ADVANCING GI PATIENT CARE 2022

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Emerging Etiologies in IBS

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Disclosures

Consultant: AbbVie, Takeda, Salix

Speakers' Bureau: AbbVie, Salix, Ardelyx, QOL

2021: IBS Guidelines

- ACG Clinical Guideline: Management of IBS
- British Society of Gastroenterology Guidelines on the Management of IBS
- AGA IBS Guidelines (anticipated in 2022)

Jan 2021. Lacy BE et al. *Am J Gastroenterol.* 2021; 116: 17-44; March 2021. Vasant DH et al. *Gut*. 2021; 0:1-27; Chang L et al. *Gastroenterol.* 2021 (in press).

ACG Clinical Guideline: Diagnostic Testing

	Recommendation	Evidence
Positive diagnostic strategy	Consensus	--
Cost-effectiveness of positive diagnostic strategy	Strong	High
Categorization of IBS subtypes (improves patient treatment)	Consensus	--
Routine colonoscopy in IBS patients < age 45 without alarm sxs/signs not suggested	Conditional	Low

Lacy BE et al. *Am J Gastroenterol*. 2021; 116: 17-44.

ACG Clinical Guideline: Diagnostic Testing

	Recommendation	Evidence
Routine **stool testing** in all IBS patients not necessary	Conditional	Low
Celiac disease serology testing in IBS-D	Strong	Moderate
Fecal calprotectin and CRP in IBS-D Fecal lactoferrin	Strong Strong (lactoferrin)	Moderate Very Low
Against testing for food allergies + sensitivities	Consensus	--
Against anorectal physiology testing	Consensus	--

Lacy BE et al. *AJG.* 2021: 116:17-44.

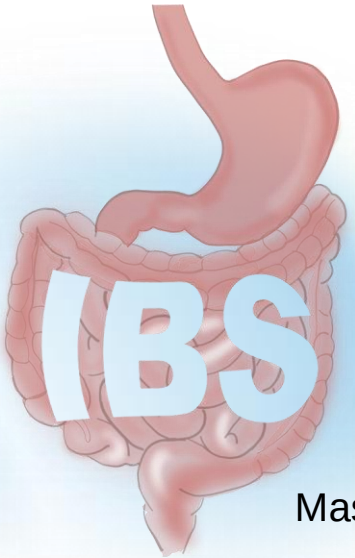
Frequently Considered IBS Etiologies: Emerging Concepts

Colonic Dysbiosis

Small Intestinal Bacterial and Fungal Overgrowth

Inflammatory bowel disease

Infectious diarrhea



Disaccharidase Deficiencies

Bile acid malabsorption (BAM)

Celiac disease

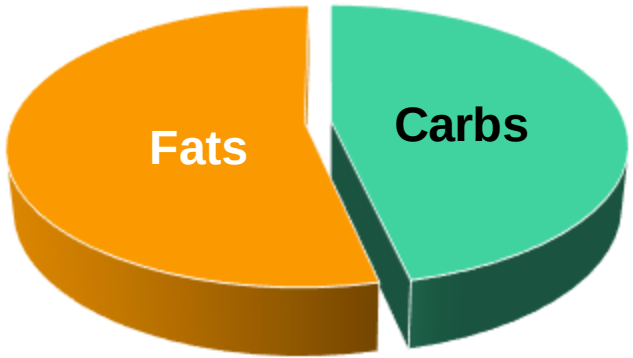
Exocrine pancreatic insufficiency

Microscopic colitis

Mast Cell Disorders / Eosinophilic GI disorders

Increasing Focus on Food as a Cause of IBS Symptoms

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

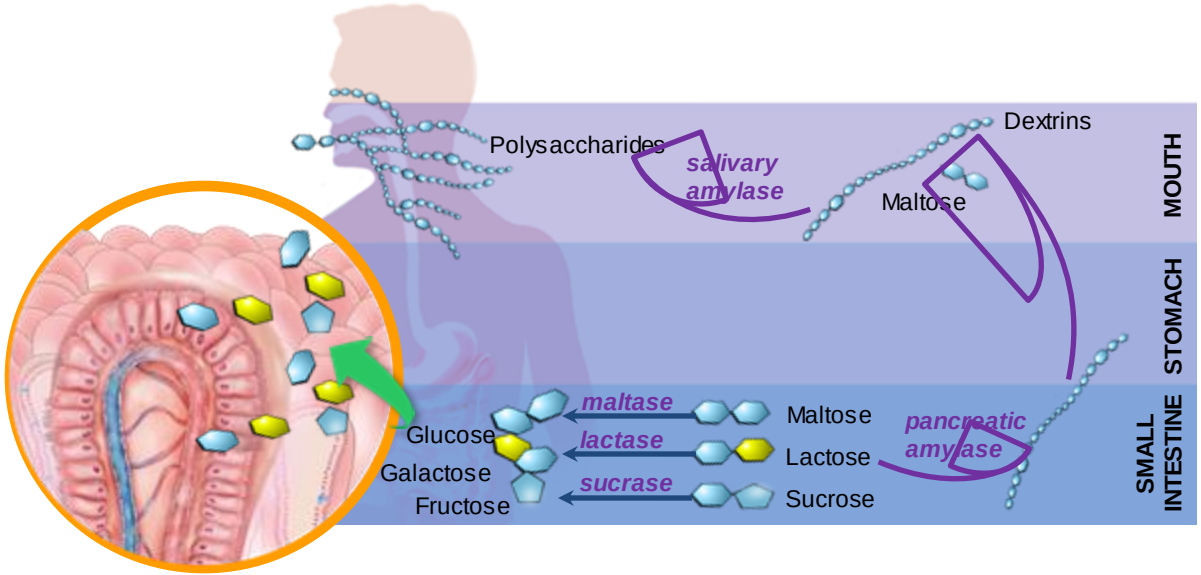


Disaccharides

- Lactose
- Sucrose
- Maltose
- Trehalose

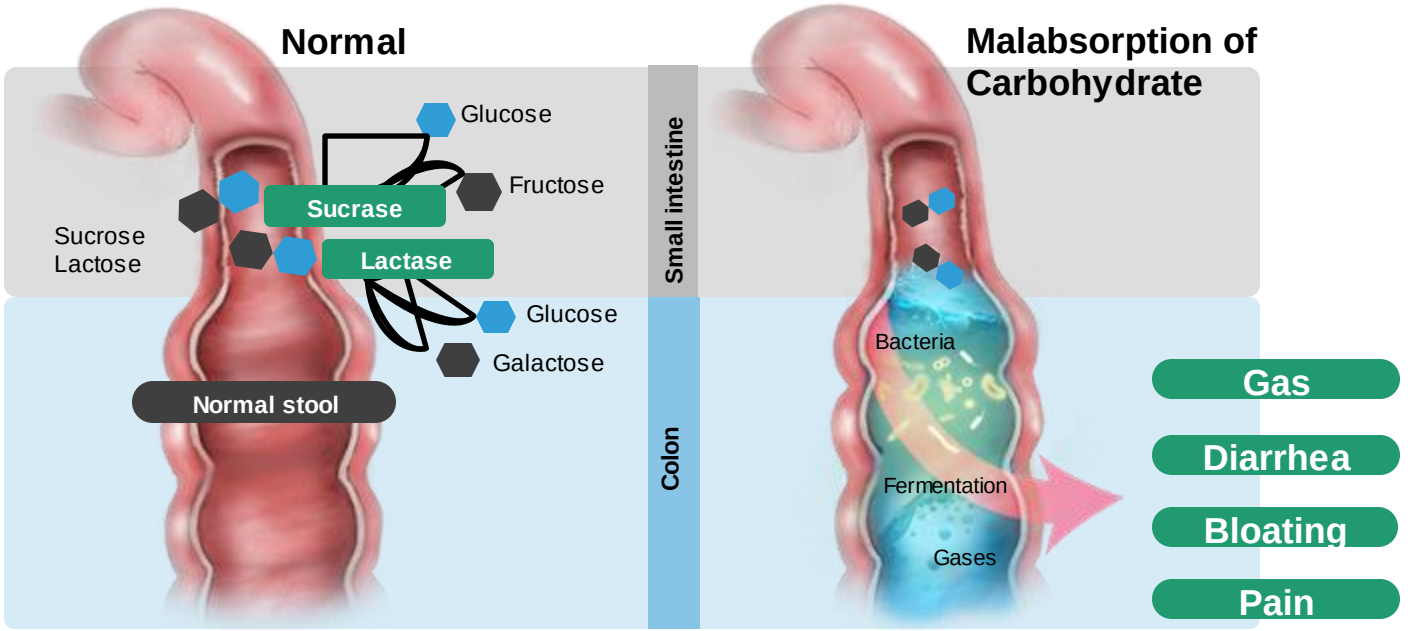
1. US Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1516/Table_1_NIN_GEN_15.pdf. Accessed September 13, 2019;
2. U.S. Department of Agriculture. https://www.nal.usda.gov/fnic/how-many-calories-are-one-gram-fat-carbohydrate-or-protein. Accessed February 9, 2021.

Getting to One: Carbohydrate Digestion and Absorption



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

Clinical Consequences of Carbohydrate Malabsorption



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

Congenital Sucrase-Isomaltase Deficiency (CSID)

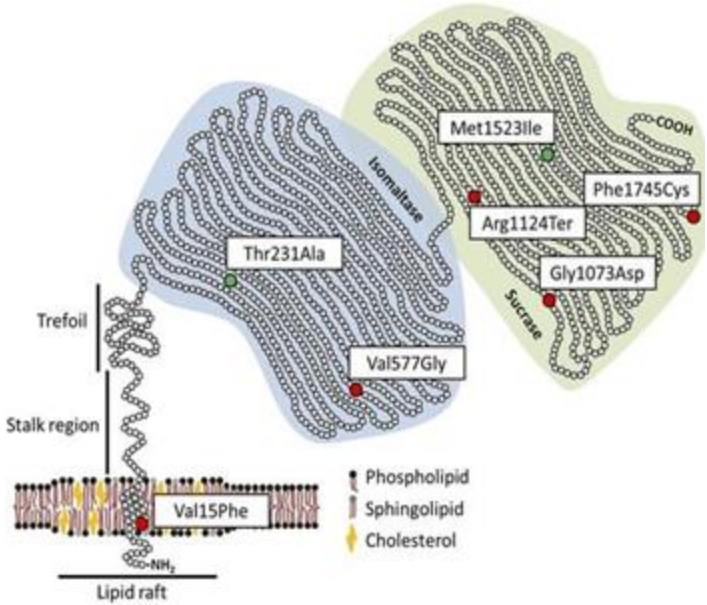
- 1960: first report of autosomal recessive Congenital Sucrase-Isomaltase Deficiency (CSID)

"Diarrhea Caused by Deficiency of Sugar-Splitting Enzymes"

Weijers HA, Van De Kamer JH, Mossel DAA, Dicke WK, et al. Diarrhoea Caused by Deficiency of Sugar-Splitting Enzymes. *Lancet*. 1960; 276 (7145): 296-7.

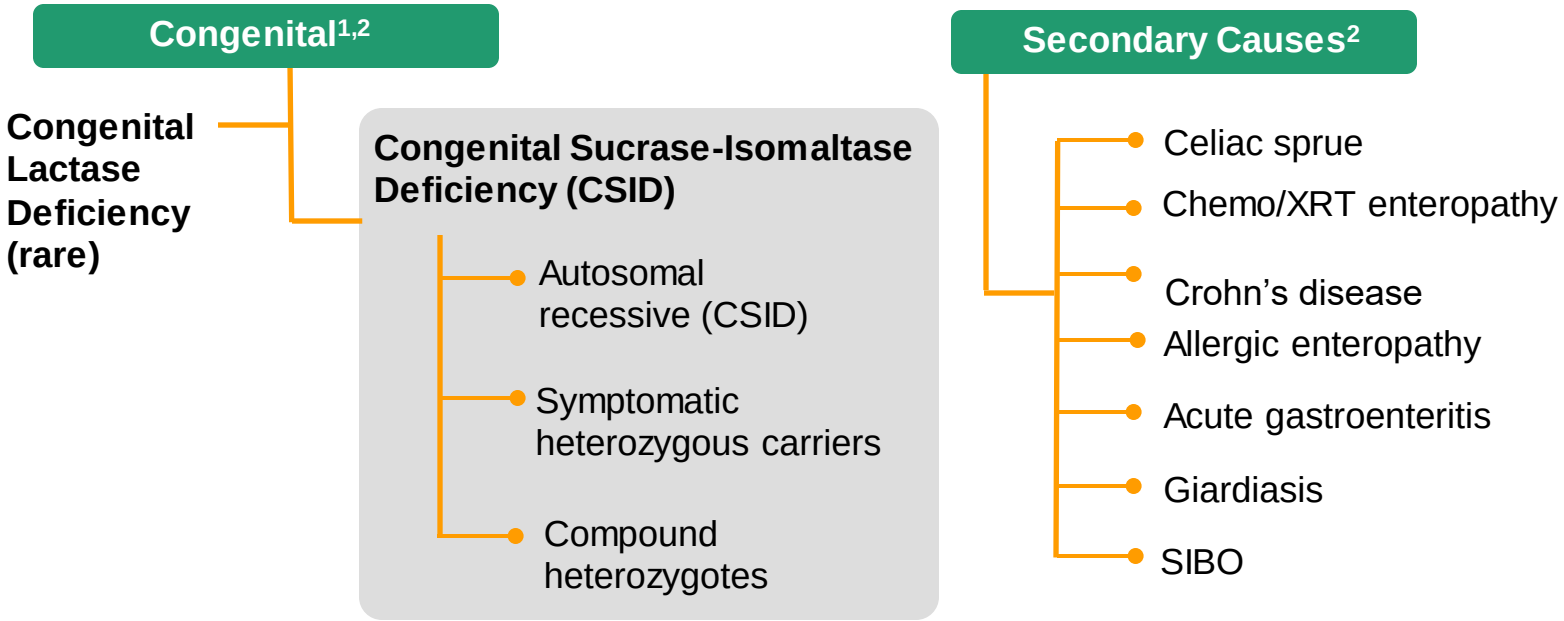
Sucrase-Isomaltase Gene (SI)

- Encodes heterodimer with 2 active sites, sucrase and isomaltase[1]
  - Located on chromosome 3, position 26.1
  - Approximately 100 kilobases
    - 48 exons encoding 1827 amino acids
- 880 SI rare pathogenic variants (SI-RPVs)[2]
- 4 variants account for ~60% of the cases in patients of European descent
- Synthesized as a single glycoprotein chain and cleaved by proteases into sucrase and isomaltase on surface of enterocyte



1. Uhrich S et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (suppl 2): S34-5; 2. Garcia-Etxebarria K et al. *Clin Gastroenterol Hepatol*. 2018; 16 (10): 1673-6; 3. Henström M et al. *Gut*. 2018; 67 (2): 263-70.

Etiologies of Key Disaccharidase Deficiencies



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.

CSID Signs and Symptoms

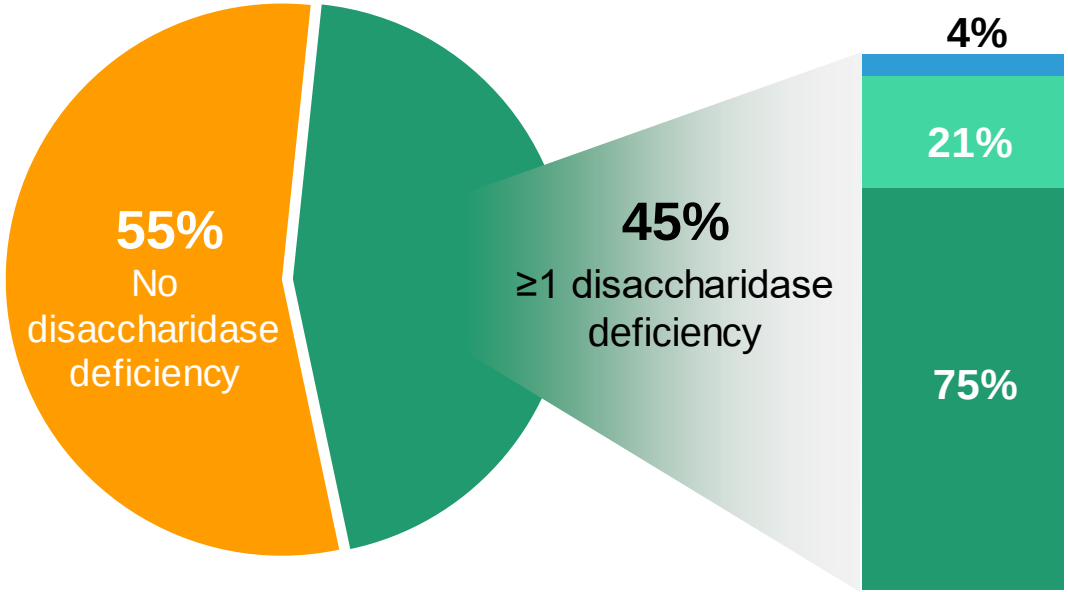
- Frequent, lifelong, and postprandial diarrhea, loose stools, gas, bloating
- Other potential signs
  - Family history
  - Avoidance of carbohydrates, sweets
  - Low BMI
- IBS symptoms not responding to therapy

BMI, body mass index.

1. Kim SB et al. *Dig Dis Sci*. 2020; 65 (2): 534-540; 2. Puertolas MV, Fifi AC. *Nutrients*. 2018; 10: 1835;
3. Treem WR et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13; 4. Cohen SA et al. *Mol Cell Pediatr*. 2016; 3: 5.

How Common Is Disaccharidase Deficiency?

Analysis of Mucosal Biopsies (N=27,875)



9.3%
were sucrase deficient overall

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

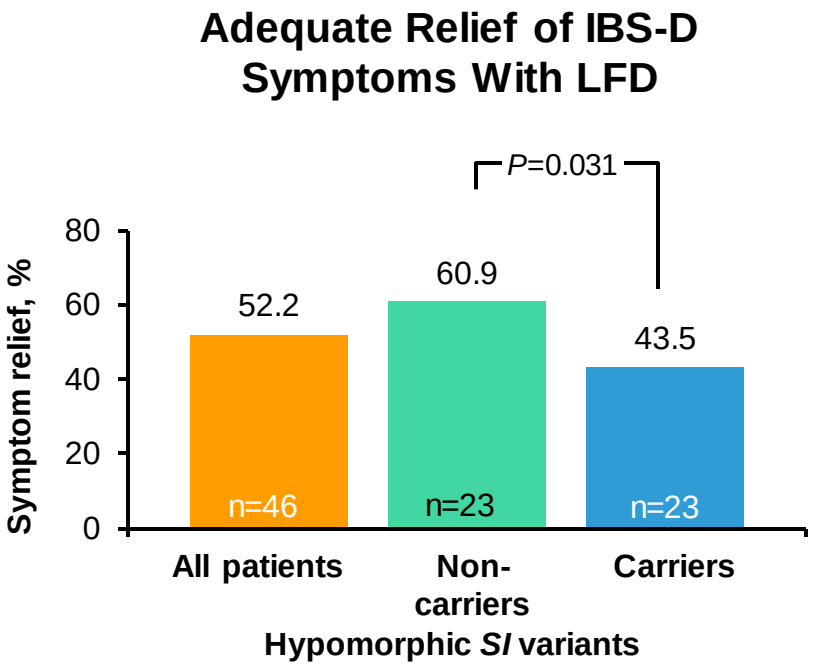
Incidence of Sucrase-Isomaltase Rare Pathogenic Variants (*SI*-RPV) in GI Patients

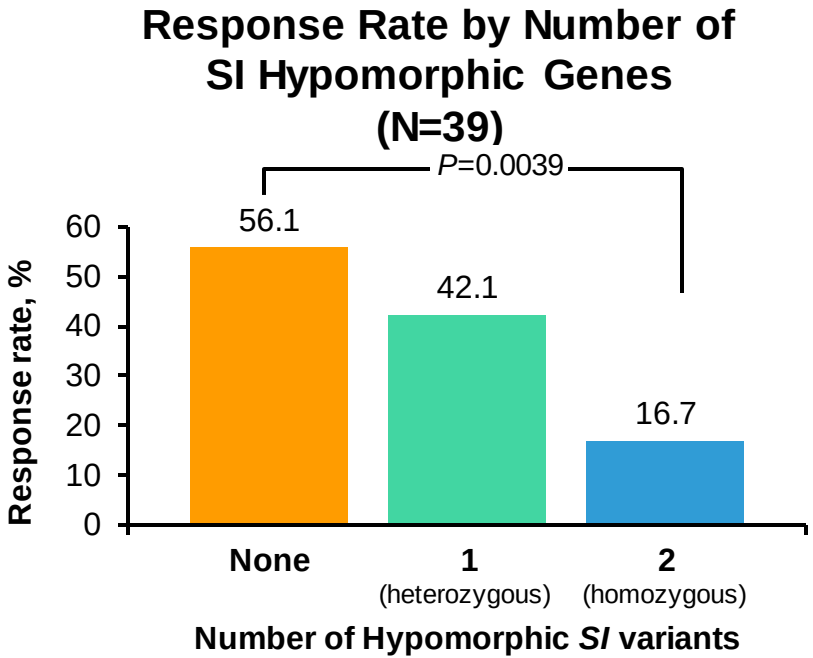
- Genetic evidence suggests link between SI variations and IBS susceptibility
- SI-RPV does not always cause CSID, but is highly correlated

	Chronic diarrhea[1]	Patients with IBS-D diagnosis
Subjects (N)	308	952
With rare CSID variants (n)	14	40
Incidence	4.5%	4.2%

1. QOL Medical. Data on file; 2. Garcia-Extebarria K et al. *Clin Gastroenterol Hepatol.* 2018; 16 (10): 1673-1676. doi: 10.1016/j.cgh.2018.01.047

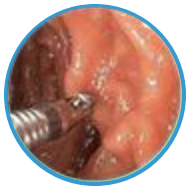
Consider CSID in Low FODMAP Diet Failures





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.

Tests for Diagnosing CSID



Duodenal biopsy[1,2]

- 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 but not validated

SI, sucrase isomaltase

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

Disaccharidase Assay Steps

Collect

- First biopsies
- 2-3 biopsies obtained from distal duodenum/proximal jejunum
  - Disaccharidase levels decreased by ≥33% in proximal duodenum
- Place samples in empty eppendorf tube
  - Do not place the tissue on gauze, filter paper, or use any type of support medium, not even saline

Freeze

- Place eppendorf tube with collected sample immediately on ice (dry or wet ice) and freeze within 2 hours of collection at -20° C to -70 ºC.

Ship

- Ship frozen on dry ice promptly on the same day
- Turn around time typically 3-7 days

1. Burke M et al. *Clin Biochem Rev*. 2019; 40 (4): 167-174; 2. Treem WR et al. *J Pediatr Gastroenterol Nutr*. 2012; 2: 55: S7-S13.

Disaccharidase Assay: Gold Standard

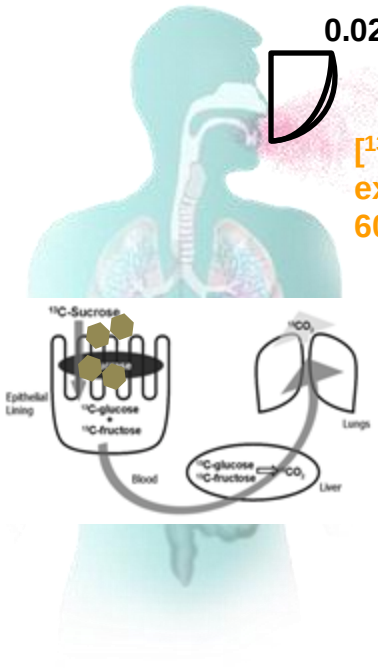
Disaccharidase Reference Intervals

Enzyme	Normal range (U/min/g protein)[a]
Lactase	15 – 46
Sucrase	25 – 70
Maltase	100 – 224
Palatinase	5 – 26

Advantages
• Ability to determine enzyme level for all disaccharidases
• Some insurance payors are requiring prior to covering enzyme replacement therapy
Limitations
• Invasive and expensive
• Assay variability (27%); does not assess function
• False positives with obtaining samples from the proximal duodenum; patchy distribution of disaccharidases in the brush border
• False positives with mishandling specimens

1. Burke M et al. *Clin Biochem Rev*. 2019; 40 (4): 167-174; 2. Treem WR et al. *J Pediatr Gastroenterol Nutr*. 2012; 2: 55: S7-S13.

^{13}C Sucrose Breath Test



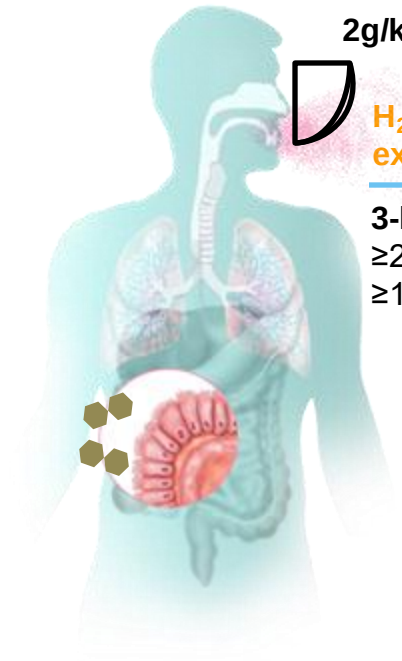
Normal sucrase activity[a]
Females: >5.10%
Males: >3.91%

Advantages
• Safe (stable isotope) and non-invasive
• Better tolerated, more specific than hydrogen/methane test
• Inexpensive (free)
Limitations
• False positives with Dumping Syndrome
• False negatives with delayed gastric emptying
• May require for further validation; unknown correlation to disaccharidase assays

[a]90-minute sucrose digestion.

1. Robayo-Torres CC et al. *J Ped Gastroenterol Nutr*. 2009; 48 (4): 412-8; 2. Rezaie A et al. *Am J Gastroenterol*. 2017; 112 (5): 775-84;
3. Treem WR et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13.

Sucrose Hydrogen Methane Breath Test



2g/kg sucrose solution

H_2 and/or methane exhalation over 3 hours

3-hr breath test positive:
≥20 ppm H_2 from baseline
≥10 ppm CH_4 from baseline

Advantages
• Safe and non-invasive
• Patient can do at home
Limitations
• Time consuming (3 hours)
• Not specific
• False positives due to Dumping Syndrome, SIBO
• False negatives due to delayed gastric emptying, recent antibiotic use, and non-hydrogen producers
• May cause symptoms in patients with CSID due to large sucrose load

1. Robayo-Torres CC et al. *J Ped Gastroenterol Nutr*. 2009; 48 (4): 412-8; 2. Rezaie A et al. *Am J Gastroenterol*. 2017; 112 (5): 775-84;
3. Treem WR. *J Pediatr Gastroenterol Nutr*. 2012; 55 (Suppl 2): S7-S13.

Genetic Testing

- Buccal swab or blood
- Tests for 37 common pathogenic variants of the SI gene
- Positive genetic test
  - Same pathogenic SI gene variant in both alleles
  - Different pathogenic SI gene variant in each allele
  - Pathogenic SI gene variant in one allele only

Advantages
• Simple • Noninvasive • If positive, confirms CSID regardless of genotype
Limitations
• Costly • Lengthy turnaround time (1 month) • Tests only 37 of >2000 *SI* variants –normal test does not rule out CSID

Chumpitazi BP et al. *J Pediatr Gastroenterol Nutr*. 2012; 55 (2): S36.

4-4-4 Sucrose Challenge

1. Stir 4 tablespoons of ordinary table sugar into a 4-ounce glass of water and mix until completely dissolved
2. Drink on empty stomach
3. Monitor for symptoms (bloating, gas, and diarrhea) during subsequent 4-8 hours

Advantages
• Simple
• Inexpensive
• Theoretically sensitive; high likelihood of symptoms in CSID
Limitations
• Not validated
• Unknown NPV and PPV
• May result in severe symptoms

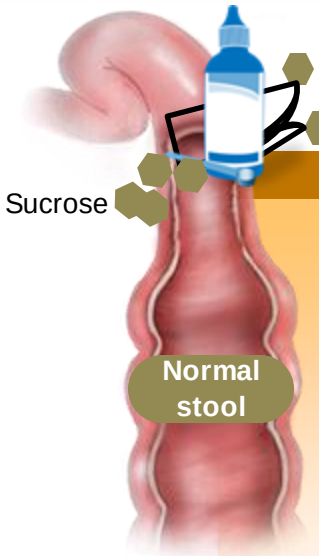
CSID Disease Information. Available at http://www.csiddiseaseinfo.com. Accessed June 16, 2020.

Dietary Management of CSID

- Use a dietician
- 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

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

Sacrosidase Oral Solution

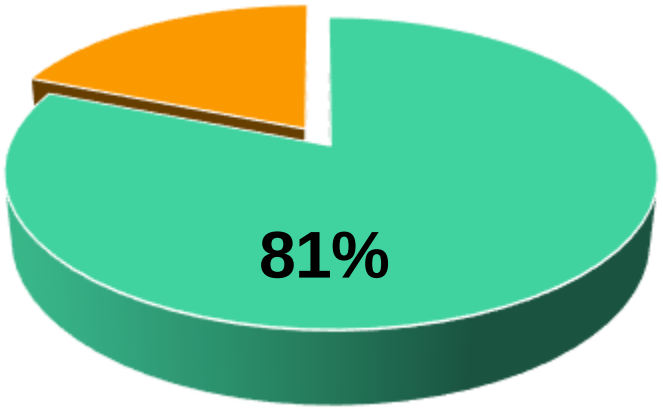


Sacrosidase

- Derived from *Saccharomyces cerevisiae*[1]
- Contains ~8500 IU sucrase activity/mL[2]
  - Hydrolyzes sucrose[1]
- No activity against starches[1]
  - 1 mL if ≤15 kg (≤33 lbs) = 28 drops = 8,500IU
  - 2 mL if >15 kg (>33 lbs) = 56 drops = 17,000IU
- Mix in 2 to 4 ounces of water, milk, or infant formula. Do not dissolve it or take with fruit juice.
- Administer before and during meals or snacks[2]

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.

Overall Symptomatic Response to Sacrosidase



Post-hoc Responder Analysis[a] (N=28 children with symptomatic CSID)

[a]Asymptomatic defined as symptom-free for ≥7 of the 10 study days.
Treem WR et al. *J Pediatr Gastroenterol Nutr.* 1999; 28 (2): 137-42.

Sacrosidase Oral Solution

- Avoid in those with known hypersensitivity to yeast or yeast products, papain, or glycerin
- Most common adverse events are constipation, insomnia, and headaches
- Caution in patients with poorly controlled diabetes due to increased 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 from heat and light

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

CSID: Conclusions

- Most dietary carbohydrates are digested by sucrase-isomaltase
- CSID is common. Current literature suggests prevalence of 4-5% in IBS-D
- Optimal diagnostic strategy remains unclear
  - Disaccharidase assay is the current gold standard; ^{13}C sucrose breath test offers a noninvasive, practical strategy
- CSID should be included in the differential diagnosis of patients with IBS symptoms, particularly in those not responding to dietary modifications
- Treatment should be individualized based on patient preferences, incorporating dietary management +/- sucrase enzyme replacement therapy


Q&A