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Masqueraders of IBS
Recognizing and Managing Congenital Sucrase-Isomaltase Deficiency in Clinic Practice

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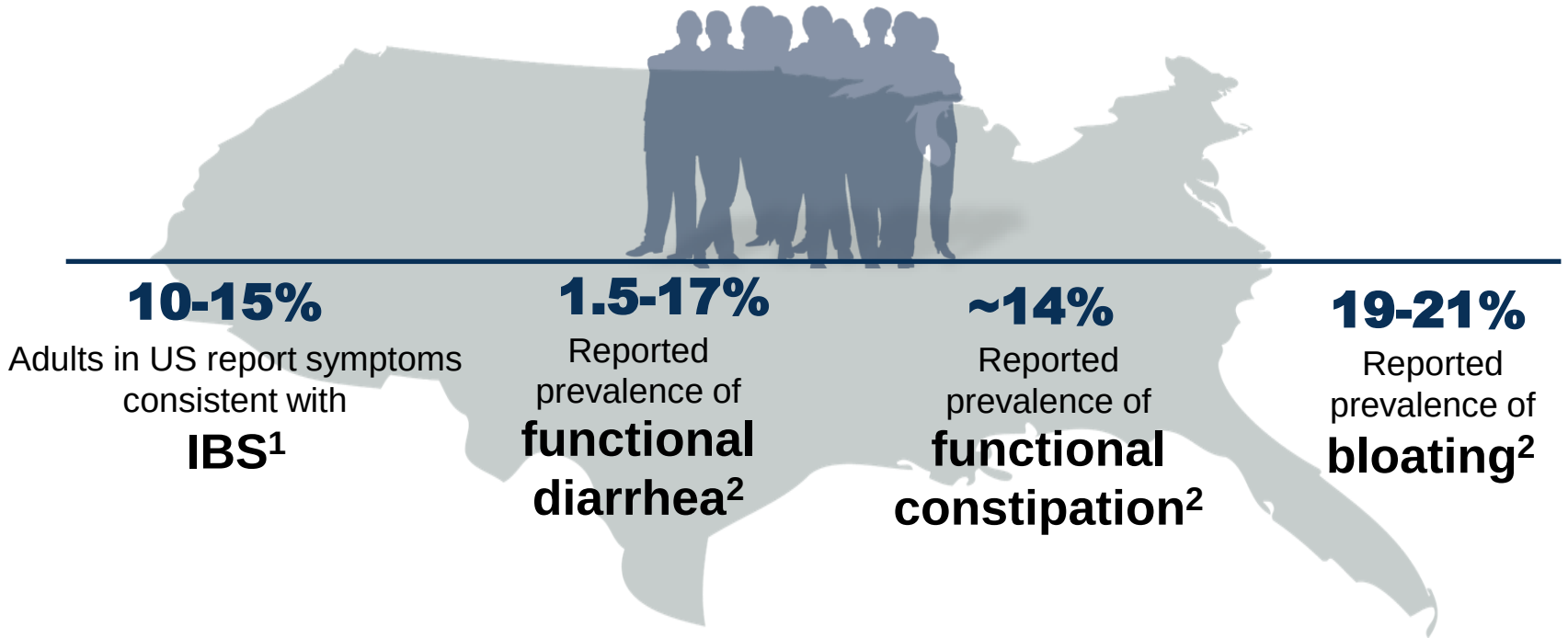
No financial relationships to disclose.

Functional GI Symptoms Are Common



10-15%
Adults in US report symptoms consistent with
IBS[1]

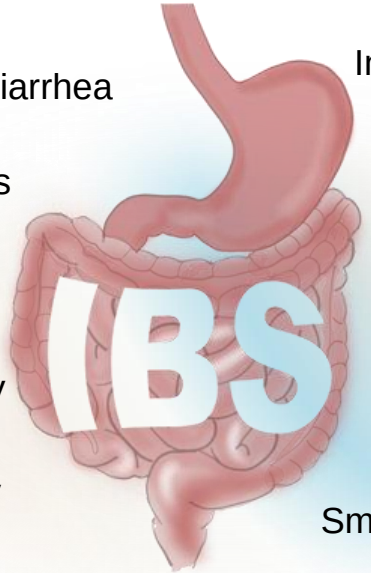
1.5-17%
Reported prevalence of
functional diarrhea[2]

~14%
Reported prevalence of
functional constipation[2]

19-21%
Reported prevalence of
bloating[2]

1. Chey WD et al. *JAMA*. 2015;313(9):949-958; 2. Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

Differential Diagnoses of IBS-D



- Bile acid diarrhea
- Microscopic colitis
- Celiac disease
- Food intolerance/allergy
- Disaccharidase deficiency
- Eosinophilic GI disease
- Inflammatory bowel disease
- Post-infectious diarrhea
- Medication-induced diarrhea
- Gastrointestinal infection
- Small intestinal bacterial overgrowth
- Exocrine Pancreatic Insufficiency

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

In patients presenting with chronic diarrhea, 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 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*)
- ✗ ESR or CRP to screen for IBD

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

Recommends

- ✓ 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
- ✗ 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 et al. *Am J Gastroenterol*. 2021;116(1):17-44.

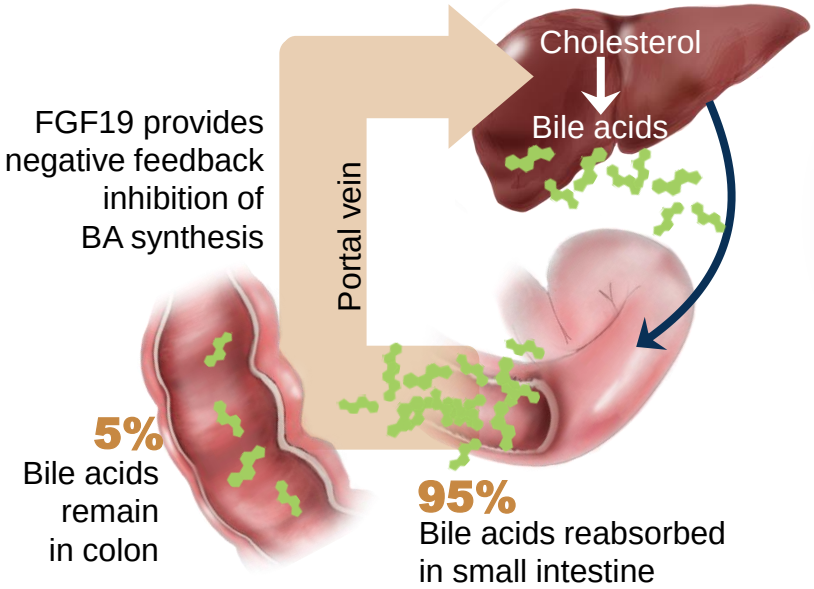
Non-Celiac Wheat Intolerance: Fact or Fad?

- Encompasses a collection of medical conditions in non-celiac patients in which wheat/rye/barley leads to an adverse effect[1, 2]
  - True population prevalence is unknown[1-3]
  - Improves with a gluten-free diet[1-4]
  - May be intolerance to other glycoproteins (e.g., hordeins), carbohydrates (e.g., fructans)[3]
  - Not convincingly associated with increased intestinal permeability
  - Innate immunity markers TLR2 & FOXP3 altered in gluten sensitivity

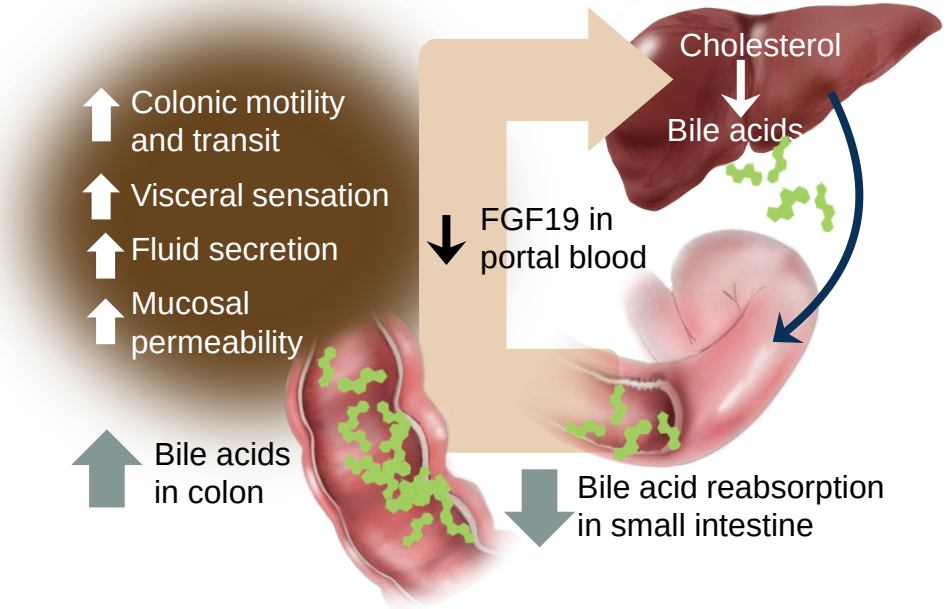
1. Volta U et al. *Best Pract Res Clin Gastroenterol*. 2015;29:477-491; 2. Green PHR et al. *J Allergy Clin Immunol*. 2015;135:1099-1106; 3. Lebwohl. B et al. *BMJ.* 2015;351:h4347; 4. Czaja-Bulsa G et al. *Clin Nutr*. 2015;34:189-194.

Bile Acids and Diarrhea

Enterohepatic circulation of bile acids



Bile acid diarrhea



Adapted from Camilleri M. *Gut Liver.* 2015;9:332-339.

How Common Is BAD?

- Common, but frequently underdiagnosed [1]
- Reported in 25-38% of patients presenting with chronic diarrhea or IBS-D[2,3]
  - Higher prevalence in patients with history of terminal ileal disease resection, cholecystectomy, or abdominal radiotherapy[1]

BAD subtypes[1,4]

Type	Etiology
Type 1	Terminal ileal disease (e.g., 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.

Eosinophilic GI Diseases

- Symptoms of GI dysfunction seen in combination with chronic eosinophilic and mast cell inflammation in specific GI tracts[1,2]
  - Eosinophilic esophagitis (EoE)
  - Eosinophilic gastritis (EoG)
  - Eosinophilic gastroenteritis (EoGE)
  - Eosinophilic colitis (EoC)
- Historically considered rare, but increasingly described[1,2]
  - <50,000 patients in the US affected[3]

Clinical symptoms of EGIDs[1]

Affected area	Symptoms
Mucosal	Diarrhea, malabsorption, GI bleeding, protein-losing enteropathy, vomiting, abdominal pain
Muscular	Vomiting, abdominal distention, abdominal pain, vomiting
Serosal	Abdominal distention, ascites, peritonitis

1. Egan M, Furuta GT. *Ann Allergy Asthma Immunol*. 2018;121:162-167;
2. Licari A et al. *J Allergy Clin Immunol Pract*. 2020;8:1994-2003; 3. Jensen ET et al. *J Pediatr Gastroenterol Nutr*. 2016;62:36-42.

Treatment of IBS Is Often Symptom-Directed

Diarrhea[1,2]

Loperamide
Rifaximin
Eluxadoline
Bile acid sequestrants

Abdominal pain[1,2]

Antispasmodics
Neuromodulators
Low FODMAP diet
Prosecretory agents[a]
Rifaximin
Eluxadoline
Peppermint oil
Tegaserod

Constipation[1,2]

Fiber
Polyethylene glycol
Prosecretory agents[a]
Tegaserod

Bloating[1,2]

Rifaximin/antibiotics
Low FODMAP diet
Peppermint oil
Probiotics?
Prosecretory agents[a]

[a]Lubiprostone, linaclotide, plecanatide.

1.Ford AC et al. *Am J Gastroenterol*. 2018;113:1-18; 2. Chey WD et al. *JAMA*. 2015;313(9):949-958.

Differential Diagnoses of IBS-D

Bile acid diarrhea

Microscopic colitis

Celiac disease

Food intolerance/allergy

Disaccharidase deficiency

Eosinophilic GI disease

Inflammatory bowel disease

Post-infectious diarrhea

Medication-induced diarrhea

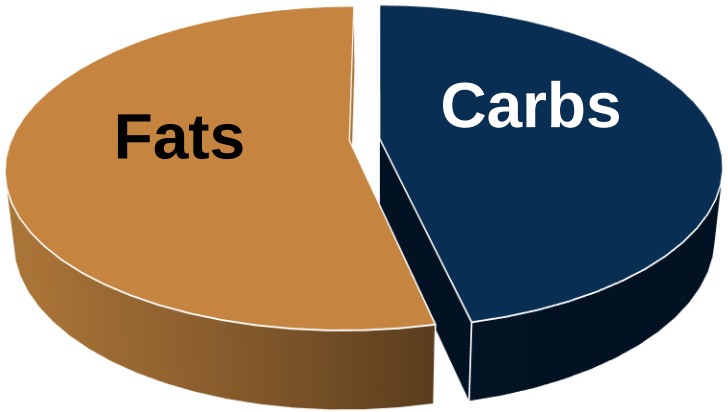
Gastrointestinal infection

Small intestinal bacterial overgrowth

Exocrine Pancreatic Insufficiency

Carbohydrates: More Than Your Daily Bread…

~ 46% of 2,000 calorie western diet[1,2]



Disaccharides

- Lactose
- Sucrose
- Maltose
- Trehalose

1. US Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1516/Table_1_NIN_GEN_15.pdf. Accessed September 13, 2019; 2. U.S. Department of Agriculture. https://www.nal.usda.gov/fnic/how-many-calories-are-one-gram-fat-carbohydrate-or-protein. Accessed February 9, 2021.

Understanding Carbohydrates

Monosaccharides

- Simple sugars $C_m(H_2O)_n$
- α⇄β anomers exist in equilibrium
- Colorless, water-soluble, crystalline solids

Glucose

Galactose

Fructose

Disaccharides

2 monosaccharides combined by condensation reaction

Maltose

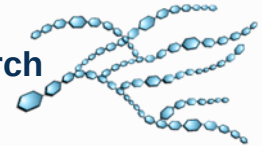
Lactose

Sucrose

Polysaccharides

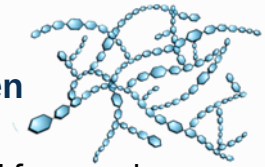
≥20 monosaccharides

Starch



Formed from α-glucose

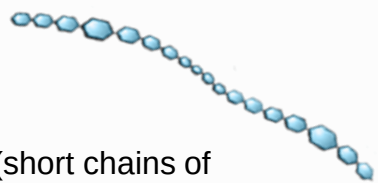
Glycogen



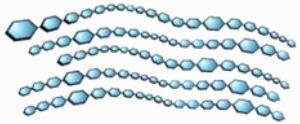
- Formed from α-glucose
- More extensively branched and compact than starch
- Not easily broken down

Oligosaccharides

<20 monosaccharides



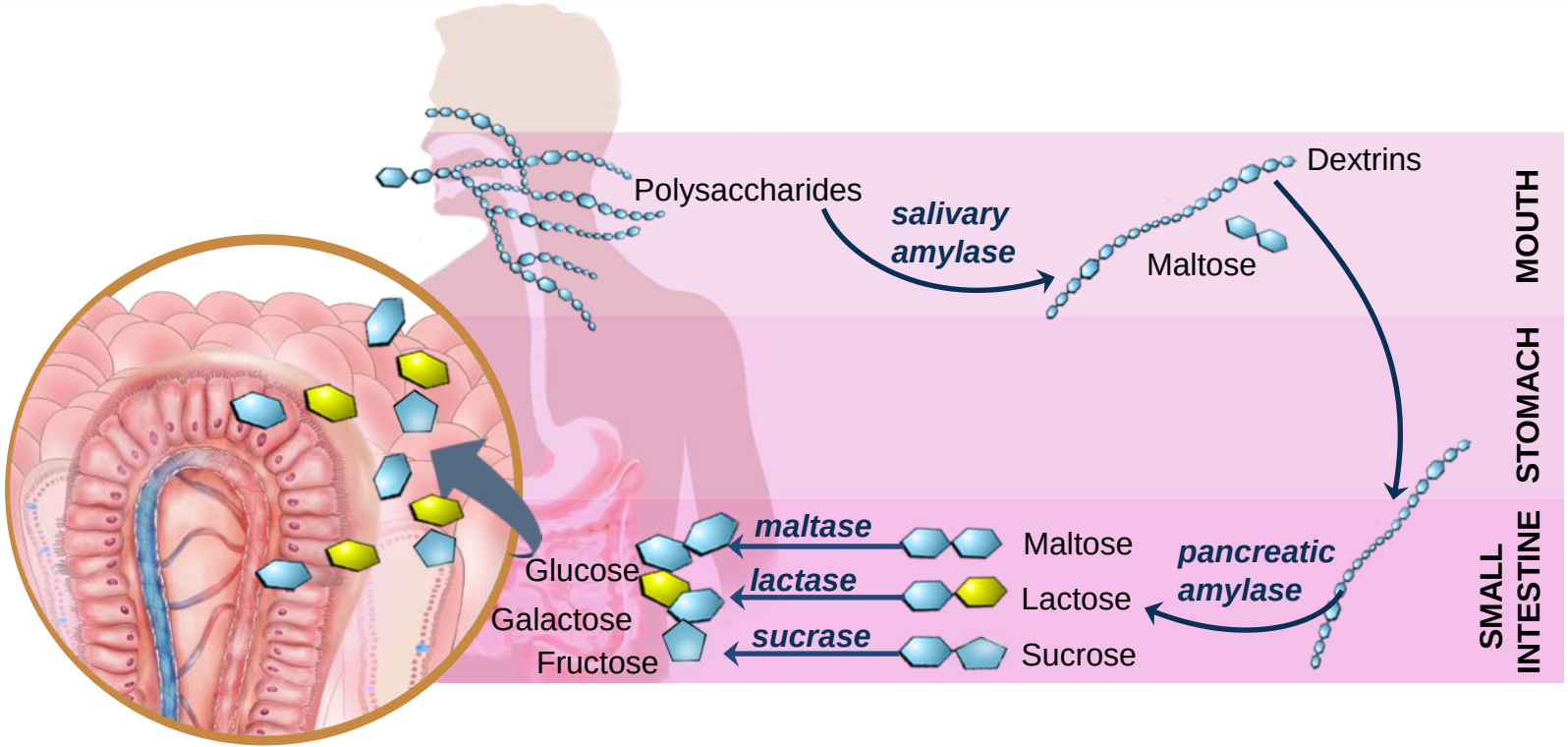
- Fructo-oligosaccharides (short chains of fructose, which are found in many vegetables)
- Galactooligosaccharides (short chains of galactose molecules)



Cellulose

- Formed from β-glucose
- Glucose-glucose bonds not broken down by amylase

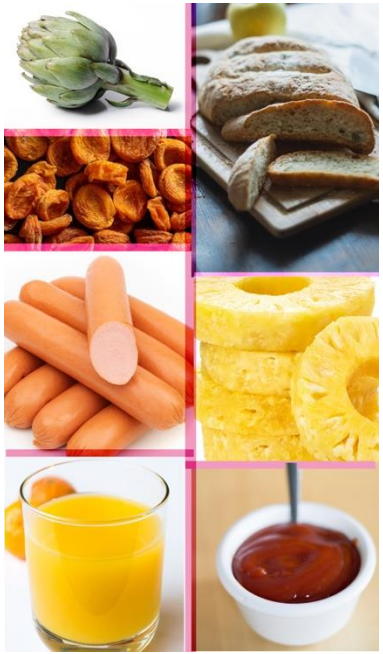
Carbohydrate Digestion and Absorption
The Road to Monosaccharides



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

Fructose Intolerance

- Fructose and fructan intolerance are common causes of unexplained GI symptoms[1]
- Up to one third of patients with suspected IBS had fructose malabsorption and fructose intolerance[2]
- Currently no established protocols or guidelines for dietary management of fructose malabsorption or intolerance[1]
  - Elimination phase (~5 g fructose/day) followed by re-introduction phase after 2-6 weeks
  - Totally fructose-free diet not usually required
  - Patients can typically tolerate 10-15 g fructose per day



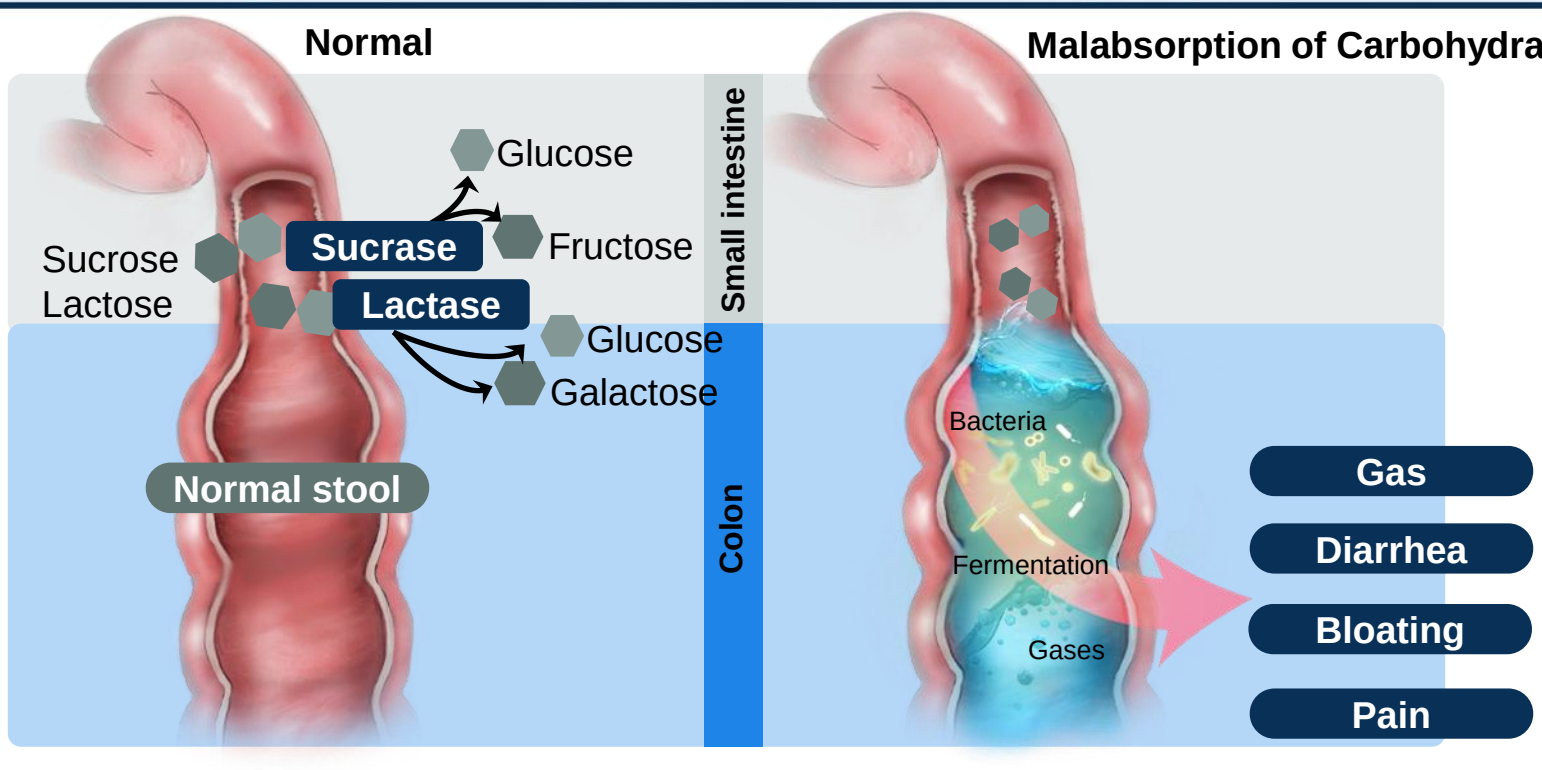
High fructose foods

Fruit juices
Dried fruits
Canned fruits
Marinated or processed meats
Certain vegetables (artichokes, asparagus, broccoli, tomato paste, canned tomato paste, ketchup)
Any product with HFCS

HFCS, high fructose corn syrup.

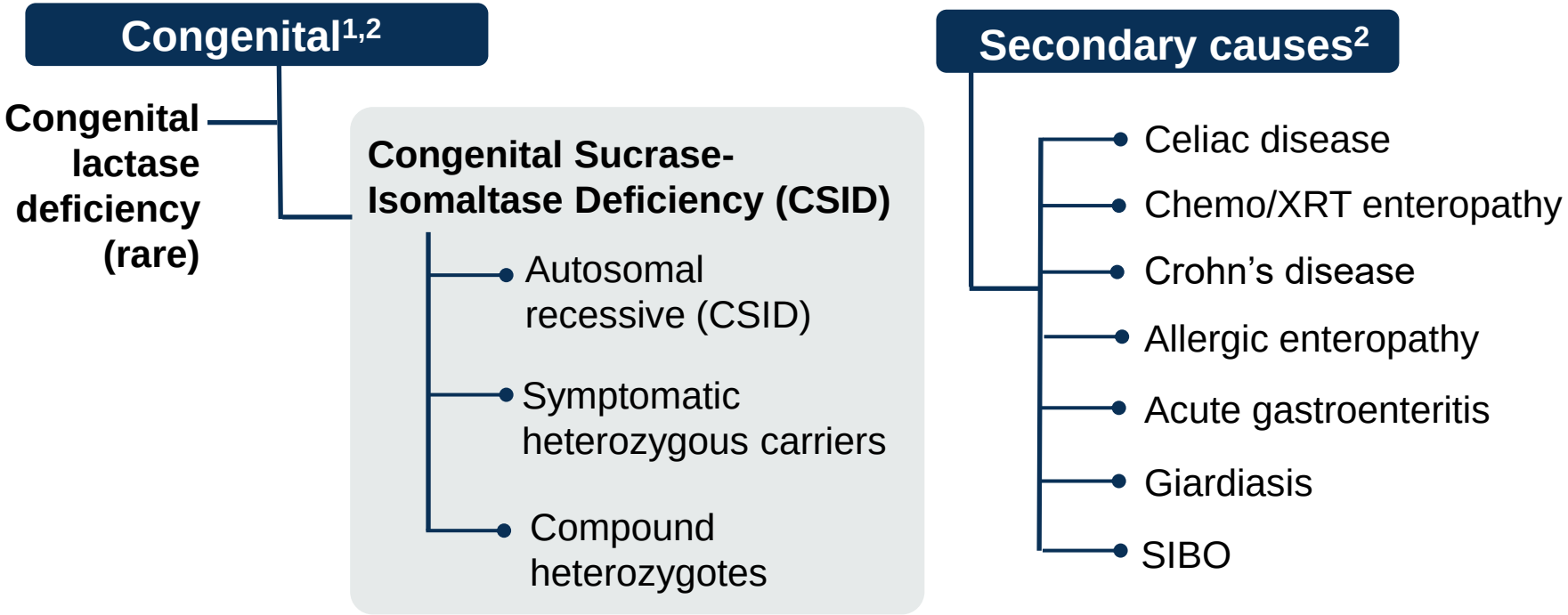
1. Fedewa A, Rao SCC. *Curr Gastroenterol Rep*. 2014;16(1):370; 2. Choi YK et al. *J Clin Gastroenterol*. 2008;42:233-238.

Clinical Consequences of Disaccharide Maldigestion



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

Etiologies of Key Disaccharidase Deficiencies: Lactase and Sucrase-Isomaltase



CSID, congenital sucrase isomaltase deficiency; IBD, inflammatory bowel disease.

1. Cohen S. *Molecular Cellular Pediatr*. 2016;3:5; 2. Naim HY et al. *J Pediatr Gastroenterol Nutr*. 2012; 55(Suppl 2):S13-S20.

Fructose Fun Facts

- Fructose is the sweetest sugar[1]
- Consumption has increased dramatically in the US[2-4]
  - Annual fructose consumption increased from <1 ton in 1966 to 8.8 million in 2003[2]
  - Consumption of HFCS increased >1000% between 1970 and 1990[3]
- Humans have limited absorptive capacity for fructose since its absorption is an energy-independent process[4]

HFCS, high fructose corn syrup.

1. Bantle JP. *J Nutr*. 2009;139(6):1263S-1268S; 2. Economic Research Service, USDA. Table 49–US total estimated deliveries of caloric sweeteners for domestic food and beverage use, by calendar year. 2003;
3. Bray GA et al. *Am Clin Nutr.* 2004;79:537-543; 4. Fedewa A, Rao SCC. *Curr Gastroenterol Rep*. 2014;16(1):370.

Lactose Fun Facts

- Dairy accounts for 14% of daily energy intake
- Average dairy intake in US:
  - 2.5 cups/day (<10 yrs) to ~1.5 cups/day (>20 yrs)
  - Milk (51%) and cheese (45%) comprise majority of dairy consumption
  - 12.5 grams of lactose in 250 mL of milk
- Only sugar that does not increase risk of dental caries
- Intestinal lactase expression decreases in the first 2 decades of life

Common Terms

Lactose Intolerance

Lactase deficiency

Lactose malabsorption

Misselwitz B et al. *Gut*. 2019;68:2080–2091; NHANES: 2007 to 2010: What we Eat in America.

Sucrose Fun Facts

- Most used sweeter in the world and accounts for ~15% of daily energy intake in the US
- Sugar cane (70%) and beets (30%) have the highest concentrations of sucrose and are the most common sources of table sugar
- Excellent preservative at high concentration due to strong osmotic effect
- Main ingredient of rum

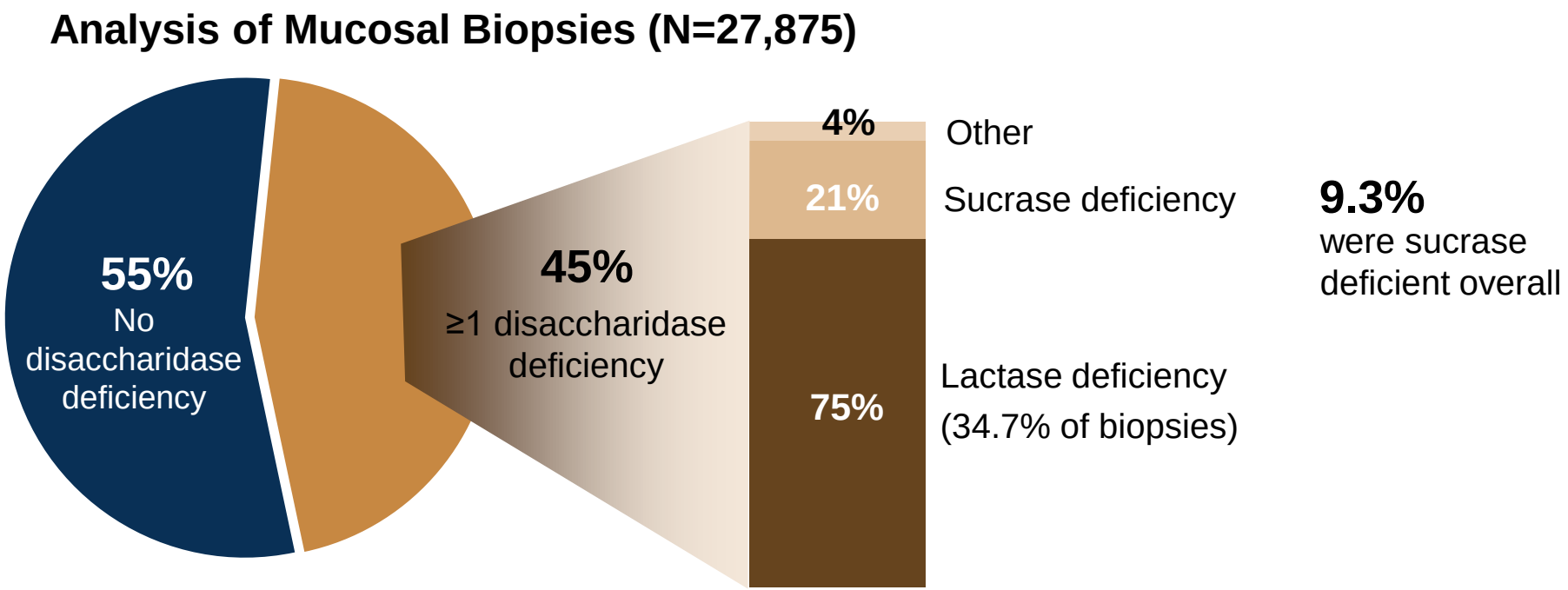
Common Terms

Sucrose Intolerance

Sucrose deficiency

Sucrose malabsorption

How Common Is Disaccharidase Deficiency?



Nichols BL et al. *J Pediatr Gastroenterol Nutr.* 2012; (Suppl 2):S28-S30.

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Recognizing and Managing CSID in Clinical Practice

Congenital Sucrase-Isomaltase Deficiency (CSID)

- The first report of an autosomal recessive Congenital Sucrase-Isomaltase Deficiency (CSID) was published in 1960
- “Diarrhoea Caused by Deficiency of Sugar-Splitting Enzymes”


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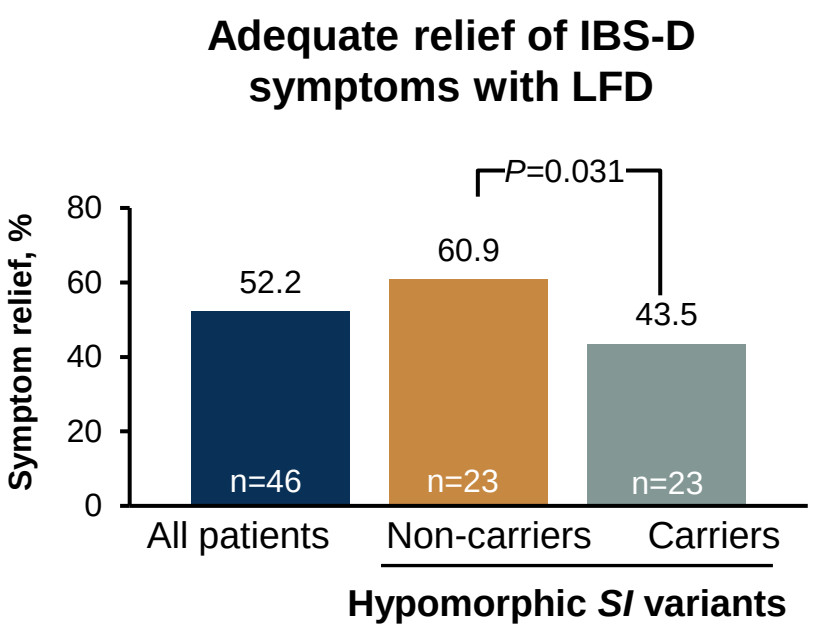
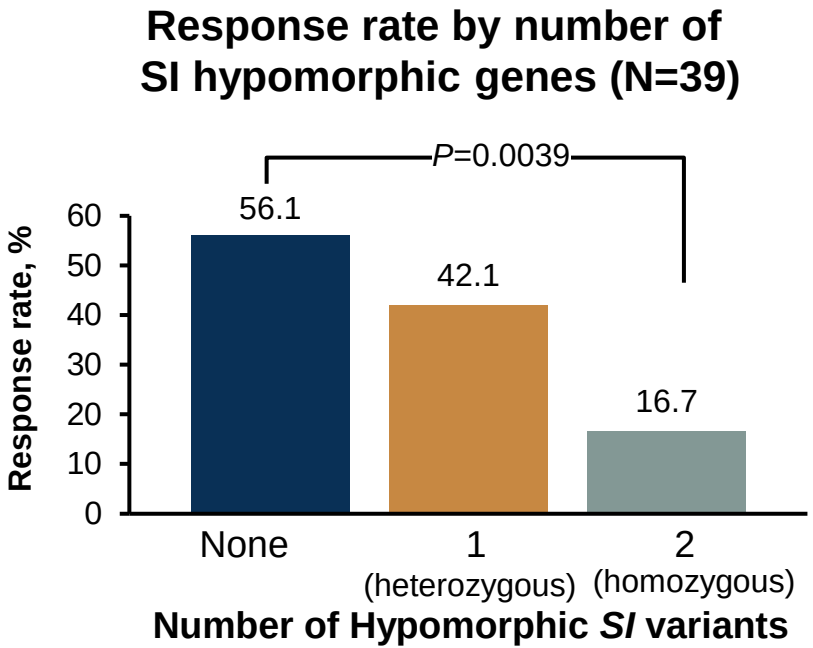
Consider CSID in Low FODMAP Diet Failures





LFD, low FODMAP diet; mNICE, modified National Health and Care Excellence; RCT, randomized controlled trial.

Zheng T et al. *Gut*. 2020;69(2):397-398.

Diagnostic Process for CSID

1

Assess signs and symptoms

Frequent, **lifelong**, and **postprandial** diarrhea, loose stools, gas, bloating

2

Key tests that aid in the diagnosis of CSID

- Disaccharidase assay
- Breath testing
- Sucrose challenge

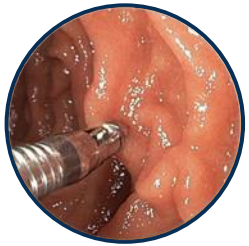
3

Rule out secondary deficiencies

Likely secondary if

- Abnormal histology
- Recent onset or infrequent symptoms
- Lack of consistent therapeutic response

Tests That Aid in Diagnosing CSID



Small bowel biopsy[1,2]

- Considered gold standard
- Specimens sent to specialty lab

Genetic test[2]

- Buccal swab, saliva, or blood
- Detects 37 polymorphisms in *SI* gene

Breath tests[2]

- Hydrogen-methane
- ^{13}C-sucrose

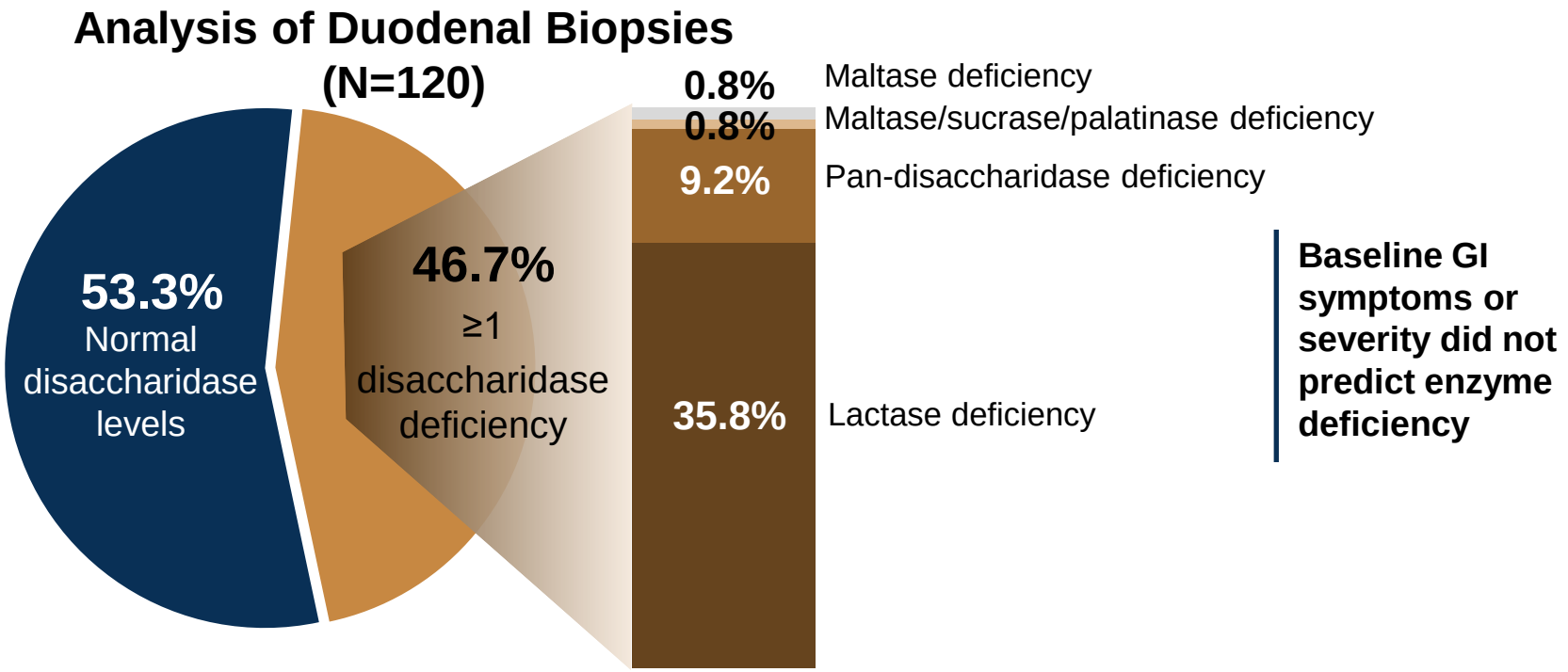
Sucrose challenge[3]

- Simple test, but not validated

SI, sucrase isomaltase

1. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13; 2. Cohen S. *Molecular Cellular Pediatr*. 2016;3:5;
3. Puntis JW and Zamvar V. *Arch Dis Child*. 2015;100(9):869-871.

Prevalence of Disaccharidase Deficiency in Adults With Unexplained GI Symptoms



Viswanathan L et al. *J Neurogastroenterol Motil*. 2020;26(3):384-390.

Dietary Management of CSID

- **Treat with a low sucrose diet**
- Consider reducing dietary starch consumption if moderate symptoms remain
  - If maltase or isomaltase activities are low
  - If patient reports symptoms after starch consumption

All CSID patients are sucrose intolerant; some may also be starch intolerant

McMeans AR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S37-S38.

Limit or Avoid High Carbohydrate Ingredients

Eliminate sugar first

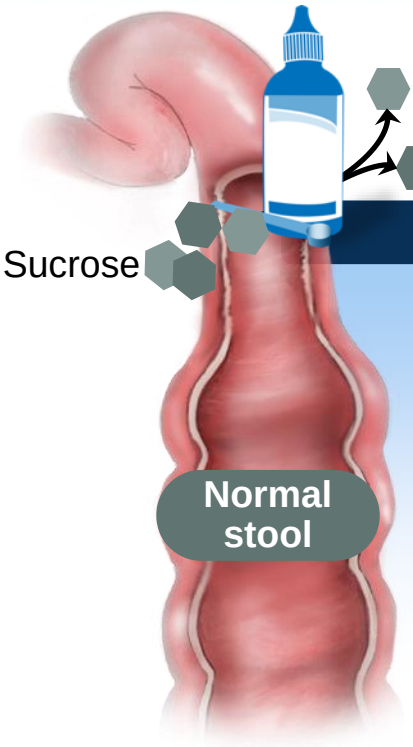
- Table sugar
- Beet sugar
- Brown sugar
- Cane sugar
- Caramel sugar
- Coconut sugar
- Confectioner’s sugar
- Date sugar
- Raw sugar

Reduce starch if still symptomatic

- Potatoes
- Rice
- Bread
- Pasta
- Limit dextrins
- Maltodextrin
- Modified tapioca starch
- Glucose polymers
- Maltose (brown rice syrup, corn syrup solids, malt)

McMeans AR. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S37-S38.

Sacrosidase Oral Solution



Sacrosidase

- Derived from *Saccharomyces cerevisiae*[1]
- Contains ~8500 IU sucrase activity/mL[2]
- Hydrolyzes sucrose[1]
- No activity against starches[1]
- Administer before and during meals or snacks[2]
  - 1 mL if ≤ 15 kg (≤ 33 lbs)
  - 2 mL if > 15 kg (> 33 lbs)

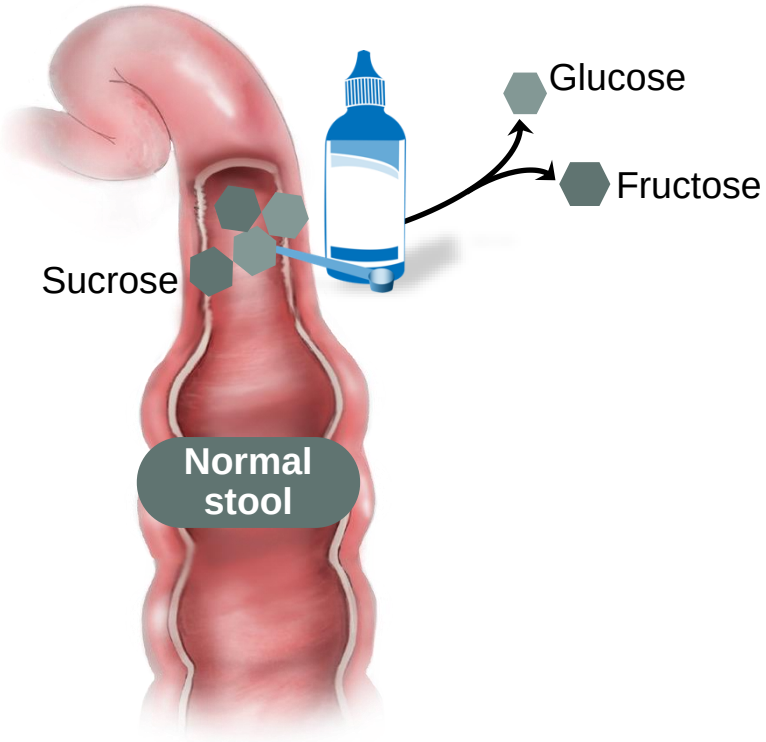
1. Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999;28(2):137-42;
2. Sucraid® (sacrosidase) [prescribing information]. QoL Medical, LLC; Vero Beach, FL; 2019.

Sacrosidase Oral Solution

- May cause an allergic reaction so avoid in those with a known hypersensitivity to yeast or yeast products, papain, or glycerin
- Most common adverse events reported are constipation, insomnia, and headaches
- Caution in patients with poorly controlled diabetes since sacrosidase can raise blood glucose levels by hydrolyzing sucrose
  - Do not heat solution or mix in hot or acidic beverages (juice)
  - Keep refrigerated at 36°F to 46°F (2°C - 8°C) to protect it from heat and light

Sucraid® (sacrosidase) [prescribing information]. QoL Medical, LLC; Vero Beach, FL; 2019.

Sacrosidase Therapeutic Challenge



Advantages[1,2]
• Simple • Supports diagnosis in combination with positive breath test without need for endoscopy • Access issues in absence of diagnosis
Limitations[1,2]
• Best used with dietary restrictions • Self-administered/compliance • Dose response may be variable • Cannot distinguish between CSID and secondary deficiencies

1. Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999;28(2):137-42; 2. Puntis JWL, Zamvar V. *Arch Dis Child.* 2015;100:869-871.

Conclusions

- The majority of dietary carbohydrates are digested by sucrase-isomaltase
- CSID is likely more common than previously believed. Current literature suggests an overall CSID prevalence of 4-5%
- Optimal diagnostic strategy for CSID remains unclear
  - While disaccharidase assay is the current gold standard, the ^{13}C sucrose breath test offers a noninvasive, practical strategy to help establish the diagnosis
- Although current evidence is insufficient to recommend early testing, CSID should be included in the differential diagnosis of patients with presumed IBS, particularly in those that are not responding to dietary modifications
- Treatment of CSID should be individualized based on patient preferences, using an iterative approach that incorporates dietary management and/or enzyme replacement therapy