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

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Carol Antequera, DMSc, PA-C

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Functional GI Symptoms Are Common


Adults in US report symptoms consistent with

- IBS\(^1\)

Reported prevalence of

- functional diarrhea\(^2\)
- functional constipation\(^2\)
- bloating\(^2\)

Differential Diagnoses of IBS-D

- Celiac disease
- Food intolerance/allergy
- Bile acid diarrhea
- Microscopic colitis
- Post-infectious diarrhea
- Medication-induced diarrhea
- Inflammatory bowel disease
- Gastrointestinal infection
- Small intestinal bacterial overgrowth
- Disaccharidase deficiency
- Exocrine Pancreatic Insufficiency
- Eosinophilic GI disease
- Exocrine Pancreatic Insufficiency
AGA Recommendations: Laboratory Evaluation of Functional Diarrhea and IBS-D in Adults

In patients presenting with chronic diarrhea, the AGA1...

**Recommends**
- Testing for *Giardia*
- Testing for celiac disease with IgA-anti-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 ACG2...

**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.

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

Bile Acids and Diarrhea

Enterohpatic circulation of bile acids

- FGF19 provides negative feedback inhibition of BA synthesis
- 5% Bile acids remain in colon
- 95% Bile acids reabsorbed in small intestine

Bile acid diarrhea

- Colonic motility and transit
- Visceral sensation
- Fluid secretion
- Mucosal permeability
- FGF19 in portal blood
- Bile acids in colon
- Bile acid reabsorption in small intestine

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-D²,³
  - Higher prevalence in patients with history of terminal ileal disease resection, cholecystectomy, or abdominal radiotherapy¹

### BAD subtypes¹,⁴

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>Terminal ileal disease (e.g., CD, resection) Radiation injury resulting in impaired reabsorption of bile acids</td>
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<tr>
<td>Type 2</td>
<td>Idiopathic or primary</td>
</tr>
<tr>
<td>Type 3</td>
<td>Secondary to other conditions that alter intestinal motility or bile acid absorption (e.g., celiac disease, cholecystectomy, SIBO, radiation enteritis)</td>
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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\(^1\)

<table>
<thead>
<tr>
<th>Affected area</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td><strong>Mucosal</strong></td>
<td>Diarrhea, malabsorption, GI bleeding, protein-losing enteropathy, vomiting, abdominal pain</td>
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<tr>
<td><strong>Muscular</strong></td>
<td>Vomiting, abdominal distention, abdominal pain, vomiting</td>
</tr>
<tr>
<td><strong>Serosal</strong></td>
<td>Abdominal distention, ascites, peritonitis</td>
</tr>
</tbody>
</table>

Treatment of IBS Is Often Symptom-Directed

**Diarrhea**
- Loperamide
- Rifaximin
- Eluxadoline
- Bile acid sequestrants

**Abdominal pain**
- Antispasmodics
- Neuromodulators
- Low FODMAP diet
- Prosecretory agents
- Rifaximin
- Eluxadoline
- Peppermint oil
- Tegaserod

**Constipation**
- Fiber
- Polyethylene glycol
- Prosecretory agents
- Tegaserod

**Bloating**
- Rifaximin/antibiotics
- Low FODMAP diet
- Peppermint oil
- Probiotics?
- Prosecretory agents

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*Lubiprostone, linaclotide, plecanatide.
Differential Diagnoses of IBS-D

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- Exocrine Pancreatic Insufficiency
- Disaccharidase deficiency
- Eosinophilic GI disease
Carbohydrates:
More Than Your Daily Bread…

~ 46% of 2,000 calorie western diet\textsuperscript{1,2}

Disaccharides
- Lactose
- Sucrose
- Maltose
- Trehalose

Understanding Carbohydrates

Monosaccharides
- Simple sugars $C_m(H_2O)_n$
- $\alpha \leftrightarrow \beta$ anomers exist in equilibrium
- Colorless, water-soluble, crystalline solids

Glucose  Galactose  Fructose

Disaccharides
- 2 monosaccharides combined by condensation reaction

Maltose  Lactose  Sucrose

Oligosaccharides
- <20 monosaccharides
- Fructo-oligosaccharides (short chains of fructose, which are found in many vegetables)
- Galactooligosaccharides (short chains of galactose molecules)

Polysaccharides
- $\geq 20$ monosaccharides

Starch
- Formed from $\alpha$-glucose

Cellulose
- Formed from $\beta$-glucose
- Glucose-glucose bonds not broken down by amylase

Glycogen
- Formed from $\alpha$-glucose
- More extensively branched and compact than starch
- Not easily broken down
Carbohydrate Digestion and Absorption
The Road to Monosaccharides

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

<table>
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<tr>
<th>Fruit juices</th>
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<tbody>
<tr>
<td>Dried fruits</td>
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<tr>
<td>Canned fruits</td>
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<tr>
<td>Marinated or processed meats</td>
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<tr>
<td>Certain vegetables</td>
</tr>
<tr>
<td>Artichokes, asparagus, broccoli, tomato paste, canned tomato paste, ketchup</td>
</tr>
<tr>
<td>Any product with HFCS</td>
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</tbody>
</table>

HFCS, high fructose corn syrup.
Clinical Consequences of Disaccharide Maldigestion

**Normal**
- Sucrose
- Lactose
- Fructose
- Glucose
- Sucrase
- Lactase
- Normal stool

**Malabsorption of Carbohydrate**
- Bacteria
- Fermentation
- Gases
- Gas
- Diarrhea
- Bloating
- Pain

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Etiologies of Key Disaccharidase Deficiencies: Lactase and Sucrase-Isomaltase

**Congenital**

- Congenital lactase deficiency (rare)
- Congenital Sucrase-Isomaltase Deficiency (CSID)
  - Autosomal recessive (CSID)
  - Symptomatic heterozygous carriers
  - Compound heterozygotes

**Secondary causes**

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

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

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?

Analysis of Mucosal Biopsies (N=27,875)

- 55% No disaccharidase deficiency
- 45% ≥1 disaccharidase deficiency
  - 21% Sucrase deficiency
  - 75% Lactase deficiency (34.7% of biopsies)
- 4% Other

9.3% were sucrase deficient overall

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”
Consider CSID in Low FODMAP Diet Failures

Adequate relief of IBS-D symptoms with LFD

- All patients: 52.2% (n=46)
- Non-carriers: 60.9% (n=23)
- Carriers: 43.5% (n=23)

\[ P = 0.031 \]

Response rate by number of SI hypomorphic genes (N=39)

- None: 56.1% (responders, n=5)
- 1 (heterozygous): 42.1% (responders, n=15)
- 2 (homozygous): 16.7% (responders, n=2)

\[ P = 0.0039 \]

LFD, low FODMAP diet; mNICE, modified National Health and Care Excellence; RCT, randomized controlled trial.
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
  - ¹³C-sucrose

- **Sucrose challenge**³
  - Simple test, but not validated

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SI, sucrase isomaltase

Prevalence of Disaccharidase Deficiency in Adults With Unexplained GI Symptoms


Analysis of Duodenal Biopsies (N=120)

- Normal disaccharidase levels: 53.3%
- ≥1 disaccharidase deficiency: 46.7%
- Lactase deficiency: 35.8%
- Maltase/sucrase/palatinase deficiency: 9.2%
- Maltase deficiency: 0.8%
- Pan-disaccharidase deficiency: 0.8%

Baseline GI symptoms or severity did not predict enzyme deficiency.
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

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)

Sacrosidase Oral Solution

- 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)

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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
Sacrosidase Therapeutic Challenge

**Advantages**

1. Simple
2. Supports diagnosis in combination with positive breath test without need for endoscopy
3. Access issues in absence of diagnosis

**Limitations**

1. Best used with dietary restrictions
2. Self-administered/compliance
3. Dose response may be variable
4. Cannot distinguish between CSID and secondary deficiencies

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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.