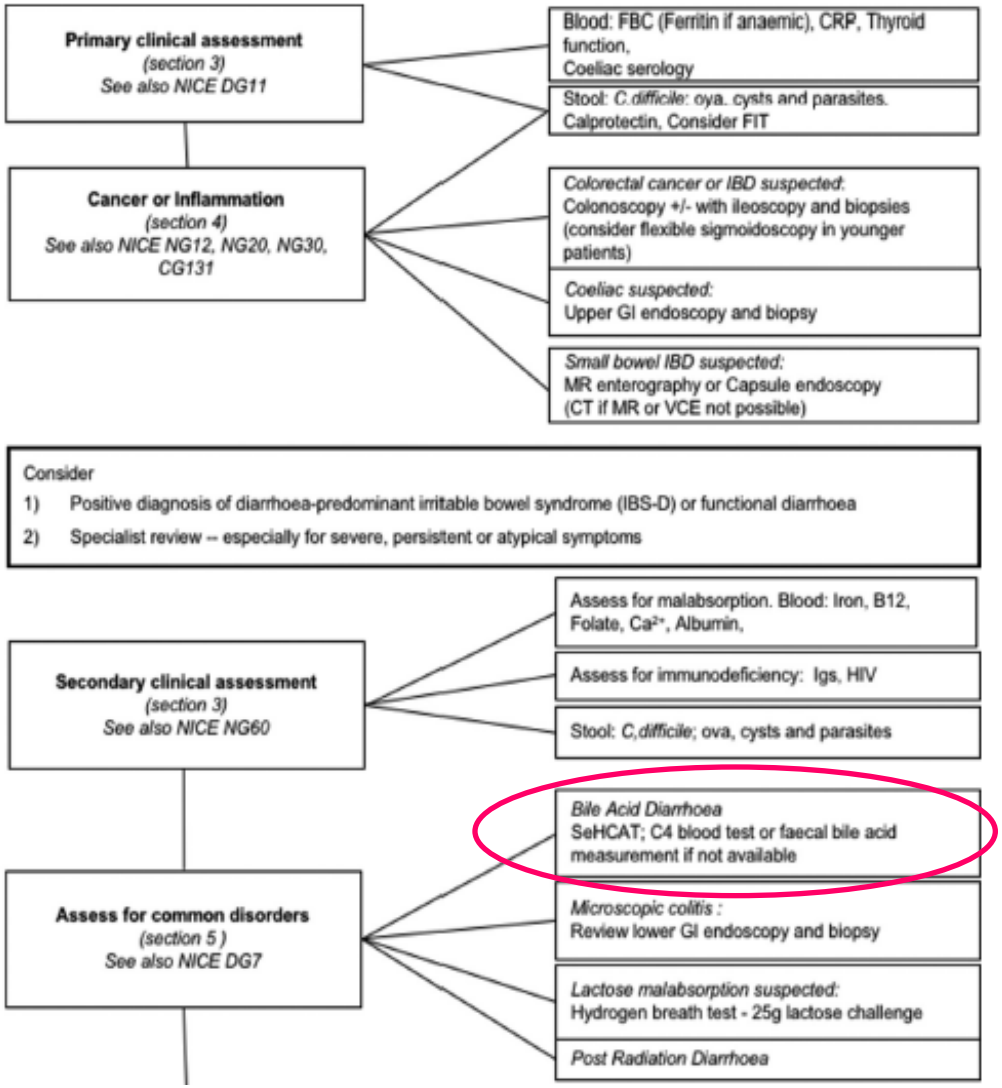
US and blood test use was higher but did not differ significantly.

(***Turner JM , 2017)***

Use of the SeHCAT scan early in the diagnostic process for patients with appropriate symptoms will save many unnecessary **endoscopic procedures**, reducing waiting lists and significantly cut the number of patients who need to be seen in **gastrointestinal clinics** in secondary care.

(***Fernandes DCR, 2018)***

Where is the SeHCAT's place in the FD diagnostic flow chart?



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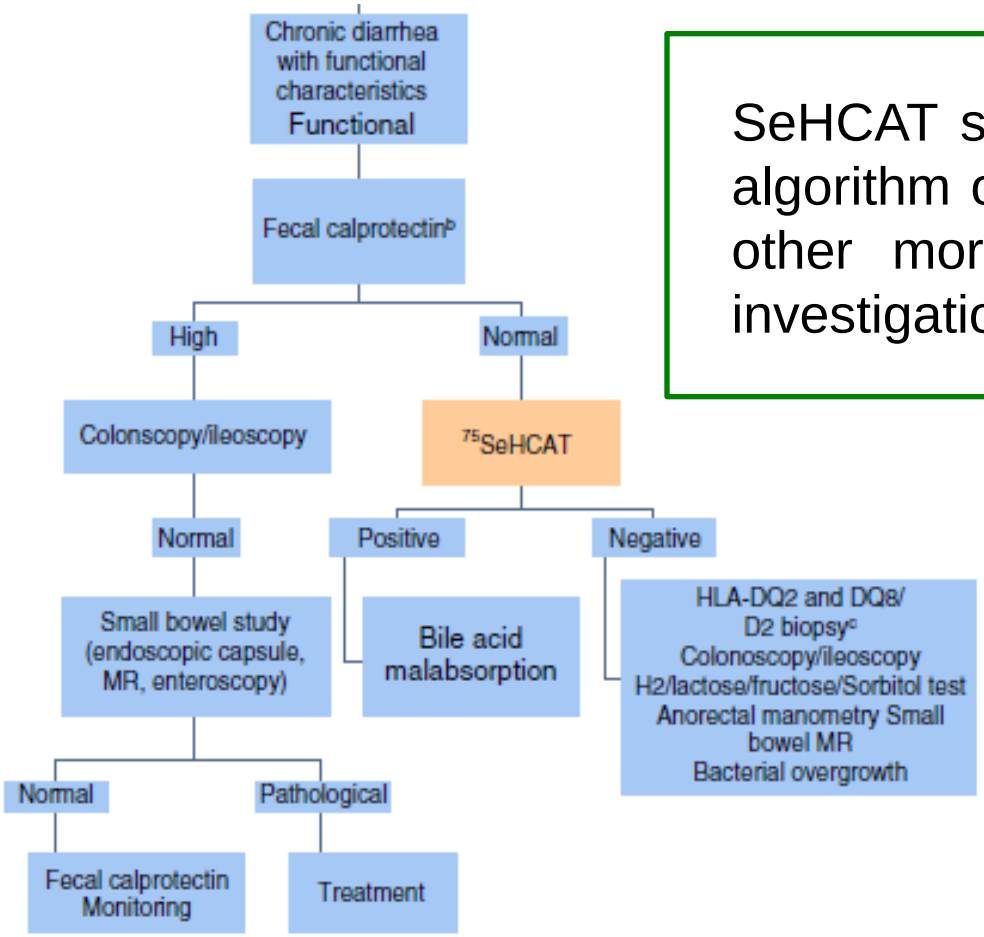

L.M. Mena Bares et al. / Rev Esp Med Nucl Imagen Mol. 2017;36(1):37–47

SeHCAT should be used earlier in an algorithm of diagnostic tests to reduce other more invasive and expensive investigations. ***(Murray IA, 2017)***

What's the BAM actual prevalence in Italy?