1

Disclosures for Patsy Catsos, MS, RDN, LD

- Patsy Catsos Advanced Nutrition LLC, telehealth practice, editor www.ibsfree.net, author of various consumer publications, recipe developer
- Nutrition Works LLC, Portland ME, consultant providing patient care
- American College of Gastroenterology, Nutrition Expert, Functional GI Circle
- Advisory Panel: American College of Gastroenterology, Monash University Department of Gastroenterology
- ModifyHealth Inc. Advisory board (shareholder) and consultant

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Session Learning Objectives

At the end of this session, participants will be able to…

Identify signs and symptoms c/w histamine intolerance or sucrase isomaltase deficiency	Communicate status of (and limitations of) evidence-based recommendations for histamine intolerance and sucrase-isomaltase deficiency	Identify resources for managing histamine intolerance and sucrase-isomaltase deficiency

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Irritable Bowel Syndrome (Cash *Gastroenterol Hepatol 2018*)

Rome IV Criteria for IBS

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

IBS Subtypes Based on Bristol Stool Forms

IBS-C
Hard/lumpy stools ≥25%
Loose/watery stools <25%

IBS-M
Hard/lumpy stools ≥25%
Loose/watery stools ≥25%

IBS-D
Hard/lumpy stools <25%
Loose/watery stools ≥25%

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Low-FODMAP Diets for IBS

Effective: Help up to 85% of patients get significant relief of symptoms; now part of standard practice for all types of IBS

Limitation: Cannot "cure" IBS for most patients

Potential risks:

- Long-term effects on gut microbiome
- Must be carefully planned to meet nutrition needs
- Not for patients at risk for eating disorders

Lacy et al. *Am J Gastroenterol* 2021, Gibson et al *Aliment Pharmacol Ther* 2020, Whelan et al *J Hum Nutr Diet* 2018.

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FODMAPs

Fermentable
Oligosaccharides (fructans, GOS)
Disaccharides (lactose)
Monosaccharides (fructose)
And
Polyols (mannitol, sorbitol)

FODMAPs are poorly absorbed, short-chain carbohydrates

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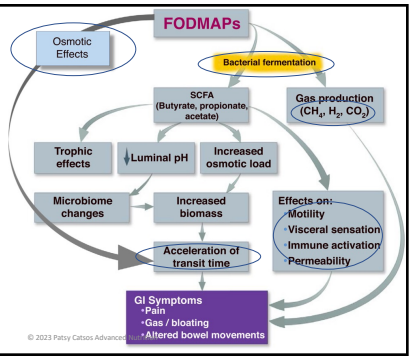
Mechanisms FODMAPs/ GI Symptoms



Eswaran *Curr Opin Pharmacol* 2017

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IBS-Like Symptoms Can Arise From Other Causes

Illustration from The Human Body Book, DK Publishing, 2007

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Histamine Intolerance (HIT)
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Case #1 62 y.o. Female
• Long-standing IBS: Almost daily excess gas, bloating, loose stools with intermittent bouts of severe abdominal pain and fecal urgency.
• FODMAP elimination diet process identified several triggers; routine symptoms now well-managed.
• Frequent violent post-prandial diarrhea when dining out, always fish and a glass of wine.
• Very fresh fish prepared at home is fine. Rarely drinks at home.
• Fish/seafood allergy r/o by board-certified allergist.
• Working hypothesis: histamine intolerance
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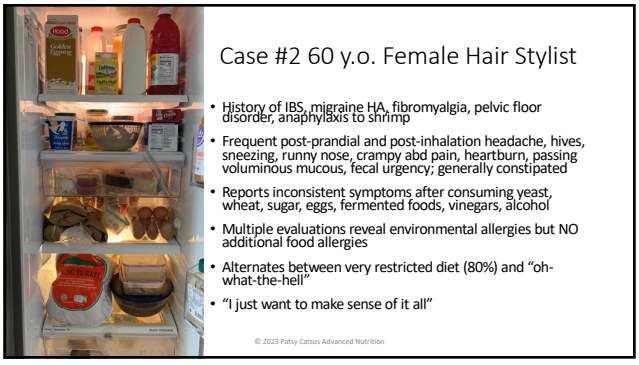
Case #2 60 y.o. Female Hair Stylist
• History of IBS, migraine HA, fibromyalgia, pelvic floor disorder, anaphylaxis to shrimp
• Frequent post-prandial and post-inhalation headache, hives, sneezing, runny nose, crampy abd pain, heartburn, passing voluminous mucous, fecal urgency; generally constipated
• Reports inconsistent symptoms after consuming yeast, wheat, sugar, eggs, fermented foods, vinegars, alcohol
• Multiple evaluations reveal environmental allergies but NO additional food allergies
• Alternates between very restricted diet (80%) and "oh-what-the-hell"
• "I just want to make sense of it all"
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Histamine

- Histamine is a "biogenic amine" (BA)
- Neurotransmitter& local hormone
- Multiple functions in normal human physiology and disease

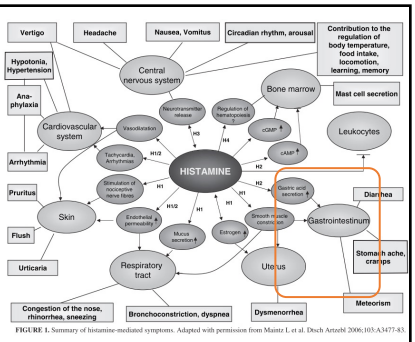

FIGURE 1. Summary of histamine-mediated symptoms. Adapted with permission from Maintz L et al. Dtsch Arztebl 2006;103:A3477-83.

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Fig. 1.
Frequency and distribution of symptoms in patients with histamine intolerance.

Symptoms in HIT

- 62 patients with HIT
- Blue = % of patients reporting symptoms

Schnedl *Intest Res* 2019

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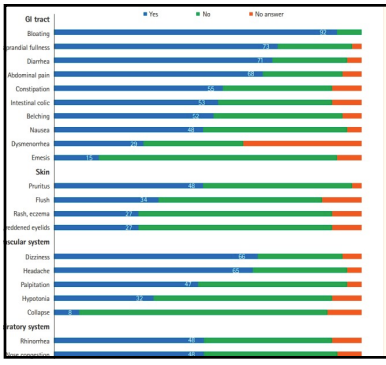

Symptoms in HIT

62 patients with with HIT were surveyed

- Bloating most common and severe symptom
- Often in combination with other GI sx, headache, dizziness congestion, palpitations.
- Pruritis in just 48% of patients

Schnedl *Intest Res* 2019

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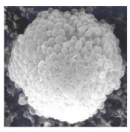
Endogenous Histamine

Scanning electron micrograph of a rat peritoneal mast cell and its major secretory products



- Histamine
- Proteases
- Proteoglycans
- LTB4, LTC4
- PGD2, PAF
- Many cytokines
- Superoxide dismutase

- Produced in mast cells in mucosal and epithelial tissues
- Endogenous histamine release is triggered by "environmental" stress
  - Allergens (IgE response)
  - Viral infection
  - Exercise, heat, mechanical stress, drugs, hormones
  - Psychological stress (less studied)
  - What we eat and drink

Kyrstel-Whittemore *Front Immunol* 2015; Zhang *J Neuro Gastroenterol Motil*, 2016

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Foods Purported to Trigger Release of Endogenous Histamine

Potentially different for everyone.

Citrus	Papaya	Straw berries	Pine apple	Nuts
Peanuts	Tomatoes	Spinach	Chocolate	Fish
Crust acea	Pork	Egg White	Additives	Spices

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Exogenous Histamine

- Is consumed in foods and beverages that contain histamine
- May be produced by gut bacteria (possibly increased in presence of high FODMAP diet—needs corroboration (McIntosh K *Gut* 2015)
- Other BAs are important, too, especially tyramine.

Microbes proliferate in food and produce the enzyme histidine decarboxylase.

Histamine is produced when histidine converts to histamine, catalyzed by histidine decarboxylase

Ingested histamine is metabolized in small bowel by enzyme diamine oxidase (DAO)

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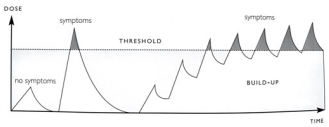
Threshold Effect

- Dose-response varies per person
- At very high levels, even healthy individuals can experience toxic effects (i.e. scombroid poisoning)
- Cumulative effect complicates questions of timing
- Histamine "poisoning" occurs in a few minutes to two hours (Becker *JAMA* 2001)



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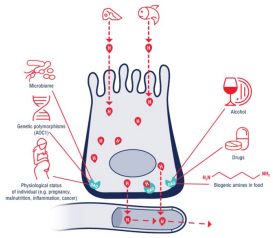
Role of DAO in HIT



Mismatch between amount ingested vs capacity to metabolize

- High intake or absorption of bioactive amines
- High endogenous release of histamine from mast cells and basophils
- Low DAO activity

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Diagnosis

No good biomarkers to ID patients with the condition though DAO activity is proposed (Serum? Mucosal?)

Table 2. Diagnosis of histamine intolerance.

Diagnostic criteria [58]	
The diagnosis of histamine intolerance is made by a combination of the following criteria: • presenting ≥2 typical symptoms of histamine intolerance (see below) • improvement through histamine-free diet • improvement through antihistaminergic medication.	
Symptom types [57,58]	
Skin	Itching, sudden reddening of the skin (flush symptoms) on the face and/or body, very rarely hives, angioedema (different to urticaria) and other exanthemas
Digestion	Nausea, vomiting, diarrhea, abdominal pain
Circulation	Tachycardia, drop in blood pressure, dizziness
Respiratory	Chronic nasal flow, sneezing attacks
Neurological	Headaches, migraines
Gynecological	Menstrual cramps

Tuck et al. *Nutrients* 2019

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Histamine Intolerance in IBS

- Unknown what % of IBS patients have HIT
- Role of mast cells in IBS
  - Some studies have shown more mast cells in the epithelial tissues of people with IBS, especially IBS-D.
  - Mast cell density correlates with severity of IBS
  - Degranulation rate of mast cells higher in subjects with IBS
  - Mast cell stabilizers and anti-histamines reduce severity of abdominal pain in IBS
  - Local IgE/mast cell response to food antigens demonstrated in mouse IBS model and to a lesser extent in humans

Zhang *J Neurogastroenterol Motil* 2016, Aguilera-Lizarranga *Nature* 2021

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Management

- Probiotics—lots of interesting talk, science not actionable
- DAO cofactors: vitamin B-6, copper, vitamin C, D
- Quercitin—purportedly stabilizes mast cells
- DAO enzyme supplements—.3 to .6 mg ae being used in trials
- Antihistamines (H1/H2 blockers)
- Histamine elimination diets

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Foods w/ Highest Mean Histamine in Milligrams per Kilogram of Food

- Histamine increases with aging, spoilage, and fermentation
- Next highest: beer, wine
- Less: other fermented foods, certain ripe fruits and vegetables
- Histamine not destroyed by heat or cold
- Freezing will slow down bacteria

**Same foods also high in other BAs*

EFSA Publication (2011)

Dried anchovies	Fish sauce	Fermented vegetables
Cheese	Other fish, esp tuna	Fermented sausage

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Three Step Dietary Adjustment

1. Avoid potentially high histamine foods (10-14 days).
   - Focus on the big sources for most patients
   - Futile to set a specific mg target for intake.
   - Freeze leftovers promptly.
   - 24-hour recall should symptoms occur
2. Reintroduce suspected foods; monitoring tolerance (6 weeks)
   - For sensitive individuals, continue to exclude the big ones
3. Personalize

German guidelines…Reese et al. *Allergo Journal* 2017; smaller bullets are my opinion.

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Reliable Sources?

- Swiss Interest Group Histamine Intolerance (SIGHI) has decent food list; contains some medical advice you would want to review
  - https://www.histaminintoleranz.ch/downloads/SIGHI-Leaflet_HistamineEliminationDiet.pdf
- Less restrictive, practical approach described by Wendy Busse, RD
  - https://wendybusse.com/histamine-intolerance/

	☒ To avoid:	? Risky:	☑ Well to
Meat, eggs	Canned meat, cured, dried, marinated, smoked or otherwise preserved meat (-preparations): dry-cured ham, bacon, ...	Fresh meat sold over the counter (no date on it)	Natural fresh m goats, cattle, p as possible, pa cutlet, fillet, ch breast, ...
	Bone-matured or dry aged meat, long hung meat (mainly certain pieces of beef; ask your butcher!)	Prepacked minced meat	Frozen meat, t
	Finely chopped / pureed meat (meatloaf, spreads, cold cuts,...). Histamine content tends to rise with the degree of comminution.	Pre-cooked sausages	Cooked ham (extract or gluta
	Almost all sausages (e.g. salami, liverwurst)	Venison, game (ripening of meat)	Eggs (chicken,
	Offal, innards (especially liver)		

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Case #2 60 y.o. Female Hair Stylist

- History of IBS, migraine HA, fibromyalgia, pelvic floor disorder, anaphylaxis to shrimp
- Frequent post-prandial and post-inhalation headache, hives, sneezing, runny nose, crampy abd pain, heartburn, passing voluminous mucous, fecal urgency; generally constipated
- Reports inconsistent symptoms after consuming yeast, wheat, sugar, eggs, fermented foods, vinegars, alcohol
- Multiple evaluations reveal environmental allergies but NO additional food allergies
- Alternates between very restricted diet (80%) and "oh-what-the-hell"
- "I just want to make sense of it all"

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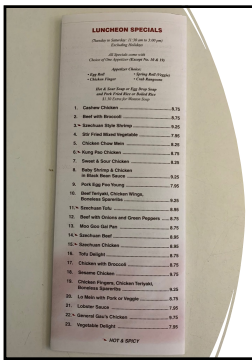

Closer Look at Diet History

- Patient suspects yeast, wheat, sugar, eggs, fermented foods, molds, vinegars, alcohol—avoids 80% of the time
- Reacts to even the smell of leftovers
- Diet history significant for regular/high intake of wheat products, deli meats, cheese, yogurt, root beer, mayonnaise, takeout Chinese food, leftovers in general, hummus, fruit smoothies
- Appears moderately high FODMAP, consuming foods of concern for histamines

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Nutrition Recommendations

Avoid	Avoid allergic foods: shrimp
Avoid	Avoid "Big Ones": Fish, cheese, aged sausages, fish sauce or paste, Asian restaurant food in general
Avoid	Avoid other fermented foods: chocolate, soy sauce, yogurt
Avoid	Avoid other potentially high histamine foods: tomatoes, grapefruit juice, eggplant, (little data, go easy here)
Avoid	Avoid suspected foods at first: yeast, wheat, sugar, eggs, fermented foods, molds, vinegars, alcohol, apples, onion, garlic
Freeze	Freeze leftovers promptly

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Follow-Up

- At Visit 2, reported symptoms were "perfect" when following the plan
- Difficult to sustain, and exceptions triggered symptoms
- Bounced back quickly

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Nutrition Recommendations

Avoid	Avoid allergic foods: shrimp
Avoid	Avoid "Big Ones": Fish, cheese, aged sausages, fish sauce or paste, Asian restaurant food in general
#2 Reintro	Avoid other fermented foods: chocolate, soy sauce, yogurt
#1 Reintro	Avoid other potentially high histamine foods: tomatoes, grapefruit juice, eggplant, (little data, go easy here)
#3 Reintro	Avoid suspected foods at first: yeast, wheat, sugar, eggs, fermented foods, molds, vinegars, alcohol, apples, onion, garlic
Freeze	Freeze leftovers promptly

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Final Thoughts on HIT

1. Consider in patients with post-prandial symptoms not c/w FODMAPs
2. Keep the "Big Ones" firmly in mind
3. Mind the dose-response and cumulative effects
4. Don't over-restrict patients' diets based on flimsy facts
5. Don't try to combine with other diets

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CSID

- A rare genetic disorder w/ absent or reduced sucrase-isomaltase (SI) activity
- Sucrase isomaltase is a two-part brush border enzyme
- Sucrase unit is always affected
- Effects of CSID on isomaltase are more variable

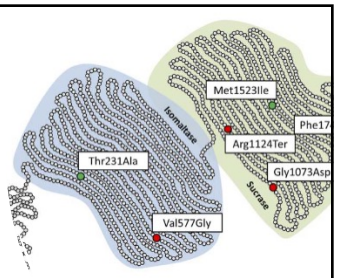

Figure 1. Henström et al. Gut 2016. Sucrase isomaltase

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Normal Carbohydrate Digestion

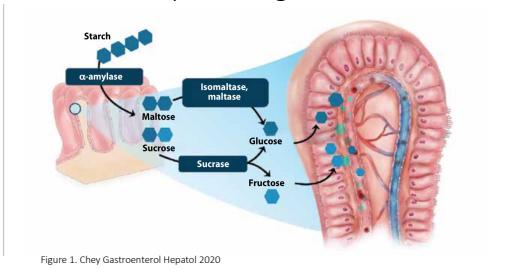

Figure 1. Chey Gastroenterol Hepatol 2020

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Clinical Consequences

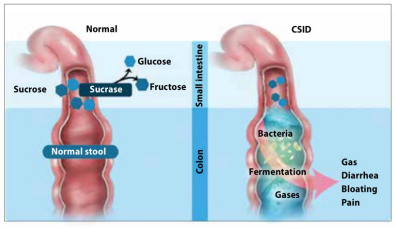

Figure 2. Chey Gastroenterol Hepatol 2020

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CSID in IBS

- Swedish study looked at common SI coding mutations in 1887 IBS cases and controls
- CSID mutations were more common in patients (OR 1.84, p=0.074)

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Sucrose Malabsorption in Patients w/ Common Functional Symptoms

- Chart review of 258 consecutive adults
- Subjects had chronic unexplained symptoms and had been screened with hydrogen-methane or ^{13}C-sucrose breath tests
- 34.4% were positive for sucrose malabsorption
- A subgroup received dietary counseling and/or enzyme replacement with 26/43 (60%) reporting symptomatic improvement.

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Response to Low FODMAP diet in IBS patient with SI Mutations

- Re-evaluated results from a previous RCT with low FODMAP diet for patients with IBS-D
- 46 patients selected based on available genotype data
- 60.9% of non-carriers had responded to low FODMAP diet versus 43.5% of those who carried SI mutations

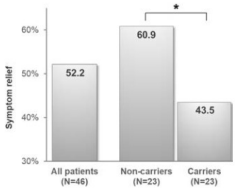

Figure 1. Zheng Gut 2020

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Sucrase Isomaltase Deficiency Can Also Be Secondary

Villous Atrophy
- Celiac disease
- Crohn's disease
- Malnutrition
- Chemotherapy or radiation enteropathy

Dysbiosis
- Gastroenteritis
- Giardiasis
- SIBO

Rapid Transit
- IBD
- Dumping syndrome
- Medications

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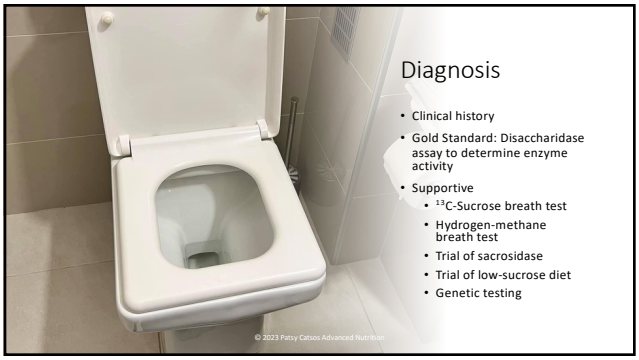

Diagnosis

- Clinical history
- Gold Standard: Disaccharidase assay to determine enzyme activity
- Supportive
  - ^{13}C-Sucrose breath test
  - Hydrogen-methane breath test
  - Trial of sacrosidase
  - Trial of low-sucrose diet
  - Genetic testing

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^{13}C-Sucrose Breath Tests Report

Sucrose Digestion (%) = 0.92

Result: **Low Sucrase Activity**

Comment:

Normal Criteria: A 90 minute sucrose digestion greater than 5.10% for females or 3.91% for males is normal sucrase activity.

***The Sucrose Breath Test measures $^{13}CO_2$ in exhaled breath to determine sucrase activity.**

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Pediatric Case Study

- 5-year-old female referred to me failure to thrive, question of FODMAP intolerance
- Daily bloating and belly aches with multiple school absences
- Daily diarrhea since weaning
- Diaper dermatitis with burning stools; still in a diaper
- No relevant family history
- Negative genetic testing but positive response to sacrosidase and low sugar, low starch diet

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Adult Case Study, Referral for CSID

- New diagnosis: CSID
- History: SIBO, Lactose intolerance, anemia, eating disorder NOS, GERD, hypothyroidism, IBS, migraine headache, osteopenia, sensitive to metals, light, sound.
- Symptoms: Three times weekly bouts of post-prandial excess gas, bloating, abdominal pain, diarrhea
- Other studies: normal
- Patient did not give permission for me to coordinate care with her providers

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Diet and Nutrition History

- History of underweight; Currently 5' 9.5", stable at 138 lbs (BMI 20.38)
- Long history of food intolerances and GI issues
- Eats chicken, turkey, fish, a few vegetables, cashews, almonds, pecans, pumpkin seeds. Less often, rice, oatmeal, quinoa, gluten-free bread. Regular intake of gluten-free sweets, candy.
- No dairy or fruit
- Reports a "sugar addiction"

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Nutrition Plan

Limit sucrase intake; work on starch aspect of CSID later to avoid overwhelm

Increase variety in diet, using resources provided to identify foods that may be well tolerated in setting of sucrase insufficiency.

Doctor prescribed sacrosidase

Foods likely to be well tolerated:

- Berries
- Pears
- Grapes
- Strawberries
- Greens
- Broccoli
- Unprocessed meat, fish, poultry
- Eggs
- Milk products (milk, unsweetened yogurt or kefir, natural cheeses, butter)
- Oils
- Later: nuts and seeds

www.csidcares.org/treatment/diet/

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Sacrosidase

- Derived from baker's yeast
- Available from QOL Medical
- Glycerin-based solution; requires refrigeration
- Taken with each meal or snack (half before, half during)
- Dosing is based on patient's weight
- Dilute with cold liquid
- Does not help with starches
- Contraindicated for those with hypersensitivity to yeast, glycerin or papain

www.sucraid.com

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Follow-up:

- Tried sacrosidase enzyme but found it unpalatable; unclear whether it worked.
- Educated on CSID, normal and abnormal digestion and absorption of CHO, label reading, alternative sweeteners. Provided recipes.
- Finds it difficult to reduce intake of sweets
- Referred to a colleague with experience in EDO for help with sugar addiction

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Foods Containing Significant Sucrose

- Sweeteners
- Prepared foods with added sugars
- Certain fruits: apples, bananas, melons, mangoes, oranges, peaches, pineapple
- Certain vegetables: beets, green peas, sweet potatoes

www.csidcares.org

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Sweeteners and CSID

Tolerated by Most	Tolerated by Some	Sugars to Avoid
Dextrose	Agave nectar	Cane
Glucose	Corn syrup	Coconut
Lactose	Honey	Dates
Fructose	Stevia	Maple syrup
		Molasses

www.csidcares.org

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Foods Containing Significant Starch

- Potatoes
- Rice
- Grains and grain products like bread, pasta, baked goodies
- Pulses

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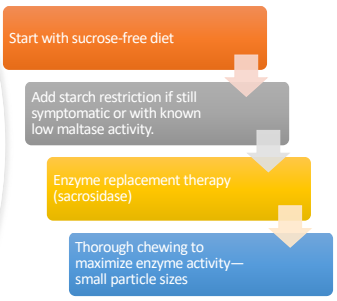
Management of CSID/SID



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Final Thoughts on CSID/SID

1. Consider in patients with symptoms since weaning or w/ family hx
2. Consider in patients with IBS who fail to improve on low-FODMAP diet
3. There is a continuum of malabsorption (and intolerance); restrict only as needed
4. SID can be secondary, so reconsider if an underlying diagnosis is resolved.

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