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# Diagnosis and Management of Carbohydrate-Induced Diarrhea

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# Learning Objectives

Upon completion of this activity, participants should be better able to:

- Explain the pathophysiology of carbohydrate-induced diarrhea
- Utilize current diagnostic approaches
- Provide individualized and appropriate management to meet specific patient needs
- Educate patients and parents on etiology and physiologic consequences as well as the importance of dietary modifications



# Target Audience

- This activity is designed for pediatricians, pediatric and adult gastroenterologists, primary care physicians, physician assistants, nurse practitioners, dietitians, and other health care professionals who are interested in treating children and young adults with carbohydrate-induced diarrhea.

# AMA PRA Statement

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# Disclosures

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# Faculty Disclosures

**Looi Ee, MBBS** has nothing to disclose.

**Martín G. Martín, MD** has nothing to disclose.

**John F. Pohl, MD** has nothing to disclose.

**Yul Reinstein, MD** has nothing to disclose.

**J. Marc Rhoads, MD** has nothing to disclose.

**Robert Shulman, MD** has nothing to disclose.

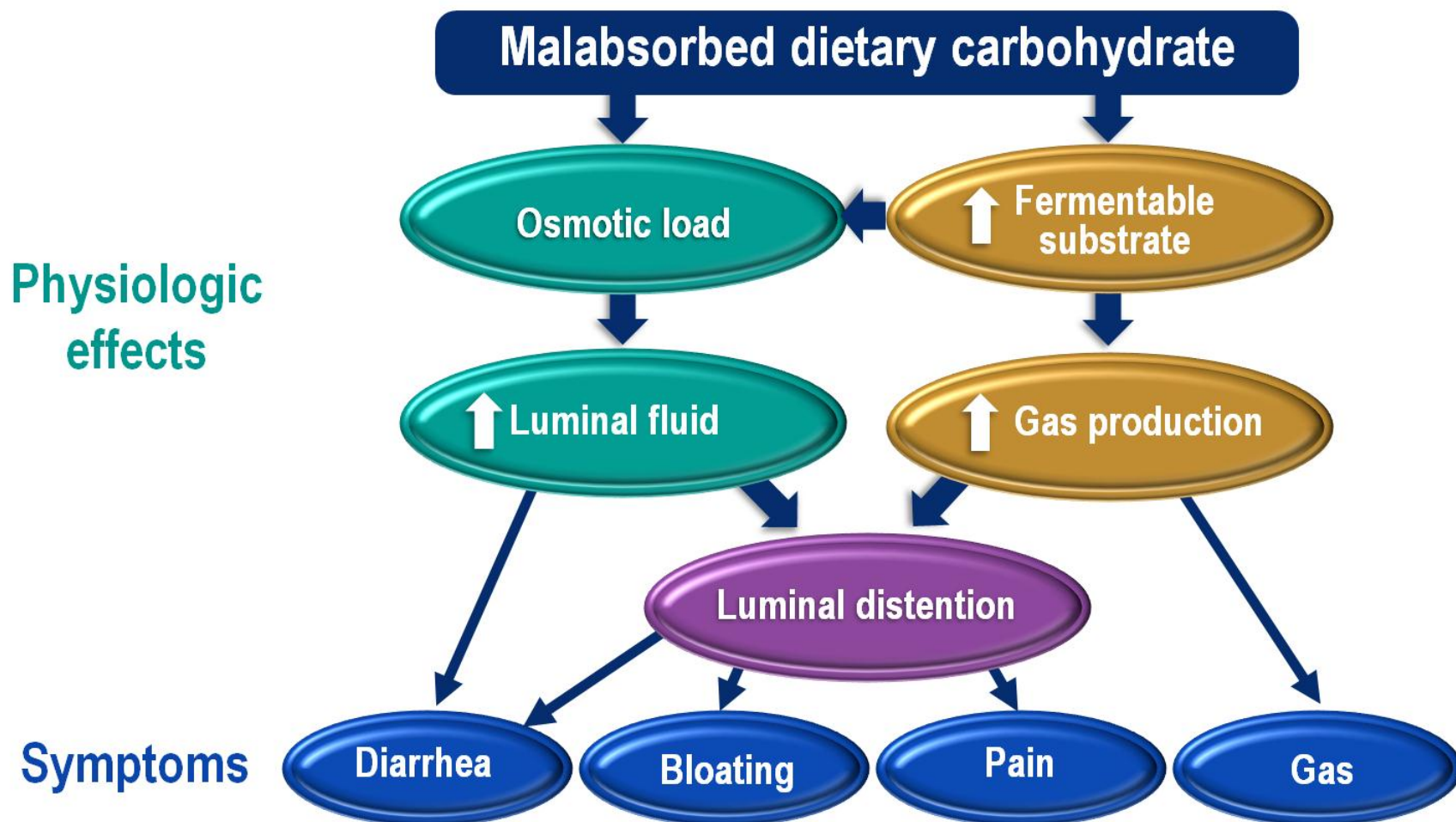
**Emily Contreras, MD** has nothing to disclose.

**Martin H. Ulshen, MD** has nothing to disclose.

# General Principles



# Carbohydrate Malabsorption: Pathogenesis of Symptoms



# Fermentation of Malabsorbed Carbohydrate

- Incompletely digested carbohydrates pass into the colon
- Anaerobic bacteria ferment malabsorbed carbohydrate to:
  - Hydrogen and methane gas
    - Excreted in breath (basis of breath hydrogen testing)
  - Short-chain fatty acids
    - Absorbed, providing energy to colonic epithelial cells and systemically
    - Are osmotically active, contributing to diarrhea

# Carbohydrate Malabsorption: Diagnosis

- Signs and symptoms
  - Diarrhea
  - Abdominal pain
  - Bloating and flatulence
  - Failure to thrive in infants - rare
- History
  - Age at presentation
  - Careful nutritional history

Tori AJ, et al. *J Pediatr Gastroenterol Nutr.* 2007;45:194-198.

Gupta SK, et al. *J Pediatr Gastroenterol Nutr.* 1999;28:246-251.

Treem WR. *J Pediatr Gastroenterol Nutr.* 1995;21:1-14.

# Carbohydrate Maldigestion/Malabsorption Disorders: Typical Age of Onset

## 1-7 days

Glucose-galactose malabsorption  
Congenital lactase deficiency  
Sucrase-isomaltase deficiency

## 3-6 months

Fructose malabsorption  
Glucoamylase deficiency  
Sucrase-isomaltase deficiency

## 3-15 years

Fructose malabsorption  
Adult-onset lactase deficiency

Martin MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management*, 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

Tori AJ, et al. *J Pediatr Gastroenterol Nutr.* 2007;45:194-198.

Gupta SK, et al. *J Pediatr Gastroenterol Nutr.* 1999;28:246-251.

Treem WR. *J Pediatr Gastroenterol Nutr.* 1995;21:1-14.

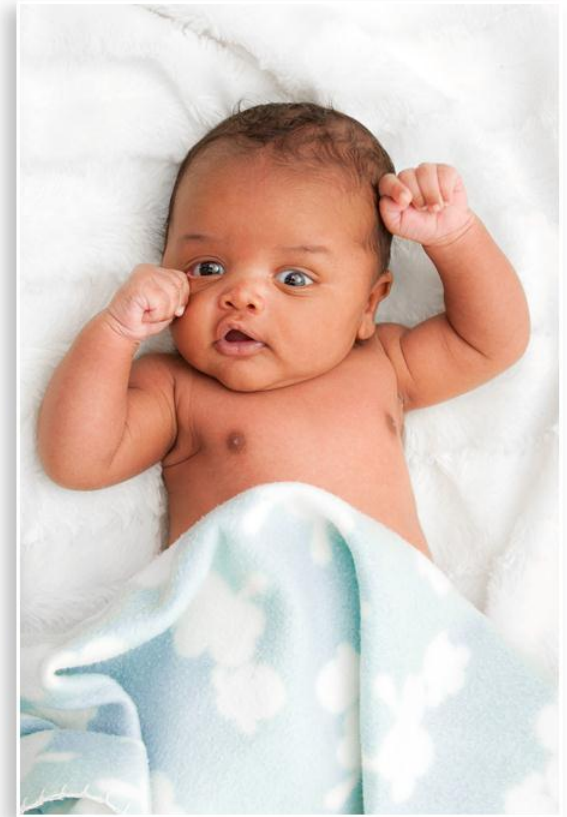


# Glucose-Galactose Malabsorption



# Case Study: Alice

- 1-week-old African American female
- Infant is discharged on the day after delivery and parents immediately note watery diarrhea



# Glucose-Galactose Malabsorption

- Distinguishing feature<sup>1</sup>
  - Onset of diarrhea - first week of life
  - Selective malabsorption of glucose/galactose
- Inheritance<sup>1</sup>
  - Autosomal recessive
    - Parents without symptoms
    - Associated with consanguinity
- Molecular basis<sup>2,3</sup>
  - Defect sodium/glucose cotransporter protein
  - Mutation of SGLT1 gene (SLC5a1)

<sup>1</sup>Genetics Home Reference Web site. <http://ghr.nlm.nih.gov/condition/glucose-galactose-malabsorption>. Published October 30, 2012. Accessed February 15, 2013.

<sup>2</sup>Turk E, et al. *Nature*. 1991;350:354-356.

<sup>3</sup>Martin MG, et al. *Nat Genet*. 1996; 12:216-220.

# Glucose-Galactose Malabsorption: Diagnosis

- Present with osmotic diarrhea during first week of life
  - Severe metabolic acidosis and stool pH < 6, positive for reducing substances with increased osmotic gap
- Sibling with similar history
- Small bowel biopsies - normal
- Selective malabsorption of glucose and galactose
- Meticulous recording of intake and output
- Dietary challenge - tolerance/intolerance not subtle
  - Formulas containing glucose induce diarrhea

Martin MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management*, 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.  
Abdullah AM, et al. *J Pediatr Gastroenterol Nutr.* 1996;23:561-564.

# Glucose-Galactose Malabsorption: Treatment

- Lifetime restriction of glucose and galactose (modified Atkins diet)
- First 12 months of life, carbohydrate-free formula (RCF®) with fructose required
  - Many patients stay on beyond 12 months, but not required
- When solids are introduced
  - Pureed food, glucose-free, protein/fat and fructose-based
- Adequate dietary calcium via supplementation must be provided





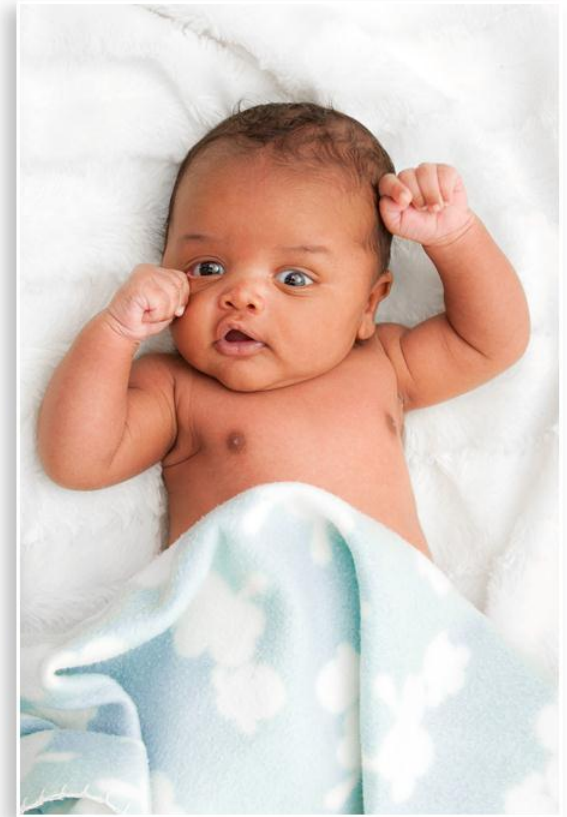
# Glucose-Galactose Malabsorption: Parent/Patient Education

- Early input of dietitian
  - May require multiple visits centering around education
- Parents need to become familiar with the amount of glucose/galactose in a broad group of foods
- Parents encouraged to explore level of glucose tolerance
- Make family aware that most liquid medicines are dissolved in glucose-based syrup; use crushed tablets instead
- High fat/protein and fructose-based diet not associated with obesity or other medical problems



# Alice: Follow-Up

- Stool pH is 4.5
- Diarrhea induced with dietary challenge of glucose-containing formulas
- Alice is diagnosed with glucose-galactose malabsorption
- Carbohydrate-free formula with fructose for first 12 months
- Extensive education regarding carbohydrates in food and medications



# Fructose Malabsorption

# Case Study: Manny

- 12-year-old male
- Symptoms
  - Bloating, pain, and excessive flatulence after eating
  - Symptoms manifest or worsen after eating/drinking:
    - Fruits and fruit juices
    - Soft drinks
    - Pizza



# Fructose Malabsorption

- Absorption capacity increases with age
- Malabsorption is directly related to dose
  - Limited ability to transport fructose
  - Malabsorption most commonly seen with excessive juice intake, with diarrheal symptoms associated with the daily consumption of  $> 15$  mL/kg
  - GLUT5 expression is inducible by fructose, therefore slow, incremental increases in fructose may improve absorption

# Fructose Malabsorption: Clinical Presentation

- Bloating, abdominal pain, and flatulence are characteristic
- Ingestion of fructose alone more likely to induce symptoms than when ingested with glucose
- Positive breath test along with subsequent symptoms may be most reliable for diagnosis
  - Suggested dose 0.5 g/kg (maximum dose 15 g)
    - Positive test > 20 parts per million (ppm) over baseline
    - 30-min sampling interval for 3 hr

Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.

Latulippe ME and Skoog SM. *Crit Rev Food Sci Nutr*. 2011;51:583-592.

Kyaw MH and Mayberry JF. *J Clin Gastroenterol*. 2011;45:16-21.



# Diagnosis/Treatment of Fructose Malabsorption: Dietary Exclusion

- Eliminate foods in which fructose is sole or main carbohydrate (fruits and honey)
  - Consumption of other foods likely to reduce symptoms
- Not all high-fructose corn syrups (HFCSs) may cause symptoms
  - HFCS-42 (42% fructose, 58% glucose) likely not to cause symptoms, as glucose in excess of fructose facilitates fructose absorption

Latulippe ME and Skoog SM. *Crit Rev Food Sci Nutr*. 2011;51:583-592.

Kyaw MH and Mayberry JF. *J Clin Gastroenterol*. 2010;45:16-21.

Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.

# Dietary Fermentable Substrates in IBS

- FODMAPs
  - Fermentable, Oligosaccharides (fructans/galactans), Disaccharides, Monosaccharides, And Polyols
- Poorly absorbed, osmotically active, rapidly fermented
- Elimination from diet relieves symptoms in some adults with irritable bowel syndrome (IBS)
  - Likely related to increased gut sensitivity in IBS rather than greater malabsorption in IBS versus healthy individuals

# Manny: Follow-Up

- Breath testing with 15 g of fructose resulted in 30 ppm rise of breath hydrogen over baseline
- Breath testing also induced bloating and pain
- Manny is diagnosed with fructose malabsorption
- Exclusion diet implemented to avoid foods that induce symptoms



# Lactase Deficiency

# Case Study: Miles

- 15-year-old male
- Symptoms
  - Occasional diarrhea
  - Abdominal pain and bloating within 1-2 hours of eating
  - No weight loss or other constitutional symptoms





# Lactase Deficiency: Lactose Intolerance Versus Malabsorption

- Lactose malabsorption detected by breath  $H_2$  test is more common than actual symptoms of lactose intolerance
- Lactose intolerance frequency varies less among different ethnic/racial groups than does lactose malabsorption
- Frequency of lactose malabsorption is low in children < 6 years of age
  - Frequency of lactose malabsorption peaks between 10 and 16 years of age

# Lactose Malabsorption With Intolerance: Clinical Presentation

- Symptoms: bloating, abdominal pain, flatulence, diarrhea, and vomiting (especially in adolescents)<sup>1</sup>
- Stools may be watery, frothy, and acidic<sup>1</sup>
- There is significant interindividual variability in symptoms
  - Symptoms are usually minimal if intake of milk < 240 mL/day<sup>2</sup>
  - Not all patients who report these symptoms with lactose ingestion have lactose malabsorption on breath hydrogen testing<sup>3</sup>

<sup>1</sup> Guandalini S. Pediatric lactose intolerance. <http://emedicine.medscape.com/article/930971-overview>. Modified May 11, 2012. Accessed February 15, 2013.

<sup>2</sup> Suarez FL, et al. *N Engl J Med*. 1995;333:1-4.

<sup>3</sup> Suarez FL, et al. *Am J Clin Nutr*. 1997;65:1502-1506.

# Lactose Malabsorption: Diagnostic Testing

- Stool testing<sup>1,3</sup>
  - pH < 6 and positive for reducing substances confirm carbohydrate malabsorption
- Lactose breath hydrogen testing<sup>2,3</sup>
  - 1 g/kg lactose (max 25 g) oral load after 6-hour fast
  - $\geq 20$  ppm over baseline is positive
  - False positive if rapid intestinal transit
  - False negative if taking antibiotics
- Duodenal biopsy and disaccharidase analysis<sup>3</sup>

<sup>1</sup>Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

<sup>2</sup>Gasbarrini A, et al. *Aliment Pharmacol Ther.* 2009;29(Suppl 1):1-49.

<sup>3</sup>Montgomery RK, et al. *J Pediatr Gastroenterol Nutr.* 2007;45(Suppl 2):S131-S137.

# Treatment of Lactase Deficiency

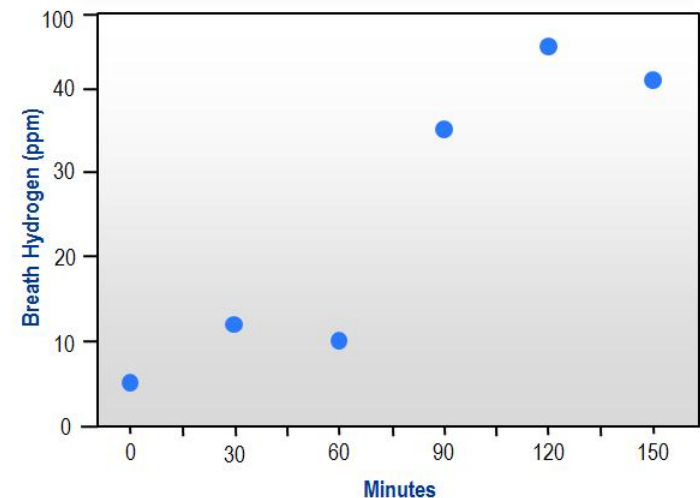
- Reduce dietary lactose intake<sup>1</sup>
- Enzyme replacement<sup>2</sup>
  - Lactase preparations are ingested prior to eating lactose-containing foods or added to lactose-containing foods to hydrolyze lactose prior to ingestion (symptom relief is variable)
- Maintain adequate calcium intake<sup>3</sup>
  - Infants < 1 years                      260 mg
  - Age 1-3 years                              700 mg
  - Age 4-8 years                              1000 mg
  - Age 9-18 years                            1300 mg

<sup>1</sup>Jarvis JK and Miller GD. *J Natl Med Assoc.* 2002;94:55-66. <sup>2</sup>Rosado JL, et al. *Gastroenterology.* 1984;87:1072-1082. <sup>3</sup>Institute of Medicine of the National Academies Web site. <http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx>. Published November 30, 2010. Accessed February 15, 2013.



# Miles: Follow-Up

- Miles was diagnosed with hypolactasia
- Over-the-counter lactase supplement recommended when dietary lactose intake leads to intolerance
- Educated on importance of calcium supplementation if milk avoidance is required





# **Congenital Sucrase-Isomaltase Deficiency**

# Case Study: Sarah

- 8-month-old Caucasian female
- History
  - Breastfed
  - 2-3 months of diarrhea and colicky discomfort
  - Faltered weight gain over same period
  - No vomiting and normal appetite
  - Abdominal distention after feeding



# CSID: Clinical Presentation

- Typical presentation is in infancy, after weaning, with introduction of sucrose-containing foods or drinks (e.g., fruits, juices, and grains)
  - May present earlier if dextrans and isomaltose are present in the diet
- Symptoms include abdominal cramping, bloating, excessive gas, fermentative diarrhea, failure to thrive, and malnutrition
- Most affected children are able to tolerate increased amounts of sucrose and maltose as they grow older
- A number of patients are not diagnosed as children or adults and misdiagnosed as having IBS

Tori AJ, et al. *J Pediatr Gastroenterol Nutr.* 2007;45:194-198.

Gupta SK, et al. *J Pediatr Gastroenterol Nutr.* 1999;28:246-251.

Treem WR. *J Pediatr Gastroenterol Nutr.* 1995;21:1-14.

# CSID: Diagnosis

- Stool testing<sup>1,2</sup>
  - pH < 6 suggestive of carbohydrate malabsorption
- Sucrose breath hydrogen testing<sup>2,3</sup>
  - 1-2 g/kg sucrose ( $\leq 50$  g) oral load after 6-hour fast
  - $\geq 10$  ppm is positive
  - False positive if rapid intestinal transit
  - False negative if taking antibiotics
- C<sup>13</sup>-sucrose breath test<sup>4</sup>
  - Preliminary data suggest utility

<sup>1</sup>Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management*, 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

<sup>2</sup>Ford RP and Barnes GL. *Arch Dis Child*. 1983;58:595-597.

<sup>3</sup>Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

<sup>4</sup>Robayo-Torres CC, et al. *J Pediatr Gastroenterol Nutr*. 2009;48:412-418.

# CSID: Diagnosis

- Duodenal biopsy and disaccharidase analysis<sup>1</sup>
  - Gold standard
  - Absent sucrase activity and marked reduction of isomaltase activity
  - Normal histology
- Unclear if milder forms exist<sup>2</sup>

<sup>1</sup>Treem WR. *J Pediatr Gastroenterol Nutr.* 1995;21:1-14.

<sup>2</sup>Karnsakul W, et al. *J Pediatr Gastroenterol Nutr.* 2002;35:551-556.



# CSID: Dietary Treatment

- Adherence to a sucrose-free diet
- Reduction in starch-containing foods
  - Beetroot, peas, soybean flour, onions
  - Cereals, breads, pastas, and potatoes in the first years of life
  - Avoid glucose polymer formulas and medications with sucrose
- Tolerance improves with age

# CSID: Treatment

- Lyophilized baker's yeast
  - Has sucrase activity but low isomaltase and maltase activity
  - Effective
  - Not very palatable
- Sacrosidase
  - Has sucrase activity but no isomaltase and maltase activity
  - Approved by US Food and Drug Administration
  - Oral liquid solution used with each meal as replacement
  - Palatable
  - Expensive

# Sarah: Follow-Up

- Breath hydrogen increased by 40 ppm after weight-appropriate sucrose load
- Biopsy results:
  - Complete absence of sucrase activity
  - Reduction of isomaltase and maltase activity
- Sarah diagnosed as sucrase-isomaltase-deficient
- Restrictive diet implemented
  - Avoid sucrose- and starch-containing foods, such as cereals, peas, and sucrose-containing medications



# Disaccharidase Deficiencies Related to Specific Diseases

*Generalized Malabsorption*

# Case Study: Beverly

- 4-year-old Indian American female
- Symptoms
  - Chronic diarrhea for 5 weeks
  - Abdominal bloating and pain



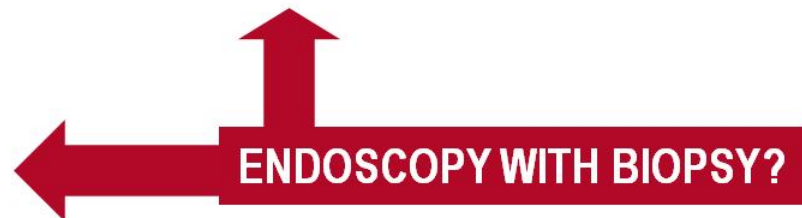


# Causes of Disaccharidase Deficiencies

- Brush border defect (primary deficiency: lactase deficiency, sucrase-isomaltase deficiency)
- Disordered motility, leading to small bowel bacterial overgrowth (e.g., primary dysmotility, stricture, short bowel syndrome)
- Mucosal disease (e.g., celiac disease, inflammatory bowel disease, food allergy, infection)

# Evaluation of Dysmotility and Mucosal Disease: Potential Pertinent Tests

- Blood tests
    - Complete blood count, erythrocyte sedimentation rate, C-reactive protein
    - Tissue transglutaminase and immunoglobulin A (IgA)
    - T4/thyroid-stimulating hormone
  - Stool tests
    - Culture, *C. difficile* toxin
    - Calprotectin
    - Reducing substances, pH
  - Urine culture
  - Breath hydrogen testing
- Radiographic tests
    - Abdominal x-ray
    - Abdominal ultrasound
    - Magnetic resonance enterography
    - Abdominal computed tomography
    - Upper gastrointestinal (GI)  $\pm$  small bowel follow-through



# Celiac Disease: Treatment

## • Foods to avoid

- Grains and flours
  - All flours containing wheat, rye, barley, and oats
- Breads
  - All breads containing wheat, rye, barley, and oats
- Cereals
  - All cereals containing wheat, rye, barley, and oats
- Noodles and pasta
  - Any type made of wheat, rye, barley, and oats
- Alcohol derived from grain (adolescent/adult issue)

# Celiac Disease: Treatment

- **Foods to allow**

- Grains and flours

- Almond, arrowroot starch, artichoke, corn starch, cornmeal, maize, legumes, potato starch, rice bran, rice flours, sesame, soybean flours, sunflower, tapioca starch

- Breads

- Only those breads with allowed gluten-free flours (see above)

- Cereal

- Cereal from corn, rice, or hominy

- Noodles and pasta

- Gluten-free corn, rice, or bean pasta



# Beverly: Follow-Up

- Serum tissue transglutaminase IgA antibody positive
- Duodenal scalloping visible on upper GI endoscopy
- Characteristic findings on duodenal biopsy
- Beverly is diagnosed with celiac disease
- Started on gluten-free diet
  - No foods containing wheat, rye, or barley





# Functional Diarrhea in Toddlers

*Toddler's Diarrhea/Chronic  
Nonspecific Diarrhea of Infancy*

# Case Study: Owen

- 2-year-old Caucasian male
- Symptoms
  - Intermittent diarrhea over last 3 months
    - No effect on weight gain or activity level
    - Stools shortly after eating
    - Mushy to watery
  - Drinks 5-6 cups of juice daily
  - Family friend recommended low fat diet, which made diarrhea worse



# Functional Diarrhea in Toddlers: Presentation

- First stool of the day often more formed than subsequent ones<sup>1</sup>
- Daily painless passage of  $\geq 3$  large, unformed stools<sup>2</sup>
  - May contain food and mucus
  - Often foul-smelling
- Symptoms last  $> 4$  weeks<sup>2</sup>
- Passage of stool during waking hours<sup>2</sup>
- No failure to thrive if caloric intake adequate<sup>2</sup>

<sup>1</sup>Davidson M and Waserman R. *J Pediatr*. 1966;69:1027-1038.

<sup>2</sup>Hyman PE, et al. *Gastroenterology*. 2006;130:1519-1526.

# Functional Diarrhea in Toddlers: Diagnosis

- Clinical diagnosis<sup>1</sup>
- Requires very detailed history<sup>1</sup>
- Exclude possibility of<sup>1</sup>
  - Enteric infections (including Giardia)
  - Antibiotics
  - Laxatives
  - Celiac disease
  - Disaccharidase deficiency
- Dietary history critical<sup>2-4</sup>
- Overfeeding<sup>2-4</sup>
  - Excessive fluid intake ( $> 190 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ )
- Excessive fruit juice intake<sup>2-4</sup>
  - Fructose, sorbitol
- Low fat intake<sup>2-4</sup>
  - $\leq 27\%$  of calories
- Food allergy<sup>2-4</sup>

<sup>1</sup>Hyman PE, et al. *Gastroenterology*. 2006;130:1519-1526. <sup>2</sup>Kneepkens CM, et al. *Eur J Pediatr*. 1989;148:571-573. <sup>3</sup>Hoekstra JH, et al. *Arch Dis Child*. 1995;73:126-130.

<sup>4</sup>Cohen SA, et al. *Am J Dis Child*. 1979;133:490-492.

# Functional Diarrhea in Toddlers: Treatment

- 80% improved on a normal diet for age
  - Appropriate fat, carbohydrate, and protein ratio
  - Limiting juice and excessive fluid intake
- Psyllium can be used as a bulking agent (1 tbsp twice daily)
- Ask parents to keep diet and stool diary for 1 week

Davidson M and Wasserman R. *J Pediatr*. 1966;69:1027-1038.

Smalley JR, et al. *J Pediatr Gastroenterol Nutr*. 1982;1:361-363.

Boyne LJ, et al. *Pediatrics*. 1985;76:557-561.



# Functional Diarrhea in Toddlers: Patient Education

- Balanced diet for age cornerstone of treatment
- Consultation with a dietitian may be helpful
- Reassurance that there are no known long-term consequences of the disorder
- Discussion of the utility of keeping a diet and stool diary

# Owen: Follow-Up

- Growth parameters normal
- Examination of stool showed no pathogens or blood
- Owen diagnosed with functional diarrhea
- Juice intake restricted and fat and fiber dietary content increased (appropriate diet for age); stool consistency improved and normal growth continued
- Parents advised to keep daily diet/defecation diary for 1 week



# Summary

- Carbohydrates are a critical dietary component, especially in growing children
- Carbohydrate malabsorption creates a barrier to development
  - Consideration of the diagnosis can quickly establish cause of symptoms
  - Appropriate treatment reduces symptoms and ensures patients receive essential nutrients
- Education on appropriate adjustment to carbohydrate intake empowers parents to regain control of their child's nutrition