

INS AND OUTS OF IBD

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SIBO Vs. CSID

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Disclosures



Carol Antequera, DMSc, PA-C

- No relevant relationships.

Objectives

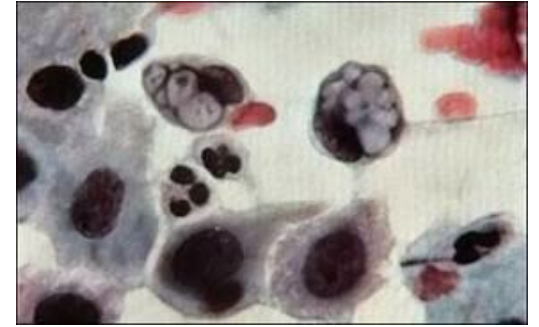


- Define SIBO and CSID
- Differentiate between the two conditions
- How to test for SIBO and CSID
- Interpretation of diagnostic testing
- Treatment options

What Is SIBO?



- Presence of excessive number of bacteria in the small bowel leading to symptoms of **bloating**, gas, abdominal distension, nausea, abdominal pain or diarrhea
- Positive glucose breath test
- Small bowel aspirate
 - $>10^3$ cfu/ml (duodenum)



ACG Clinical Guideline Diagnosis of SIBO

- 1. We suggest the use of breath testing (glucose or lactulose hydrogen) **for the diagnosis of SIBO in patients with IBS** (conditional recommendation, very low level of evidence).
- 2. We suggest using glucose or lactulose hydrogen breath tests **for the diagnosis of SIBO in symptomatic patients with suspected motility disorders** (conditional recommendation, very low level of evidence)
- 3. We suggest testing for SIBO using glucose or lactulose hydrogen breath tests **in symptomatic patients (abdominal pain, gas, bloating, and/or diarrhea) with previous luminal abdominal surgery** (conditional recommendation, very low level of evidence).

What do we know about methane?



- Methanogens are archaea
 - prokaryotic organisms distinct from bacteria & eukaryotes
- Methanobrevibacter smithii (*M. smithii*) is the key methanogen responsible for breath methane production in humans
- Diagnosis: CH₄ > 10 ppm (a rise or baseline) at any point during the 90 min breath test
- Production of Methane requires metabolism of hydrogen thereby resulting in lower levels of hydrogen on breath testing
- Methane is associated with slowing of gut transit
- A meta-analysis found that methane is associated with chronic constipation (OR 3.51, 95% CI 2.00-6.16)
- Very limited treatment data:
 - Rifaximin 550 mg tid and Neomycin 500 mg bid x 14 days recommended

Breath Testing for SIBO: Preparation

A stylized illustration of a city skyline with various skyscrapers and palm trees, rendered in shades of blue, green, and orange, positioned along the top edge of the slide.

- **Before:**
 - Avoid antibiotics for 4 weeks
 - Avoid promotility agents & laxatives for 1 week.
 - Day before test, avoid fermentable foods (e.g., complex carbohydrates) and patient should fast for 8–12
- **During the breath test,**
 - Avoid smoking & minimize physical exertion

Breath Test: Collection and Analysis



Bacterial
Overgrowth

75 g Glucose 250 ml H₂O

Every
15 min – 2 h

H₂ ≥ 20 ppm
CH₄ ≥ 10 ppm
H₂ + CH₄ ≥ 20 ppm

Types of SIBO

A stylized illustration of a city skyline with various skyscrapers and buildings in shades of blue, green, and orange, set against a light orange background.

Hydrogen predominant

- Most commonly associated with symptoms of bloating and diarrhea

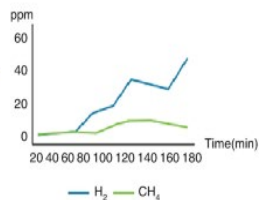
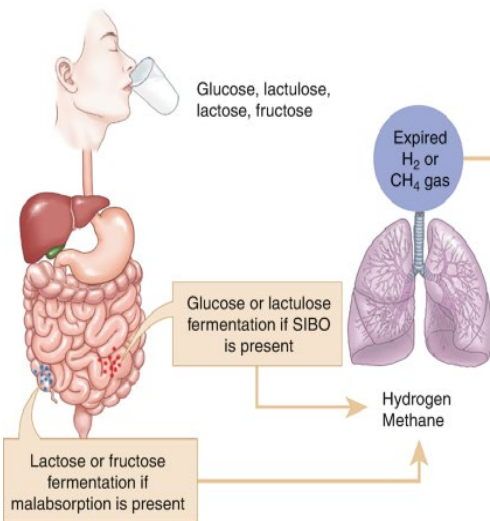
Methane predominant

- Most commonly associated more with constipation and *M. smithii* in stool
- Elevated baseline samples on Breath test

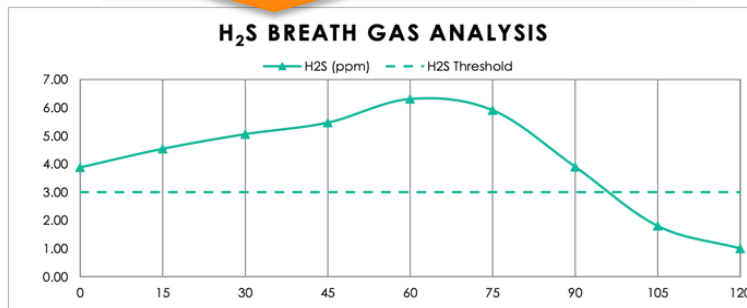
Hydrogen Sulfide

- The missing link
- 'Non-hydrogen-producing' bacteria
- Most commonly associated with IBS-D

Advances in Breath testing



Levels of $H_2S \geq 3.00$ ppm at any point during the breath test are considered excess and are associated with diarrhea and IBS-D.



HYDROGEN

Indicative of:
Small Intestinal Bacterial Overgrowth (SIBO)

Correlated with:
No correlation with symptoms

METHANE

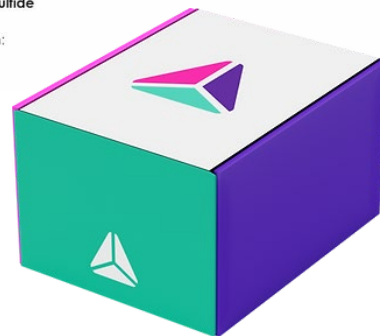
Indicative of:
Intestinal Methanogenic Overgrowth (IMO)

Correlated with:
Constipation

HYDROGEN SULFIDE

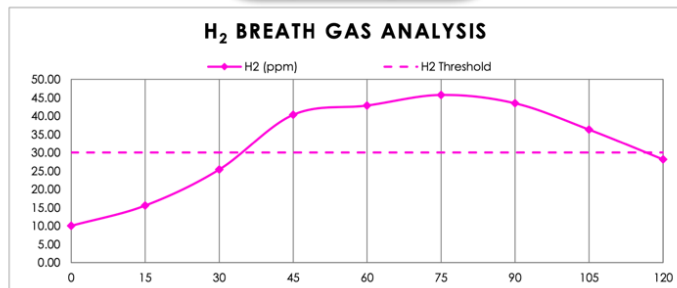
Indicative of:
Excess Hydrogen Sulfide

Correlated with:
Diarrhea



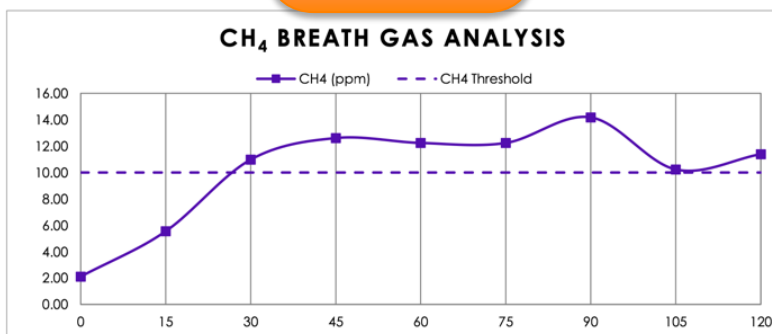
Breath Test Interpretation

Hydrogen



> 20ppm Indicative of SIBO¹

Methane



The North American Consensus defines abnormal levels of CH₄ as ≥ 10.00 ppm at ANY point during the breath test.

Indicative of intestinal methanogenic overgrowth and correlated with constipation¹

1. Rezaie A et al. *Am J Gastroenterol.* 2017;112(5):775-784. 2. Shah A et al. *Am J Gastroenterol.* 2020;115(2):190-201.

Small Bowel Aspiration

Gold
Standard



Sampling

Collection of 3ml of duodenal fluid is done via Ligo catheter with side holes.

Any bacterial growth $> 1,000\text{cfu/mL}$ is reported

Limitations

Invasive
procedure

Costly

Detection of
proximal
SIBO only

Sampling
error

ACG Clinical Guideline Diagnosis of SIBO



We suggest the use of antibiotics in symptomatic patients with SIBO to eradicate overgrowth and resolve symptoms

(conditional recommendation, low level of evidence)



Treatment of SIBO

Treatment of SIBO: ACG Guidelines

Antibiotic	Recommended Dose	Efficacy
Rifaximin	550 mg tid	61-78%
Amoxicillin-clavulanic acid	875 mg bid	50%
Ciprofloxacin	500 mg bid	43-100%
Doxycycline	100 mg qd-bid	—
Metronidazole	250 mg tid	43-87%
Neomycin	500 mg bid	33-55%
Norfloxacin	400 mg qd	30-100%
Tetracycline	250 mg qid	87.5%
Trimethoprim-sulfamethoxazole DS	160/800 mg bid	95%

- Most of the studies are small and methodologically flawed.
- Lack of a gold standard for diagnosis presents problems
- Most treat to negative BT result but others to symptom relief
- Largest amount of data with rifaximin
- Rifaximin is not FDA approved for SIBO only IBS-D

What about probiotics for SIBO?

- *Meta-analysis 14 studies/8 abstracts (10-480 pts each)*
- *Wide range of probiotics*
- *No decrease in prevalence of SIBO with probiotic vs. placebo (6 studies, RR = 0.63, 95% CI = 0.29-1.36)*
- *Eradication rate:*
 - Probiotics alone = 53%
 - Probiotics & antibiotics = 86%
 - Probiotics vs. antibiotics (6 studies) = 38% v. 18%, $p = 0.091$
 - Probiotic vs. placebo (2 trials) RR = 1.6, 95% CI = 1.19-2.17
- *Recently reported cases of lactic acidosis, brain fog, SIBO attributed to probiotics*

Future Directions in SIBO

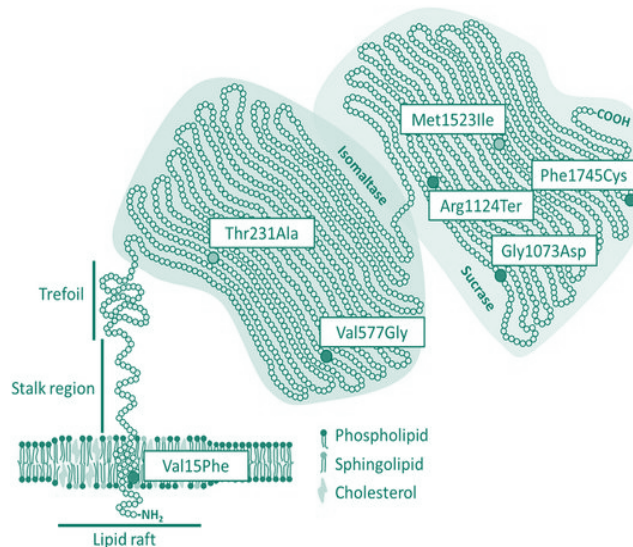
A stylized illustration of a city skyline with various skyscrapers and palm trees, rendered in shades of blue, green, and orange, positioned along the top edge of the slide.

- Use of AI to improve diagnostics in SIBO
- Development of improved aspiration techniques in SIBO
- Improved breath testing techniques and advancements in testing of intestinal gases in SIBO from various systemic conditions
- Prevention of SIBO recurrence
- Cyclic antibiotics for SIBO recurrence?

What is CSID

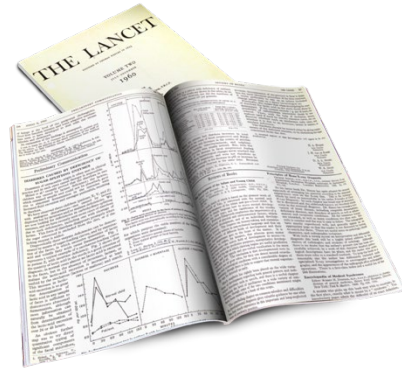
- CSID is a rare genetic disorder affecting the digestive function of sucrase and isomaltase enzymes in the small intestine.
- This autosomal recessive disorder is caused by pathogenic mutations in the sucrase-isomaltase gene (*SI*)
- sucrase and isomaltase¹
 - Located on chromosome 3, position 26.1.
 - 2146 rare variants with 880 SI rare pathogenic variants (SI-RPVs)²
 - Genetic testing is limited to only 37 pathogenic variants
- In 31 biopsy-diagnosed CSID patients, ≥ 1 of the 4 most common CSID variants was present in approximately 60% of the patients' alleles¹
- – Genotypes include homozygous, compound heterozygous, and simple heterozygous

SI protein structure and functional domains³



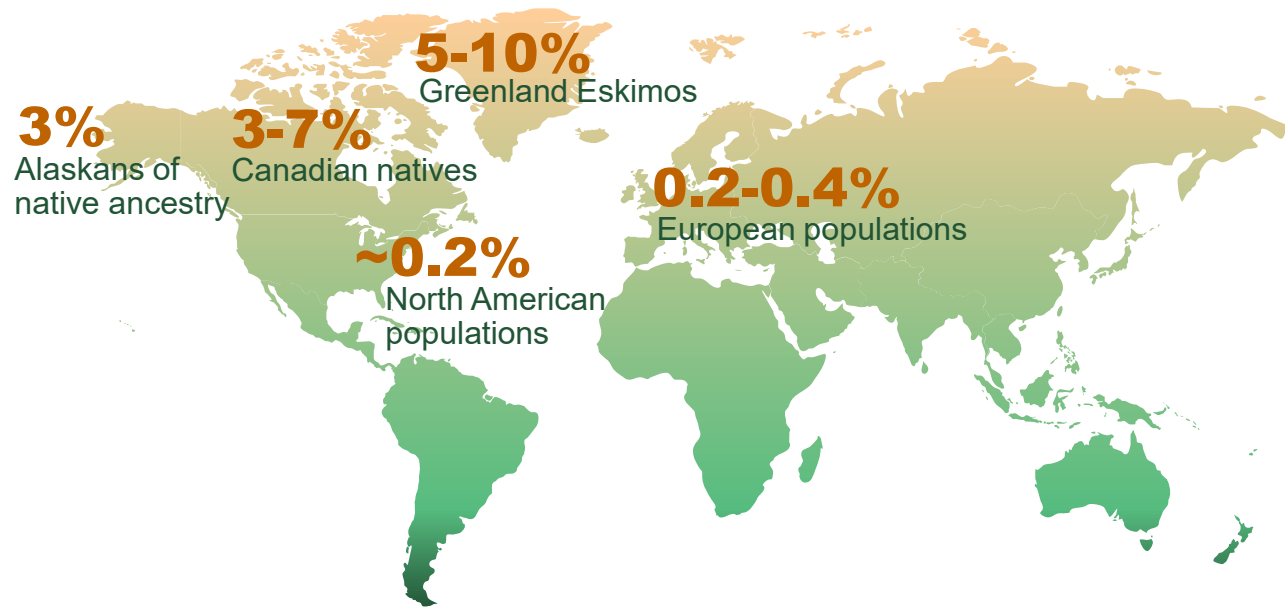
Uhrich S et al. *J Pediatr Gastroenterol Nutr.* 2012;55(suppl 2):S34-5; 2. Garcia-Etxebarria K et al. *Clin Gastroenterol Hepatol.* 2016;16(11):1670-6; 3. Hanson M et al. *Gut.* 2018;67(2):263-70.

Congenital Sucrase-Isomaltase Deficiency (CSID)



First reported in 1960
and described as “diarrhoea
caused by deficiency of
sugar-splitting enzymes”¹

Historic prevalence of sucrase deficiency²



1. Weijers HA et al. *Lancet*. 1960;276(7145):296-7. 2. Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21(1):1-14.

Sucrase-Isomaltase Deficiency



Prevalence

- Prevalence of CSID and acquired sucrase-isomaltase deficiency (SID) is not well known¹
 - CISD is particularly common in Greenland and Canadian Eskimos (5%)
 - Sucrase deficiency was present in 35% (11/31) of adults undergoing EGD for evaluation of chronic diarrhea and/or abdominal pain

Signs and symptoms

- **Frequent, lifelong, and postprandial** diarrhea, loose stools, gas, bloating¹⁻⁴
- Other potential signs¹⁻⁴
 - Family history
 - Avoidance of carbohydrates, sugary foods
 - Low BMI
- IBS symptoms not responding to therapy
- Not just children, may present later in life

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. *J Pediatr Gastroenterol Nutr*. 2012;55(Suppl 2):S7-S13. 4. Cohen SA. *Mol Cell Pediatr*. 2016;3:5.

Etiologies of Key Disaccharidase Deficiencies: Lactase and Isomaltase-Sucrase

Congenital¹⁻³

Congenital lactase deficiency

Adult-onset lactase deficiency

- Most common form of disaccharidase deficiency by far
- Highly prevalent among Asian, African, Native-American, and Mediterranean populations

Congenital Sucrase-Isomaltase Deficiency (CSID)

- Autosomal recessive (CSID)
- Symptomatic heterozygous carriers
- Compound heterozygotes

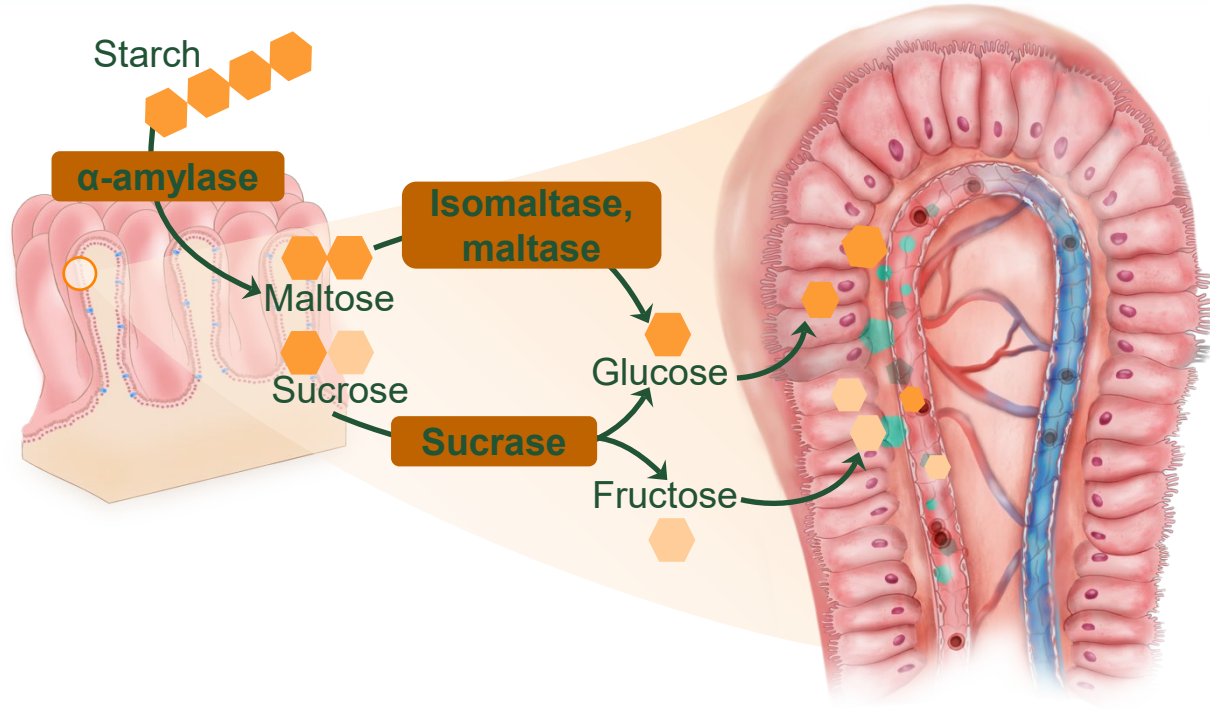
Secondary causes²

- Celiac disease
- Chemo/XRT enteropathy
- **Crohn's disease**
- Allergic enteropathy
- Acute gastroenteritis
- Giardiasis
- SIBO

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. 3. Misselwitz B et al. *Gut.* 2019;68:2080-2091.

Normal Carbohydrate Digestion

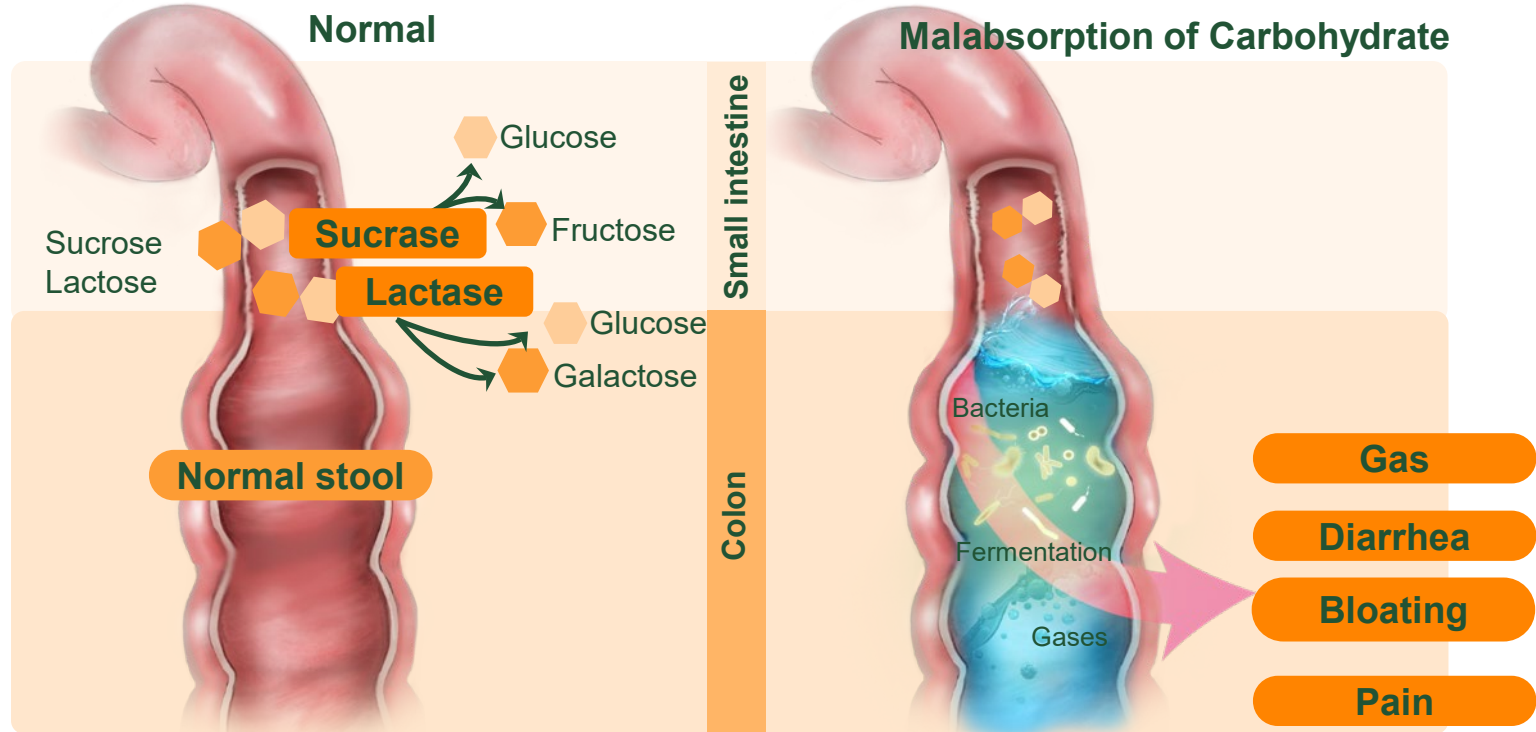


Starches need to be hydrolyzed to monosaccharides for absorption

Starts with amylase and is followed by α -glucosidases

Simple sugars are absorbed into the bloodstream, whereas **disaccharides are not absorbable directly and must be digested by disaccharidases** (eg, sucrase-isomaltase and maltase-glucoamylase)

Clinical Consequences of Disaccharide Maldigestion



Food intolerance –portion driven Diet

- Clinical manifestations will relate to amount of sugar + possibly starch in the diet.
- 60% of calories derived from carbs in US; 30% from sugar
- Added sugars represent a significant proportion of the US diet, supplying from 13.1% to 17.5% of total daily energy among children.



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

Diagnosing Disaccharide Deficiency



Small bowel biopsy¹⁻³

- Considered gold standard
- Specimens sent to specialty lab
- **Advantage:** only test to differentiate primary from secondary SID
- **Limitations:** invasive/expensive, assay variability, false positives



Genetic test^{2,3}

- Blood, buccal swab, or saliva
- Detects -13901/C/T polymorphism in lactase gene
- Detects 37 polymorphisms in SI gene
- Advantages: non invasive, if positive confirms CSID regardless of genotype
- Limitations: costly, tests only 37 of >2000 SI variables – normal test does not rule out CSID



Breath tests^{2,3}

Hydrogen-methane:

- **Advantages:** safe/non-invasive
- **Limitations:** not specific, false positives with dumping syndrome and SIBO, false negative w/ delayed gastric emptying, antibiotics use, induced symptoms with large sucrose load

¹³C-sucrose:

- **Advantages:** Safe (stable isotope), non invasive, better tolerated, more specific than hydrogen/methane test
- **Limitations:** cannot differentiate CSID from secondary causes, false positives with dumping, false negative with delayed gastric emptying, need further validation



lactose or sucrose challenge^{3,4}

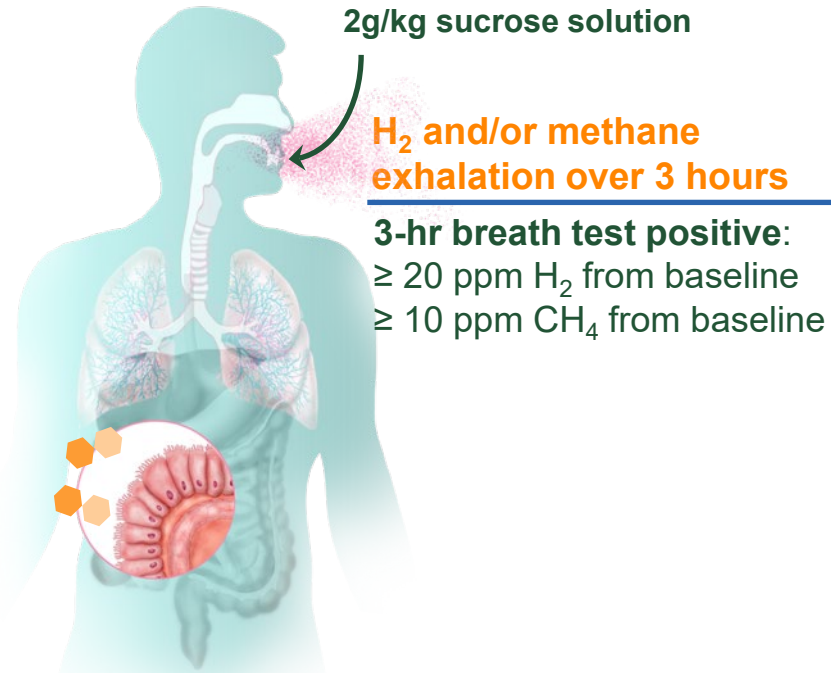
- 4 tbsp table sugar in 4 oz water
- **Advantages:** simple and easy, inexpensive, theoretically sensitive
- **Limitations:** not validated, may induce severe symptoms

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. Misselwitz B et al. *Gut.* 2019;68:2080-2091. 4. Puntis JW and Zamvar V. *Arch Dis Child.* 2015;100(9):869-871

Sucrose Hydrogen Methane Breath Test for CSID



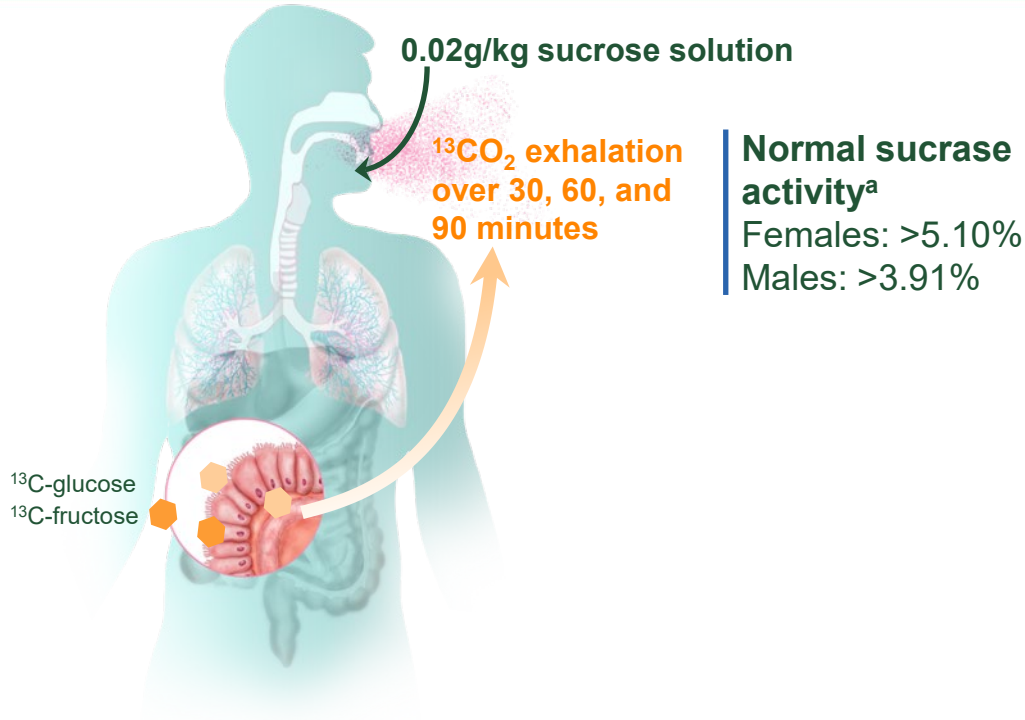
Advantages

- Safe and noninvasive
- 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

^{13}C Sucrose Breath Test for CSID/SID



Advantages

- Safe (stable isotope) and noninvasive
- Better tolerated and more specific than hydrogen/methane test

Limitations

- False positives with Dumping Syndrome
- False negatives with delayed gastric emptying
- Need for further validation

^a90-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. *J Pediatr Gastroenterol Nutr.* 2012;55(Suppl 2):S7-S13.

Enzyme Function via Disaccharidase Assay Is the Gold Standard for CSID Diagnosis

Disaccharidase Reference Intervals

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

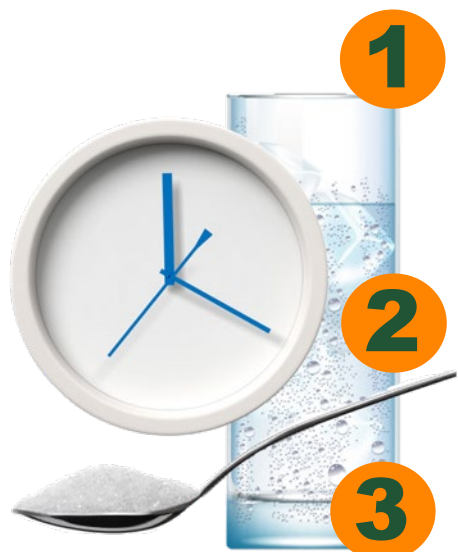
Advantages

- Only test to differentiate primary from secondary SID
- Ability to determine enzyme activity for all disaccharidases
- Increasingly, insurance payors are requiring DA prior to covering enzyme replacement therapy

Limitations

- Invasive and expensive and time consuming
- Assay variability (27%)
- False positives with obtaining samples from the proximal duodenum and due to patchy distribution of disaccharidases in the brush border
- False positives with mishandling specimens

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

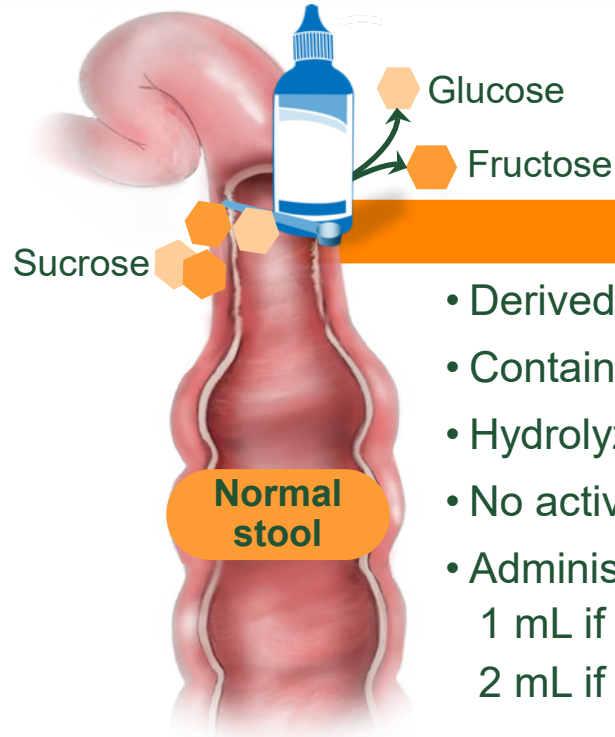
- Simple and easy
- Inexpensive
- Theoretically sensitive; high likelihood of symptoms in CSID

Limitations

- Not validated
- Unknown NPV and PPV
- May result in severe symptoms

Pharmacologic Treatment of CSID

Sucrosidase Oral Solution



Sucrosidase

- Derived from *Saccharomyces cerevisiae*¹
- Contains ~8500 IU sucrase activity/mL²
- Hydrolyzes sucrose¹
- No activity against starches¹
- Administer before and during meals or snacks²
 - 1 mL if ≤ 15 kg (≤ 33 lbs)
 - 2 mL if > 15 kg (> 33 lbs)

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)

Low FODMAP Diet

Beneficial for
both SIBO
and CSID

Fermentable oligo-, di-, monosaccharides and polyols

	Excess Fructose	Honey, apples, pears, peaches, mangos, fruit juice, dried fruit
	Fructans	Wheat (large amounts), rye (large amounts), onions, leeks, zucchini
	Lactose	Milk (cow, goat, or sheep), custard, ice cream, yogurt, soft unripened cheeses (eg, cottage cheese, ricotta)
	Sorbitol	Apricots, peaches, artificial sweeteners, artificially sweetened gums
	Raffinose	Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

Key Concepts



- Breath testing is useful for identifying SIBO noninvasively before antibiotic treatment.
- $>10^3$ CFU/mL is most suggestive of SIBO when using duodenal culture.
- *Methanobrevibacter smithii* appears to be the key methanogen responsible for breath methane production and is associated with constipation.
- Targeting methanogens may reduce methane production and improve constipation.
- There is inconsistent data to support recommending specific probiotics in the treatment of SIBO.

Key Concepts cont



- Most 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 approach that incorporates dietary management and/or enzyme replacement therapy

THANK YOU

