GI ReConnect

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GI Health Foundation

GI ReConnect

Controversies and Updates in IBS Guidelines: ACG and AGA IBS-D

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Faculty Disclosure

Baharak Moshiree, MD, Msc

- Salix/Bausch Pharmaceuticals – Speaker/consultant/Grant support
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- Progenity – Advisory board, grant support
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- EndoFLIP (Medtronic) – Grant support
- “SmurfCake” – Patent Pending (Univ of Miami/Atrium Health)- Patent
- Ingestible Capsule Device (Small bowel aspiration capsule): PCT/US17/20728 (Univ Miami- Moshiree Inventor) – Patent

IBS Is a Symptom-Based Diagnosis

Rome IV Criteria for IBS[1]

- Recurrent **abdominal pain,** on average, ≥1 day per week in the last 3 months, associated with ≥ 2 of the following:
  - Related to defecation
  - Change in frequency of stool
  - Change in form (appearance) of stool
- Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis

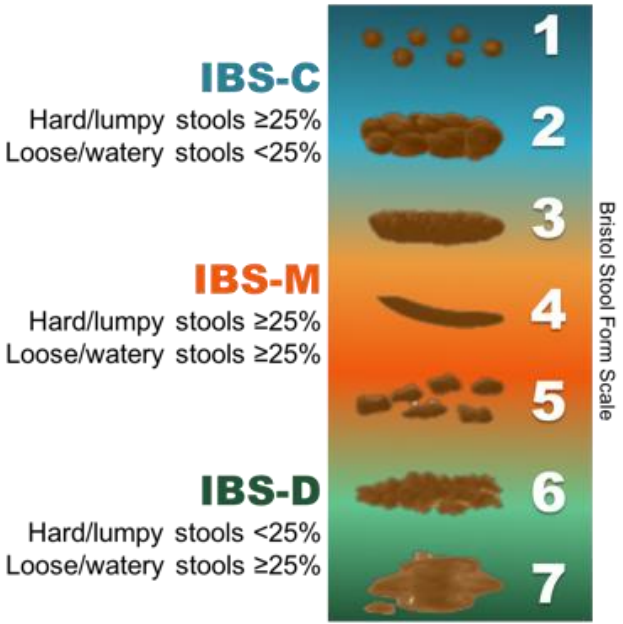
ACG Recommends a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBS to improve cost-effectiveness. **Strong recommendation, high quality evidence.**

ROME FOUNDATION

Lacy BE et al. *Am J Gastro.* 2021; 116: 17-44; Lacy BE et al. *Gastroenterology*. 2016;150:1393-140;
Longstreth GF et al. *Gastroenterology.* 2006;130:1480-1491;

ACG Consensus Recommendation: Subtyping IBS Patients Improves Therapy!

IBS Subtypes Based on Bristol Stool Forms[2,3]



O'Donnell LJD et al. *BMJ*. 1990;300:439-440;
Lacy BE et al. *Am J Gastro*. 2021; 116: 17-44.

IBS-D: Differential Diagnoses

Inflammatory bowel disease

Infectious diarrhea

Celiac disease

Bile acid diarrhea

*SCAD/SUDD

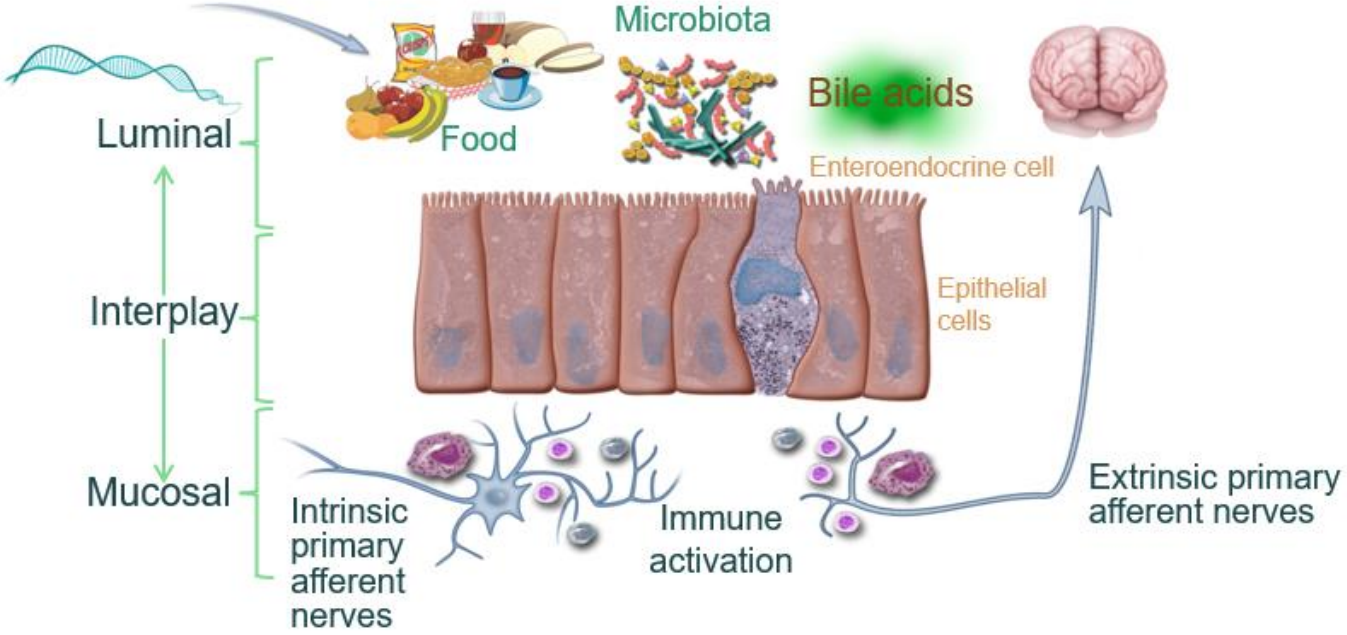
Segmental Colitis Associated with Diverticulosis
Symptomatic uncomplicated diverticular disease

Microscopic colitis

Eosinophilic GI diseases (EGIDs)

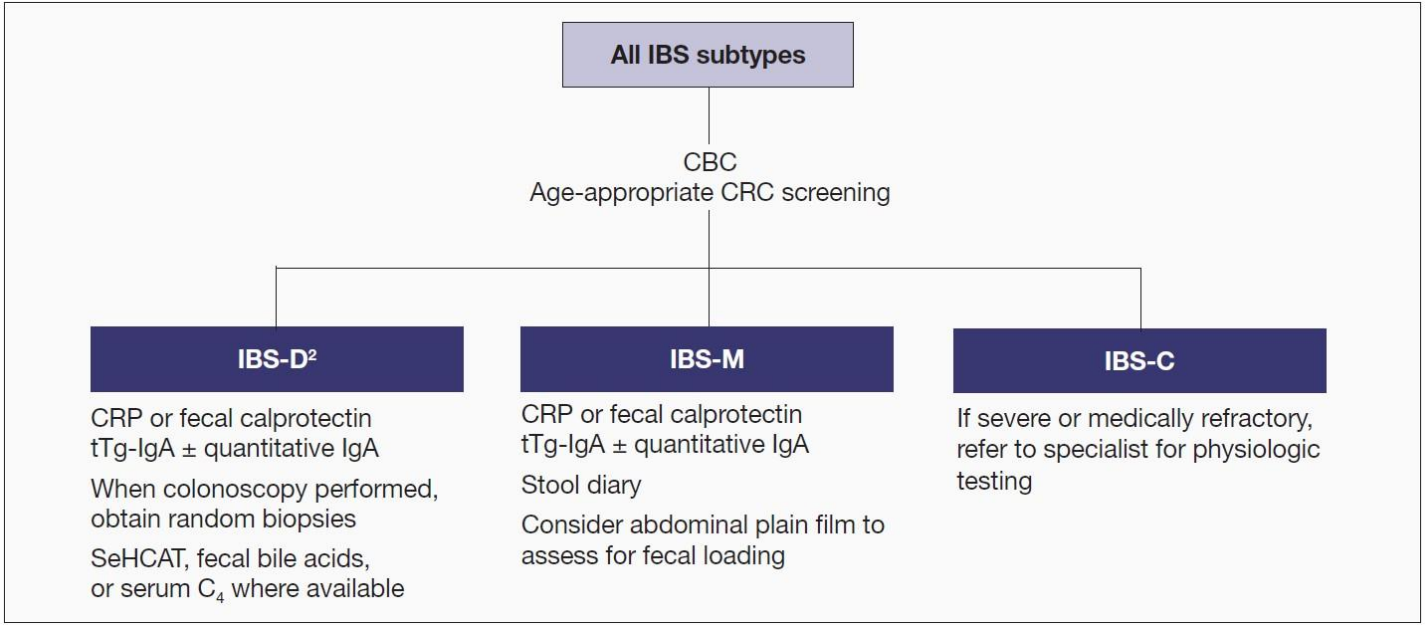
Disaccharidase deficiency

Peripheral Triggers for IBS



Barbara G et al. *Gastroenterology.* 2016;150:1305.

Previous IBS Proposed Diagnostic Work-Up



Abbreviations: C4, 7α-hydroxy-4-cholesten-3-one; CBC, complete blood count; CRC, colorectal cancer; CRP, C-reactive protein; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; IgA, immunoglobulin A; SeHCAT, selenium homocholic acid taurine; tTg, tissue transglutaminase.

Moshiree B, Rao SS. *JFP*. 2021. 70:1. S2-S15.

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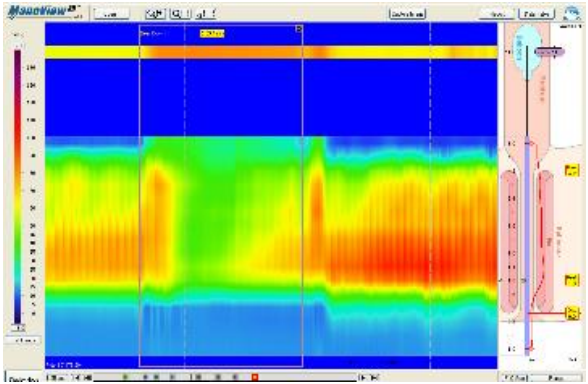
Where to Start

Diagnostic Evaluation Begins With…

- History!!! Ask about psychosocial factors, early life stressors
- Physical exam, including digital rectal exam
- ACG 2021 Consensus recommendation: Guidelines suggest anorectal physiology testing be performed in IBS (any subtype) if symptoms suggest a pelvic floor disorder and/or refractory constipation unresponsive to medications.
- Rectal *hypersensitivity* is a hallmark of IBS and is present in all subtypes

Sensitivity of DRE is 75% with specificity of 87%

PPV 61% , NPV 91%



Tantiphlachiva K et al. *Clin Gastro Hepatol*. 2010; 8:955-60; Rao SSC et al. *Am J Gastroenterol*. 2004;99:1585-1604; Lacy BE et al. *Am J Gastro*. 2021; 116: 17-44.

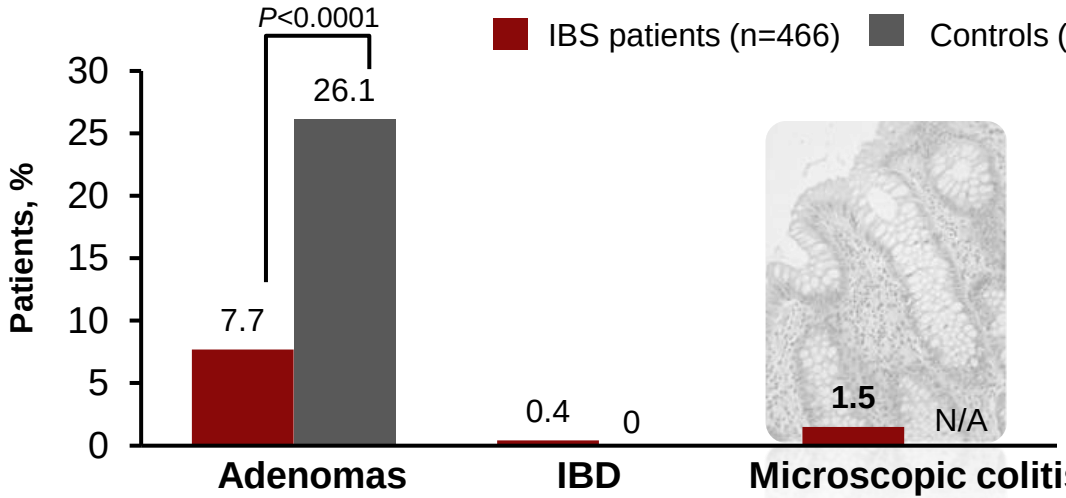
AGA Recommendations: Laboratory Evaluation of Chronic Diarrhea and IBS-D in Adults

Statement	Strength of recommendation	Quality of evidence
In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD	Conditional	Low
In patients presenting with chronic diarrhea, the AGA suggests **against** the use of ESR or CRP to screen for IBD	Conditional	Low
In patients presenting with chronic diarrhea, the AGA recommends testing for *Giardia*	Strong	High
In patients presenting with chronic diarrhea with no travel history to or recent immigration from high-risk areas, the AGA suggests against testing stools for ova and parasites (other than *Giardia*).	Conditional	Low
In patients presenting with chronic diarrhea, the AGA recommends testing for celiac disease with IgA-tTG and a second test to detect celiac disease in the setting of IgA deficiency	Strong	Moderate
In patients presenting with chronic diarrhea, the AGA suggests testing for bile acid diarrhea	Condition	Low
In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS	None	Knowledge gap

Smalley W et al. *Gastroenterology*. 2019;157:851-854.

Colonoscopy Findings in IBS Without Alarm Features Present

Prevalence of Structural Abnormalities in IBS Patients Compared with Controls



Microscopic colitis more common in IBS-D patients aged ≥45 years

ACG Taskforce: We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. **Conditional recommendation; very low-quality evidence**

IBD, inflammatory bowel disease.

Chey WD et al. *Am J Gastroenterol*. 2010;105:859-865; Shaukat A et al. *Am J Gastroenterol*. 2021: 116; 458-479.

AGA Versus ACG Take on Lab Testing for IBD

ACG statement: We suggest that fecal calprotectin[1] or fecal lactoferrin [2] AND C-reactive protein[1] be checked in patients without alarm symptoms and with suspected IBS-D symptoms to rule out IBD.

[1]Strong recommendation; moderate quality of evidence (CRP, fecal calprotectin)

[2]Strong recommendation; very low quality of evidence (fecal lactoferrin)

- AGA technical review:
- Recommends fecal lactoferrin and fecal calprotectin but NOT ESR OR CRP for ruling out IBD in IBS.
- Cutoff values suggested:
- Fecal Calprotectin : Threshold value 50 µg/g
- Fecal Lactoferrin : 4.0-7.25 µg/g

Smalley W et al. *Gastroenterology*. 2019;157:851-854; 2. Lacy BE et al. *Am J Gastroenterol*. 2021;116(1):17-44.

AGA Technical Review of the Diagnostic Accuracy of Serologic and Fecal Testing for Differentiating IBD and IBS

Test	Test cutoff	Sensitivity, range or (95% CI)*	Specificity, range or (95% CI)*	Positive likelihood ratio, range or (95% CI)*	Negative likelihood ratio, range or (95% CI)*
ESR	10-15 mm/h	0.54-0.78	0.46-0.95	1.0-16.3	0.3-0.98
CRP	5 to 6 mg/L	0.73 (0.64-0.80)	0.78 (0.58-0.91)	3.4 (1.05-5.71)	0.35 (0.27-0.42)
FL	4.0-7.25 µg/g	0.79 (0.73-0.84)	0.93 (0.63-0.99)	11.5 (-10.7-33.8)	0.22 (0.17-0.28)
Fcal	Ranges:				
	24.3 to 30 µg/g	0.92-0.98	0.96-0.98	28-59	0.01-0.07
	50 to 60 µg/g	0.81 (0.75-0.86)	0.87 (0.78-0.92)	6.12 (2.75-9.49)	0.21 (0.14-0.28)
	100-164 µg/g	0.64 (0.49-0.77)	0.90 (0.72-0.97)	6.23 (1.28-13.75)	0.4 (0.21-0.58)

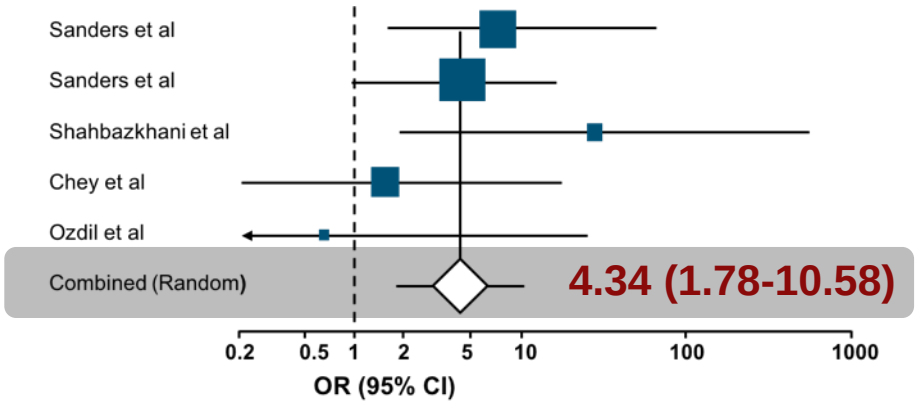
Conditional recommendation: Low-quality evidence

Modified from AGA technical review by Carrasco-Labra et al. *Gastroenterology*. 2019; 157: 859-880.

ACG and AGA Both Recommend Testing for Celiac Disease in IBS-D

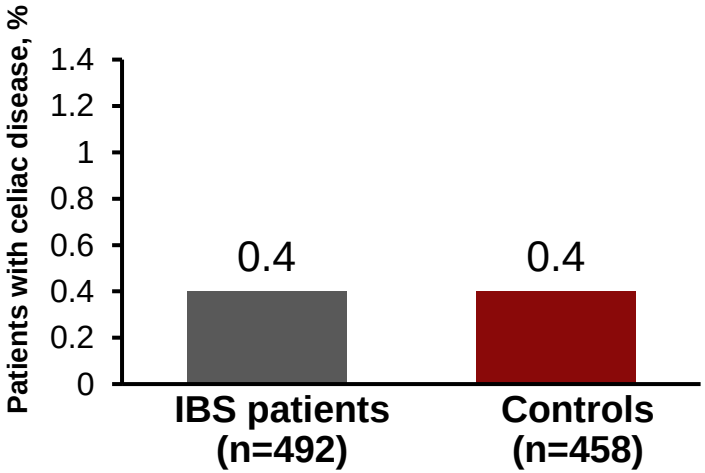
International Meta-analysis[1]

Prevalence of biopsy-proven celiac disease in IBS vs controls



US Prospective Study[2]

Non-constipated IBS patients (Rome II) biopsy-proven celiac disease



1. Ford et al. *Archives Int Med.* 2009;169:651; 2. Cash BD and Chey WD. *Gastroenterology*. 2011;141:1187.

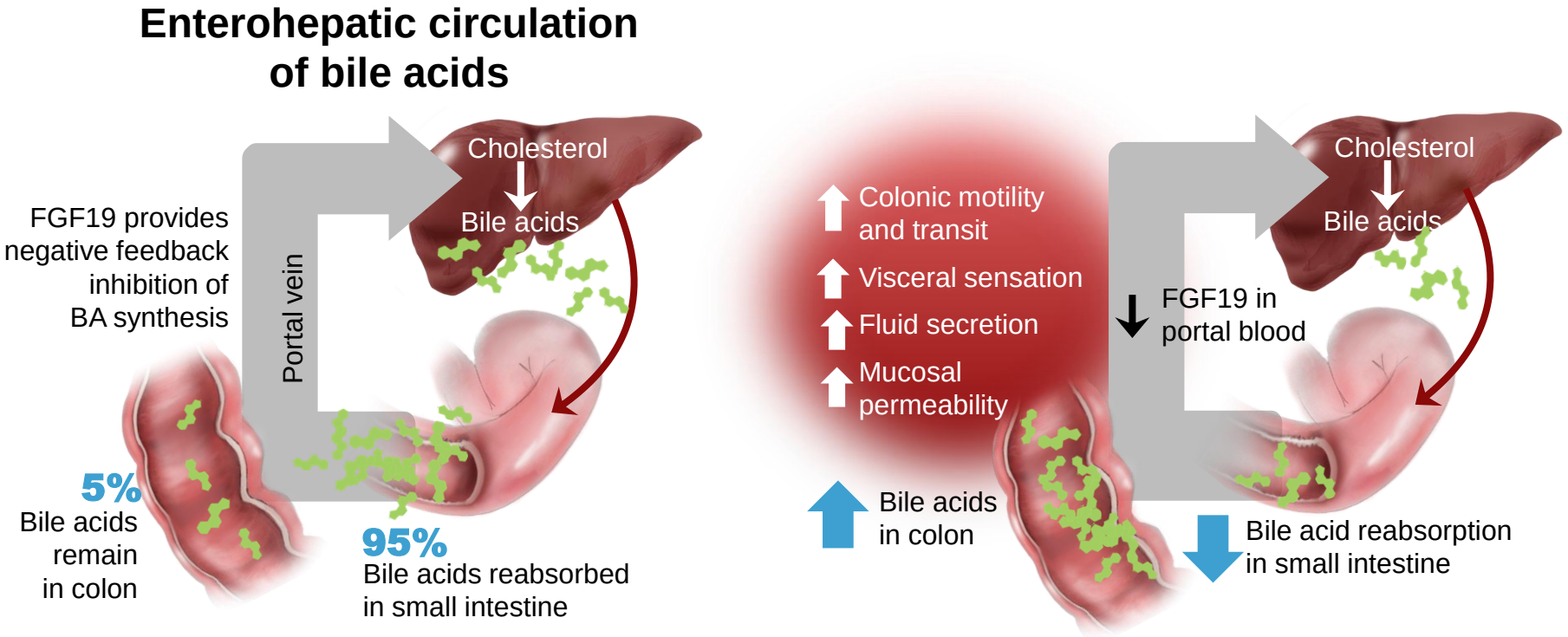
Testing for Giardia Ag in IBS-D

- ACG: We recommend against routine stool testing for enteric pathogens in all IBS patients
- AGA: Recommends testing for Giardia antigen but not other enteric pathogens for chronic diarrhea and IBS-D. Strong, high-quality of evidence.
- In patients with risk factors for giardiasis testing should be performed via fecal immunoassays or PCR with sensitivities approaching 82-100% and specificities of 91.5–100%.

Risk Factors for Giardiasis
Children in childcare settings, in particular, diaper-aged children
Close contacts of people with giardiasis (for example, people living in the same household) or people who care for those sick with giardiasis
People who drink water or use ice made from places where Giardia may live (for example, untreated or improperly treated water from lakes, streams, or wells)
Backpackers, hikers, and campers who drink unsafe water or who do not practice good hygiene (for example, proper handwashing)
People who swallow water while swimming and playing in recreational water,
People exposed to human feces (poop) through sexual contact
International travelers where Giardia may live, especially in lakes, rivers, springs, ponds, and streams

Modified from Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). 2015.
McHardy IH et al. *J Clin Microbiol.* 2014; 52: 712-720; Carrasco-Labra A et al. *Gastroenterology.* 2019; 157:859-880.

What's BAD?



Adapted from Camilleri M. *Gut Liver.* 2015;9:332-339. Courtesy GIHF; Wedlake L et al. *Ailment Pharmacol Ther*. 2009;30:707-717.

What's the Position on BAD?

- Common, but frequently underdiagnosed cause of chronic diarrhea[1]
- Tests available in US but limited:
  - Serum FGF19, 48 hour fecal stool collection for bile acids
  - Tests available outside of US: Serum C4 (7α-hydroxy-4-cholestene-3-one)
  - Sehcat- Selenium homotaurocholic acid
- Reported in 25-38% of patients presenting with chronic diarrhea or IBS-D[2,3]

BAD subtypes[1,4]

Type	Etiology
Type 1	Terminal ileal disease (eg, CD, resection) Radiation injury resulting in impaired reabsorption of bile acids
Type 2	Idiopathic or primary
Type 3	Secondary to other conditions that alter intestinal motility or bile acid absorption (eg, celiac disease, cholecystectomy, SIBO, radiation enteritis)

1. Sadowski DC et al. *Clin Gastroenterol Hepatol*. 2020;18:24-41; 2. Shihah MG et al. *Eclinical Med*. 2020;25:100465;
3. Wedlake L et al. *Aliment Pharmacol Ther*. 2009;30:707-717; 4. Wilcox C et al. *Aliment Pharmacol Ther*. 2014;39:923-939.

Bile Acid Diarrhea (BAD) Is More Common Than IBD and Celiac Disease Amongst Those With IBS

Disease	Estimated population prevalence
Crohn's disease	0.1-0.2%
Ulcerative colitis	0.2-0.3%
Celiac disease	0.7-1%
Primary bile acid diarrhea	~1%

Prevalence in IBS-D or Functional bowel disorders with diarrea
Ranged from 17% to 35%
Pooled rate = 28% (95% CI: 23–34%)*

Valentin N et al. *Gut.* 2016; 65:1951-1959; Walters J. DDW 2019. 2. Williams et al. *Gut.* 2007;56(Suppl 1):1-113.

ACG Versus AGA Recommendations for BAD

Since testing for BAD is limited in the US, routinely checking for BAD was not recommended by the ACG

However, a trial of bile acid binders may be useful and aid with diagnosis

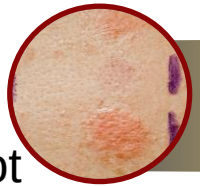
AGA recommends testing for bile acid diarrhea in chronic diarrhea

Conditional, low-quality of evidence

Lacy BE et al. *Am J Gastro*. 2021; 116: 17-44; Smalley W et al. *Gastroenterology*. 2019;157:851-854.

Lack of Data for Food Allergy Testing

ACG does not recommend routine testing for food allergies in suspected IBS-D



Skin prick test

Serum immunoassays (IgE)

Oral challenge

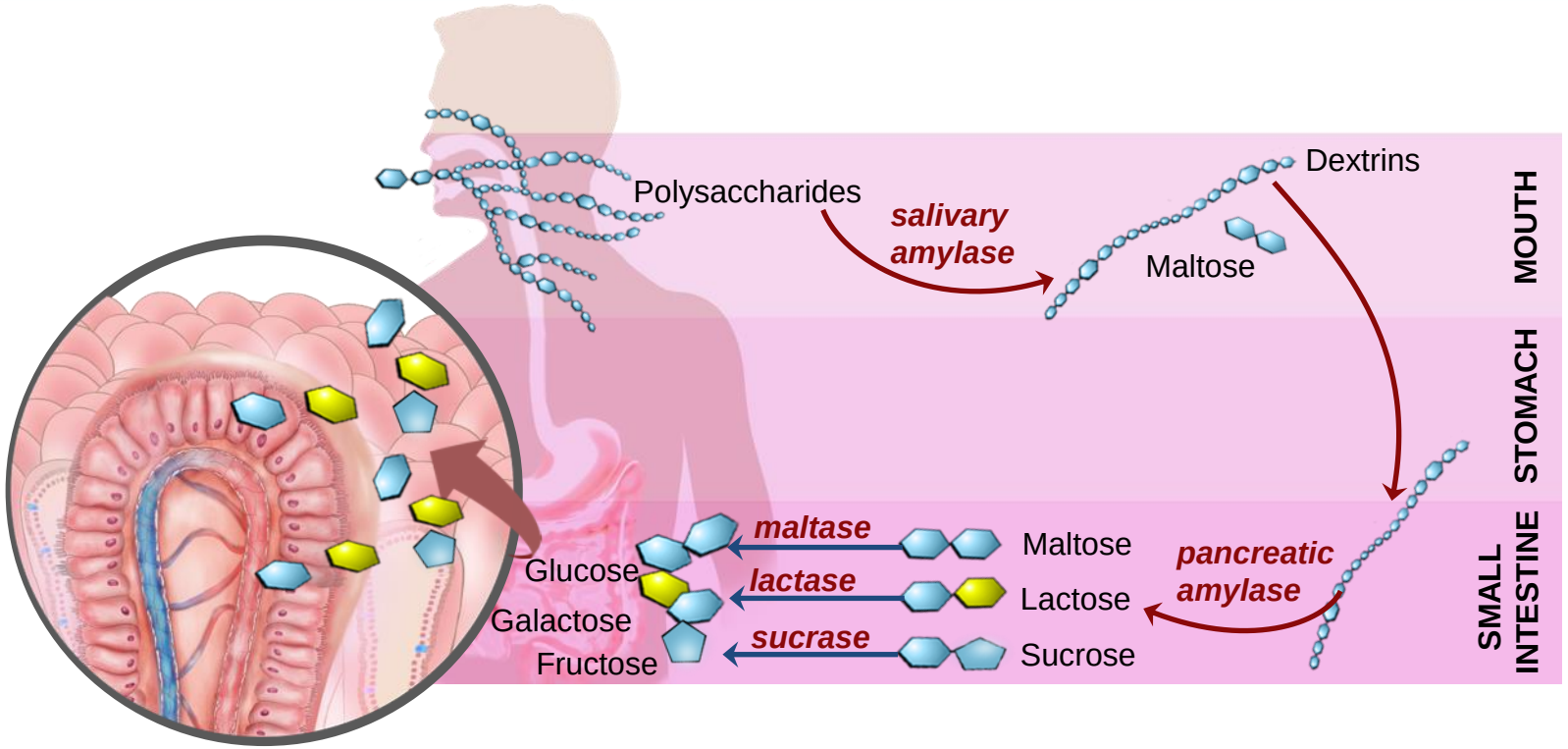
- Important to understand complexity and variety of nuances, eg:
  - + Skin/blood IgE testing may suggest sensitization
  - Cross-reactivity
  - Cooked vs raw antigens
- IgG serum antibodies are not validated:
  - Marker for food **tolerance** in people with prior IgE food allergies
  - No “normal values”
  - Doesn’t diagnose anything (doesn’t mean there is a food allergy)
  - Not valid in any disease

Costly and leads to Unnecessary diet elimination or ARFID.

1. Sicherer SH and Sampson HA. *J Allergy Clin Immunol*. 2014;133(2):291-307;
2. Valenta R et al. *Gastroenterology*. 2015;148:1120-1131.

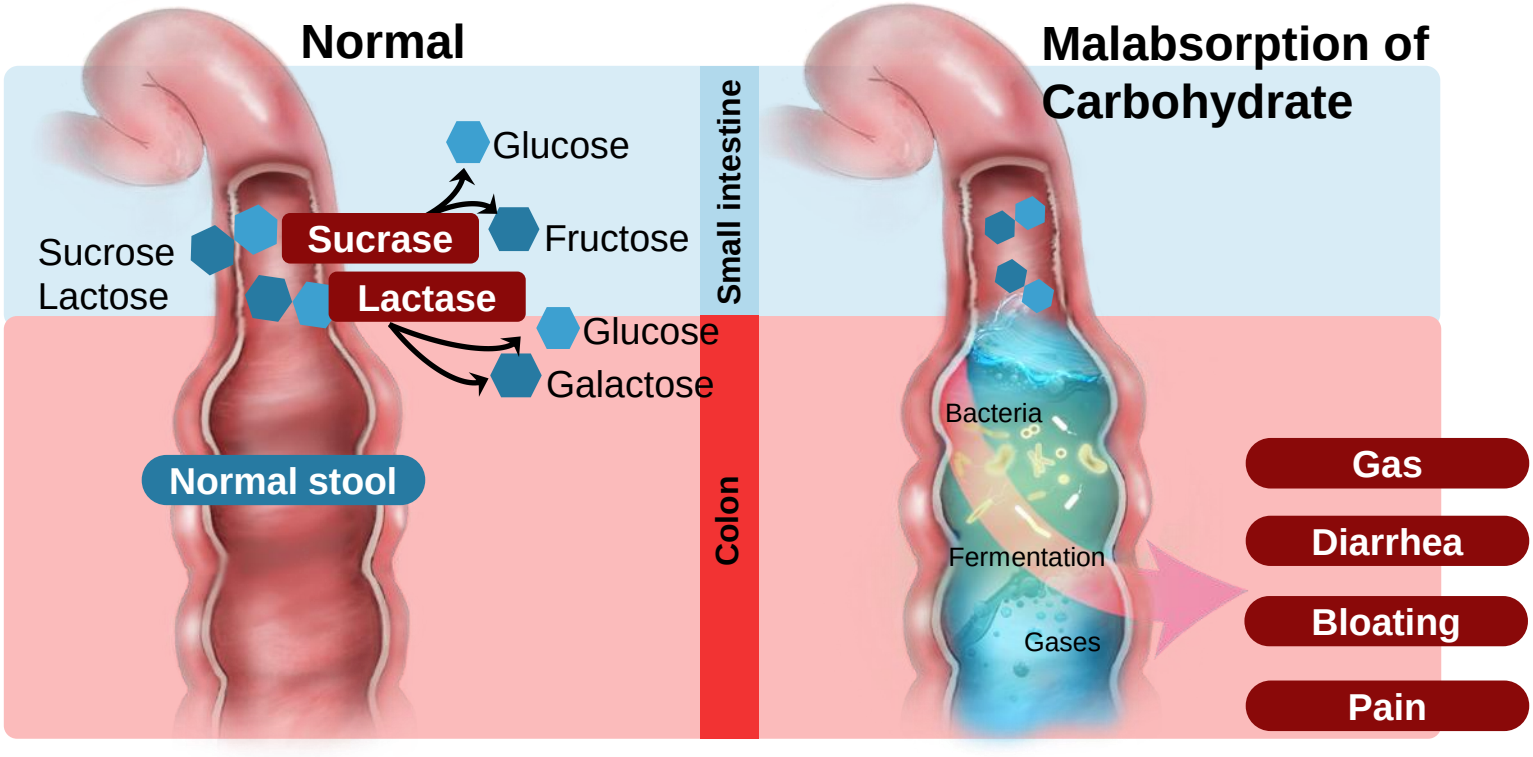
How about prevalence of a carbohydrate malabsorption in IBS?

Carbohydrate Digestion and Absorption
The Road to Monosaccharides



Sitrin MD. The Gastrointestinal System. Digestion and Absorption of Carbohydrates and Proteins. 137-158.

Clinical Consequences of Carbohydrate Maldigestion



1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13; 2. Canani RB et al. *Nutrients*. 2016;8:157.

Other Potential Carbohydrate Enzyme Deficiency in IBS-D: Sucrase-Isomaltase Deficiency

- N= 31 patients, mean age 46, 69% Female (IQR 30-60), were recruited from GI clinic with presumed diagnosis of IBS-D/M (abdominal pain, diarrhea, and/or bloating)
  - Patients with history of IBD, GI malignancy, or celiac disease excluded
- All patients underwent EGD with duodenal biopsies and testing for disaccharidase deficiency
- Patients with SID were less likely than controls to have abdominal pain (OR 0.16, 95% CI 0.03–0.81, *P* = 0.04) although no difference in diarrhea or bloating was found

Symptom	SID		OR (95% CI)	P value
	+ n (%)	– n (%)		
Abdominal pain	5 (45.5)	17 (85)	0.16	0.0037
Boating	4 (36.3)	12 (60)	0.39	0.2734
Diarrhea	7 (63.6)	8 (40)	2.54	0.2734

SID was present in **35%** of patients
100% were also lactase deficient

EGD, esophagogastoduodenoscopy; IBD, inflammatory bowel disease; OR, odds ratio.
Kim SB, Moshiree B et al. *DDS*. 2019.

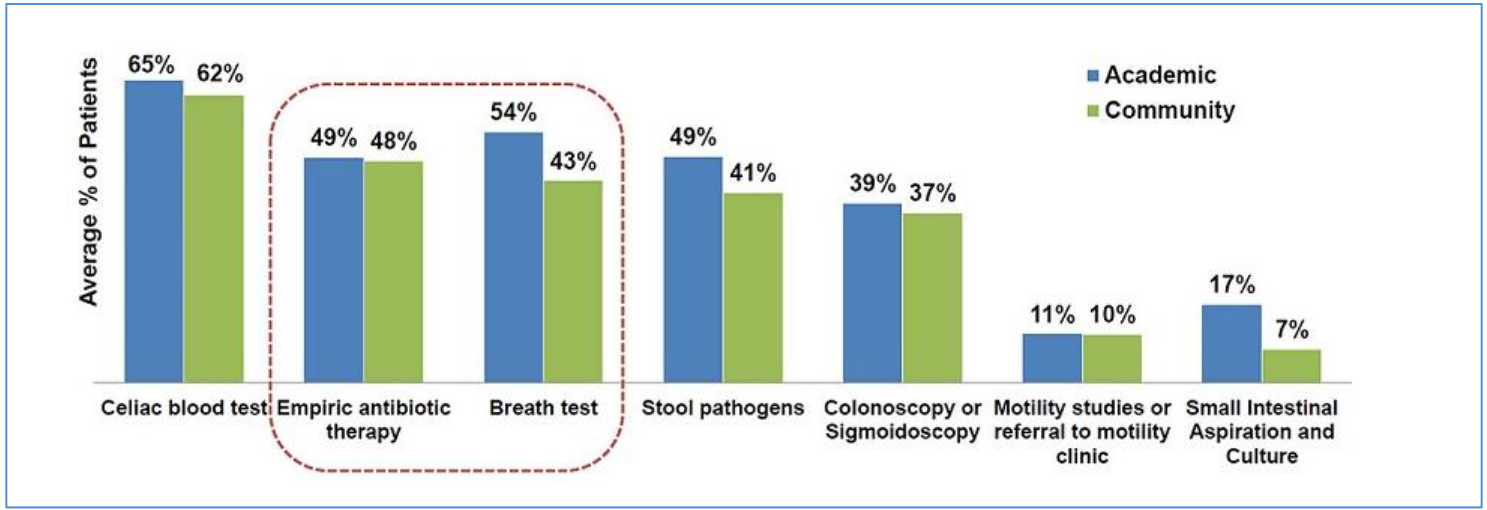
Carbohydrate Enzyme Deficiency in IBS-D

- No formal recommendations by AGA or ACG made on ruling out carbohydrate enzyme deficiency in IBS-D

SIBO in IBS and Hydrogen Breath Testing

- AGA and ACG do NOT advocate performance of Breath testing in IBS of any subtype

What Do GI Folks Think About Laboratory Testing in IBS?

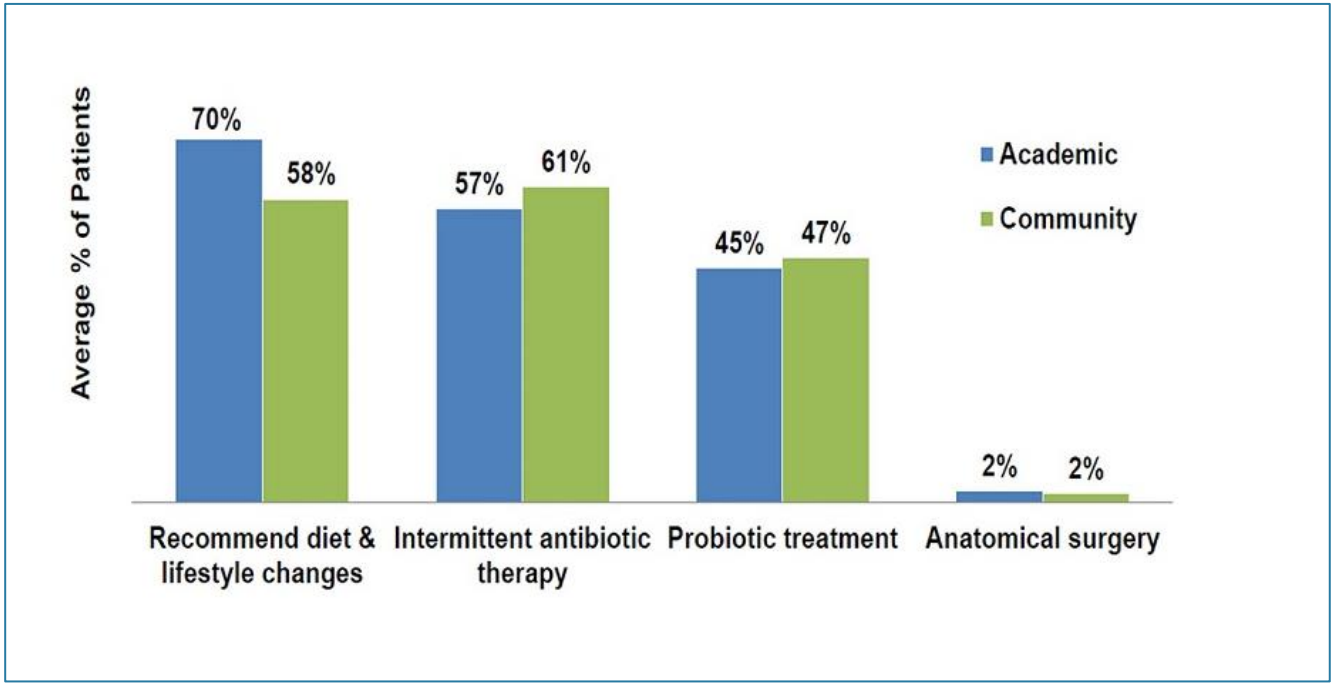


Based on a survey of gastroenterologists (N=90) from academic or community hospitals, responses to the question:

"When working up patients for SIBO or IBS, what percent of your patients receive each of the following?"

Moshiree B & Khan A. *Adv Ther Gastroenterology*. (Submitted).

How do you treat SIBO?



Moshiree B & Khan A. *Adv Ther Gastroenterology*. (Submitted).

Summary of Society Recommendations: Laboratory Evaluation of Functional Diarrhea and IBS-D in Adults

In patients presenting with chronic diarrhea and IBS-D , the AGA[1]…

Recommends

- ✓ Testing for *Giardia*
- ✓ Testing for celiac disease with IgA-tTG (and a second IgG test to detect celiac disease in the setting of isolated IgA deficiency)

Suggests

- ✓ Fecal calprotectin or fecal lactoferrin to screen for IBD
- ✓ Testing for BAD

Suggests against

- ✗ ESR or CRP to screen for IBD
- ✗ Against testing stools for ova and parasites (other than *Giardia*)

In patients presenting with IBS and diarrhea symptoms, the ACG[2]…

Recommends

- ✓ Testing for *Giardia- only if risk factors exist*
- ✓ Serologic testing to rule out celiac disease

Suggests

- ✓ Fecal calprotectin (or fecal lactoferrin) **and** CRP in patients without alarm features to rule out IBD

Suggests against

- ✗ Routine stool testing for enteric pathogens, BAD or food allergies
- ✗ Routine colonoscopy in patients <45 years without warning signs

BAD, bile acid diarrhea; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

1. Smalley W et al. *Gastroenterology*. 2019;157:851-854. 2. Lacy BE Moshiree B et al. *Am J Gastroenterol*. 2021;116(1):17-44.
2. GIHF