NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

A CONTINUING MEDICAL EDUCATION MONOGRAPH SERIES
By NASPGHAN and The NASPGHAN Foundation for Children's Digestive Health and Nutrition

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

A Case-Based Monograph

Recognition and Management of Dietary

Carbohydrate–Induced Diarrhea in Pediatric Patients

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Jointly sponsored by NASPGHAN and The NASPGHAN Foundation for Children's Digestive Health and Nutrition.
Release Date: October 20, 2011; Expiration Date: October 31, 2014

2.0 AMA PRA Category 1 CME Credits ™

Jointly sponsored by NASPGHAN and The NASPGHAN Foundation for Children's Digestive Health and Nutrition.

This educational activity is supported by an independent medical education grant from QOL Medical.

Introduction

Carbohydrates make up a large portion of the worldwide daily diet; however, approximately 70% of the world's population has some form of carbohydrate malabsorption. Incomplete absorption of carbohydrates, or disaccharidase deficiency, can cause serious problems in affected patients, including increased daily energy expenditure and metabolic requirements in infants and poor nutrition and delayed growth during childhood. Despite major advances in identifying and treating these disorders, diagnosis continues to be a dilemma, due to a lack of proper awareness and specific guidelines. In this newsletter, we will provide detailed information concerning the pathophysiology, diagnosis, and treatment of pediatric patients with carbohydrate-induced diarrhea.

Target Audience

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

Learning Objectives

In dealing with patients who have carbohydrate-induced diarrhea, participants completing this activity should be better able to:

1) Understand the pathophysiology
2) Incorporate current diagnostic approaches
3) Provide appropriate management
4) Educate patients and their parents on the etiology and physiologic consequences and the importance of dietary modifications

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and The NASPGHAN Foundation for Children's Digestive Health and Nutrition. NASPGHAN is accredited by the ACCME to provide continuing medical education for physicians.

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Introduction

Carbohydrates make up a large portion of the worldwide daily diet, accounting for an estimated 40%-80% of an individual's total energy intake.[1] This nutritional building block can be found in a majority of foods, including dairy products, fruits, and grains; however, approximately 70% of the world's population has some form of carbohydrate malabsorption.[2] Incomplete absorption of carbohydrates may be a major cause of gastrointestinal distress in children of developed countries and may cause serious problems in affected patients.[3] In infants, it can increase daily energy expenditure, leading to increased metabolic requirements.[4] As these patients age, it can affect proper nutrition and cause adverse complications, such as delayed growth. Despite major advances in identifying and treating these disorders, diagnosis continues to be a dilemma, due to a lack of proper awareness and specific guidelines.[5] In this newsletter, we will provide detailed information concerning the pathophysiology, diagnosis, and treatment of pediatric patients with carbohydrate-induced diarrhea. We will not discuss secondary causes of carbohydrate-induced diarrhea, such as cystic fibrosis, celiac disease, or postinfectious enteritis; however, these entities should be kept in mind in the evaluation of infants and children with watery diarrhea.

Etiologies of Carbohydrate-Induced Diarrhea

Lactase Deficiency

Lactose is a sugar found in milk and other dairy products and contributes significantly to the growth and development of infants and children.[6] A rare disorder, congenital lactase deficiency leads to the inability of infants to digest lactose in breast milk or formula, resulting in severe diarrhea shortly after birth that can lead to dehydration and weight loss. In contrast, lactase deficiency that occurs as a result of a developmental decline in lactase activity results in an estimated 65% of the human population having difficulty digesting lactose after infancy. This translates to estimates of 79% of Native Americans, 75% of African Americans, 51% of Hispanics, and 21% of Caucasians with a reduced ability to process lactose-containing foods.[7] Self-diagnosis has increased with the increase of public knowledge concerning lactose intolerance, a trend that may lead to insufficient intake of nutrients, including calcium.[8] In some cases, self-diagnosis may be explained by psychological factors, such as somatoform disorder. In a study of 102 patients complaining of symptoms of lactose intolerance, intolerance and malabsorption were clinically confirmed in only 29% and 33% of patients, respectively, while patients with altered somatization were 4 times more likely to report intolerance.[9] Further complicating the diagnosis of true lactase deficiency, the symptoms can be easily confused with other gastrointestinal disorders, such as toddler's diarrhea and irritable bowel syndrome.[10]

Fructose Malabsorption

Fructose is a sugar found in fruits, vegetables, and an increasing number of manufactured foods in the form of high fructose corn syrup.[11,12] Due to the various forms of fructose, dietary intake can only be estimated; however, the majority of fructose is from added sources, such as soft drinks, instead of natural sources.[12] Between 1970 and 1990, consumption of fructose rose by more than 1000%, including a 4-fold increase of consumption by 10-year-old children. The true prevalence of fructose malabsorption is unclear, as the diagnosis often is made with the use of the hydrogen breath test.[12,13] However, interpretation of the hydrogen breath test is complicated by such factors as the lack of a standard dose, the effect of gastrointestinal transit time, and intestinal bacterial composition, among other factors. Generally, the number of individuals with a positive breath test far exceeds the number of people with symptoms following fructose ingestion.[13] As noted above, this may be due to lack of knowledge of the most appropriate dose of fructose to use in the breath test. The reliability of the breath test result in an individual may be greater if the malabsorption diagnosed by breath test is accompanied by symptoms. Fructose malabsorption may result in bloating, diarrhea, excessive flatulence, and stomach pain.[11]

Congenital Sucrase-Isomaltase Deficiency

Congenital sucrase-isomaltase deficiency (CSID) is an autosomal recessive disorder that affects a patient's ability to digest sucrose, which is found in fruits and is also known as table sugar, and maltose, which is found in grains.[14] CSID is considered rare and is only found in an estimated 0.02% of Americans of European descent and 5% in the native populations of Greenland, Alaska, and Canada;[14,15] however, due to varying clinical severity and that it may be caused by a variety of genetic mutations (see below), it is possible that patients remain undiagnosed and that the incidence may be higher. Heterozygotes appear to have varying degrees of diminished sucrase activity compared with normals, but the clinical significance is unclear.[16] Compound heterozygous mutations affect protein folding and function in patients with CSID, and these patients may have mild symptoms typical of those with classical disease.[17–19] Patients with CSID suffer from diarrhea after consumption of sucrase-containing food or drink, usually at weaning.[15,20,21] However, symptoms may begin within the first few months of life in infants receiving formula containing glucose polymers, because of the contribution of sucrase-isomaltase (SI) to hydrolysis of this starch.[20,22] Nephrocalcinosis has been described to be associated with the disorder.[22] Treatment with sucrase generally results in a resolution of symptoms.[15,18]

Glucose-Galactose Malabsorption

During digestion, disaccharides, such as sucrose and lactose, are broken down into simple sugars, or monosaccharides.[23] Sucrose breaks down into glucose and fructose, and lactose breaks down into glucose and galactose. Because patients with the autosomal recessive disorder glucose-galactose malabsorption (GGM) are unable to digest any dietary components or compounds containing these disaccharides or their constituent sugars (i.e., glucose or galactose), symptoms begin shortly after birth.[24] Thus, affected

patients experience severe diarrhea that results in life-threatening dehydration, acidosis, and weight loss when fed breast milk or standard infant formulas. As with CSID, it has been associated with nephrocalcinosis.[25] Symptoms generally improve to some degree with time, likely related to changes in the fermentative ability of the intestinal bacterial population.

Dietary Excess of Sorbitol/Fructose

Certain carbohydrates can replicate symptoms of disaccharidase deficiencies or monosaccharide transport defects when ingested at high doses, even in healthy patients. In a study of 15 healthy volunteers, greater than 50% showed signs of malabsorption after a dose of 25 g of crystalline fructose mixed in water, and over 66% had similar results after a 50 g dose.[26] Sorbitol is a sugar alcohol (polyol) that is used commonly as a sweetener and to retain moisture in prepared foods. In a similar study to the one on fructose, 30 healthy volunteers ingested test solutions containing sorbitol 20 g, sorbitol 10 g, and 4 sweets that contained a total of 6.8 g of sorbitol. One hundred percent, 90%, and 62% of the volunteers, respectively, had significantly raised breath H_2 excretion that indicated malabsorption.[27] Within 8 hours, 100% of the volunteers who ingested sorbitol 20 g, 45% of those ingesting 10 g, and 50% of those who were given the 4 sweets complained of symptoms of carbohydrate intolerance. These 2 separate studies show that difficulty digesting certain sugars, such as sorbitol and fructose, is not limited to patients with malabsorption disorders, but is also common in a healthy population when too much of these sugars are ingested. This is made more relevant by the aforementioned fact that fructose consumption has increased dramatically over the years, with an equally common occurrence of sorbitol in diet-related foods and drinks.

Toddler's Diarrhea

Functional diarrhea, previously called Toddler's diarrhea, is defined by painless, recurrent passage of 3 or more large, unformed stools per day for ≥ 4 weeks with an onset between 6 and 36 months of age.[28] It is the most frequent cause of chronic diarrhea in children ages 1-5 years and often results from nutritional imbalance, such as increased intake of sugars through fruit juice and reduced intake of fat and fiber.[29] Stools are often reported as watery, containing mucus and undigested food material, and occurring almost immediately after feeding. The symptoms usually resolve spontaneously by the time the child reaches school age, and importantly, there is normally no evidence of failure to thrive if the child is receiving adequate calories.

Case Study 1: *Ben*

Ben is an 8-month-old Caucasian male, whose parents seek care because of a history of 2-3 months of diarrhea. They note that his weight gain has faltered over this time period. There has been no vomiting, and he remains hungry. Beyond the diarrhea, they have noted that his abdomen is tight and distended after feeding, and he has been colicky since the diarrhea started.

Case Study 2: *Crystal*

Crystal is a 15-year-old African American female who reports intermittent diarrhea without blood, often accompanied by abdominal pain and bloating within an hour or 2 of eating. She has had no weight loss or other constitutional symptoms.

Case Study 3: *Mary*

Mary is a 2-year-old Caucasian female whose mother is concerned about symptoms of intermittent diarrhea that began in the past few months. It has not affected her weight gain or activity level. She is a picky eater and loves to drink juice and often has 6-7 cups every day. A family friend recommended that she try a low fat diet, which seemed to make her diarrhea worse. Her diarrhea usually starts immediately after eating, is mushy to watery, and sometimes contains undigested food, such as corn.

Pathophysiology of Carbohydrate Malabsorption

Digestion and absorption of carbohydrates occurs in the proximal small intestine and, depending on the specific sugar, relies on hydrolysis by pancreatic (and to a much lesser extent, salivary) amylase, brush-border hydrolases, and specific transporters to subsequently absorb hexose monosaccharides (glucose and galactose) and the pentose fructose across the small intestinal epithelium.[12] If the luminal carbohydrate is well-hydrolyzed, optimal sugar, salt, and water absorption occurs. However, disruptions in any of these steps may cause malabsorption of dietary disaccharides, starch, and/or monosaccharides in the small intestine, increasing the osmotic load and stimulating peristalsis in the ileum and colon.[30] As the osmolality increases, osmotic pressure in the lumen increases and water flux into the lumen occurs, resulting in loss of sugar, salt, and water.

The capacity of the colonic bacteria to ferment the malabsorbed carbohydrate, as well as the ability of the colonocyte to absorb the fluid and resulting fatty acids, can be overwhelmed, causing the hallmark diarrhea in patients with a carbohydrate malabsorption disorder. Unabsorbed carbohydrates in the small intestine also affect distant gastrointestinal processes and absorption of other nutrients. Decreased water and sodium absorption may inhibit gastric emptying and speed up small intestinal transport, which may also contribute to the malabsorption of starch, fat, and monosaccharides.[31] This may also lead to a disruption of normal postprandial surges of hormones, such as insulin, C-peptide, and gastric inhibitory peptide.[31,32] Reasons for carbohydrate malabsorption differ among the varied types of deficiencies.

Pathophysiology by Disaccharidase Deficiency Type

Lactose intolerance. In infants and most toddlers, as well as adults without a maturation decline in lactase activity, lactose is efficiently hydrolyzed into the monosaccharides glucose and galactose by the enzyme lactase on the villous tip at the brush border of enterocytes.[33] As a result, carbohydrate absorption is efficient in these individuals. In addition, absorption of calcium, magnesium, zinc, and other nutrients is enhanced in the small intestine. However, lactase expression in the small intestine can be reduced by a number of mechanisms. These include, in children usually older than 5 years, mutations in the *LCT* gene, which provides instructions for lactase enzyme production, and most prominently in babies with significant damage of the intestinal mucosa by infections (such as rotavirus),[34] milk protein and other allergies,[35] celiac disease,[36] or immunodeficiency disorders, such as human immunodeficiency virus infection.[37]

Lactase deficiency due to mucosal injury in the intestines may appear at any age, though children younger than 2 years are particularly susceptible, due to high gut sensitivity to infectious agents, low reserve as a result of the small intestine surface to body area ratio, and high reliance on nutrition from milk-based products.[38] Low lactase activity in the small intestine causes undigested lactose to pass into the colon, where it is fermented into hydrogen gas and organic acids by bacteria, resulting in bowel distension. This can cause a range of symptoms, including bloating; abdominal discomfort; and flatulence beginning shortly after milk or dairy product ingestion accompanied by loose, watery, acidic stools.

Fructose malabsorption. The vast majority of intestinal sugar absorption occurs via 3 major brush border transporters: SGLT1, which is an active sodium-coupled glucose-galactose cotransporter; GLUT5, a low-affinity, facilitative brush border transporter which is specific to fructose; and GLUT2, which carries glucose, fructose, and galactose across the basolateral membrane.[12,39–41] Fructose absorption is enhanced in the presence of glucose, although the mechanism whereby this occurs is not clear, but possibly through upregulation of GLUT2 in the brush border.[42]

The occurrence of fructose malabsorption is usually due to excessive intake, because fructose is not actively transported. Research has shown that the intake of high fructose corn syrup in 10-year-old American children has increased 4-fold.[12] Similar to malabsorption of lactose in the presence of lactase deficiency, excessive luminal fructose causes an increase in osmotic load, with more water delivered to the distal small intestine and colon and accelerated small bowel transit.[12,43] Intestinal gas is formed rapidly, due to fermentation, and locally distends the colonic lumen. This process may also expand the mucosal biofilm in the distal small intestine, leading to luminal fermentation and to small intestinal bacterial overgrowth.[12,44] It is unclear how commonly fructose malabsorption causes abdominal pain in children, but its removal from the diet has been shown to improve symptoms in the majority of children with a positive breath test in open label testing.[45]

CSID. SI, unlike lactase, is an inducible brush border enzyme expressed in the small intestine throughout gestation and found in the fetal colon in gestation weeks 12-30.[31] Dietary factors are important regulators of SI activity, with induction by high-sucrose or high-carbohydrate diets and down-regulation by fasting.[31,46] Molecular defects, such as abnormalities of intracellular processing of SI (i.e., glycosylation and folding) and homing and insertion of the enzyme into the brush-border membrane, have been noted, and as many as 5 different transport incompetent enzymes or enzymes with altered function have been discovered in CSID patients.[31,47,48] While all CSID patients lack sucrase, some still have traces of isomaltase activity, others have reduced but significant activity, and others have almost normal activity, showing that SI gene expression is not completely absent in these patients.[31]

Chronic, watery diarrhea and failure to thrive are common in infants and toddlers with CSID, but they do not require parenteral nutrition. As is the case with other carbohydrate malabsorption disorders, other symptoms may include abdominal distension, gassiness, colic,

irritability, and excoriated buttocks from the diarrhea. Only a minority of severely affected patients require hospitalization for diarrhea, dehydration, malnutrition, muscle wasting, and weakness.[31,49] These symptoms depend on the patient's residual enzyme activity, quantity of the ingested carbohydrate, rate of gastric emptying, effect on small-bowel transit, metabolic activity of colonic bacteria, and absorptive capacity of the colon.[31] Thus, there is a varied clinical presentation of CSID, which depends on the timing of introduction of sucrose into an infant's diet. Infants who are breast-fed or fed lactose-containing formula will often not manifest symptoms of CSID until they ingest juices, solid foods, or medications that are sweetened by sucrose. Baby cereals also usually reduce the severity of symptoms, due to compensatory mechanisms in starch digestion.

GGM. In the absorption of glucose and galactose, the key molecule is the sodium-coupled glucose cotransporter protein SGLT1.[23,50] This brush border protein mediates the success of oral rehydration therapy, where two sodium molecules are transported with each molecule of glucose.[51] SLGT1 is found throughout the intestinal tract and, in lesser amounts, in the kidneys. Mutations in the *SLC5A1* gene, inherited as an autosomal recessive gene, result in the malabsorption of the monosaccharides glucose and galactose, as well as the inability to absorb these sugars from the disaccharides lactose, sucrose, and maltose, resulting in severe diarrhea and potential dehydration. Children with this rare disorder generally do well on diets containing fructose. Symptoms return even in adulthood with even small intakes of glucose. A high proportion of patients are from consanguineous relationships.[52]

Diagnosis of Carbohydrate Malabsorption Disorders

Diagnosing carbohydrate malabsorption should begin with a careful review of the patient's nutritional history.[53] Specific aspects of a patient's diet have the potential to illuminate the appropriate diagnostic and treatment approach. Diagnostic modalities include dietary exclusion, stool testing, breath testing, and intestinal biopsy (see **Table 1** for diagnostic recommendations based on malabsorption type); however, proper diagnosis should not be made from the result of one diagnostic approach alone, but should be confirmed in the context of a patient's symptoms and with appropriate laboratory evaluation. In chronic watery diarrhea, stools should be examined for pH, glucose or reducing substances, sodium, and the presence of blood. Consideration should be given to testing for bacterial and parasitic infection as clinically appropriate.

Table 1. *Potential Diagnostic Evaluations for Specific Malabsorption Types*[21,28,31,53–61]

Malabsorption Type	Potential Diagnostic Evaluation	Methodology
Lactose	Breath testing	• 1 g/kg lactose (max 25 g) oral load after 6-hour fast (overnight); > 20 parts per million (ppm) positive; monitor symptoms after testing
	Biopsy	• Lactase activity of < 8 U/g protein or 0.7 U/g net weight in jejunal biopsy
Fructose	Dietary exclusion	• Dietary elimination of fructose to monitor resolution of symptoms
	Breath testing	• 0.5 g/kg fructose (max 15 g) oral load after 6-hour fast (overnight); > 20 ppm positive; monitor symptoms after testing
	Biopsy	• Normal intestinal histology and disaccharidase activity with malabsorption limited to fructose
SI Deficiency	Breath testing	• 1-2 g/kg sucrose (≤ 50 g) oral load; > 10 ppm positive • ^{13}C-sucrose breath test – initial experience promising
	Biopsy	• Complete or almost complete absence of sucrase activity, markedly reduced isomaltase activity, and reduced maltase activity • Mucosa usually histologically normal; glucoamylase activity and lactase levels usually normal, though glucoamylase activity may be reduced
Glucose-Galatose	Dietary exclusion	• Dietary elimination of glucose, galactose, and lactose to monitor resolution of symptoms
	Stool testing	• Measurement of pH (< 6.0), occult blood, leukocyte analysis osmolality, and reducing sugars
	Breath testing	• Useful, but not required; most patients have levels > 100 ppm and results can be confirmed with fructose breath testing (glucose H_2 levels will be higher)
	Biopsy	• Not essential, but helpful in distinguishing from lactase or sucrase deficiency • Normal microvilli on electron microscopy and normal duodenal microscopic architecture • Normal distribution of enterocytes, Paneth, goblet, and enteroendocrine cells
Functional Diarrhea	Stool testing	• History and physical examination are essential • Visible mucus and undigested food • Absence of blood, reducing substances, pathogens

Modalities for Malabsorption Diagnosis

Dietary Exclusion

The onset of clinical symptoms often coincides with the introduction of specific disaccharides into the diet and may help identify which carbohydrate is being malabsorbed.[53] In pediatric patients, parents may restrict the patient's diet based on their personal observations of what causes symptoms, but they also may overestimate nonspecific complaints. In diagnosing carbohydrate malabsorption, dietary exclusion must result in the complete resolution of any diarrheal symptoms. While dietary exclusion alone generally is not sufficient for definitive diagnosis in most types of carbohydrate-induced diarrheal disorders, it is a crucial part of the evaluation, as elimination of the offending sugar should resolve patient complaints.

Stool Testing

Carbohydrate malabsorption may be detected in the stool by measuring the acidity (low pH) and amount of reducing substances of a watery sample of stool, although these tests are not specific.[31,53] The low pH (< 6) usually measured by nitrazine paper is caused by the presence of free fatty acids generated from the fermentation of carbohydrate by colonic bacteria. If the patient's diet includes reducing sugars (glucose, lactose, and fructose), the stool can be tested for reducing substances by the use of the Clinitest™ tablets, which if present, suggest carbohydrate malabsorption. Glucose can be tested for specifically using semiquantitative, enzyme-based glucose test strips. Although sucrose is not a reducing substance, malabsorbed sucrose can also be degraded by colonic bacteria to glucose and fructose, sometimes resulting in a positive test for reducing substances or glucose.[62]

The osmotic gap of fecal fluid can be used to estimate the relative contributions of electrolytes and nonelectrolytes to retention of water in the intestinal lumen. In an osmotic diarrhea, such as carbohydrate-induced diarrhea, nonelectrolytes (i.e., sugars) cause water retention. The osmotic gap is calculated from electrolyte concentrations in stool water by the following formula: 290 – 2([Na+] + [K+]). This formula is preferred over those that use measured stool osmolalities, because the latter may be falsely elevated due to postcollection changes or to contamination of the sample with concentrated urine.

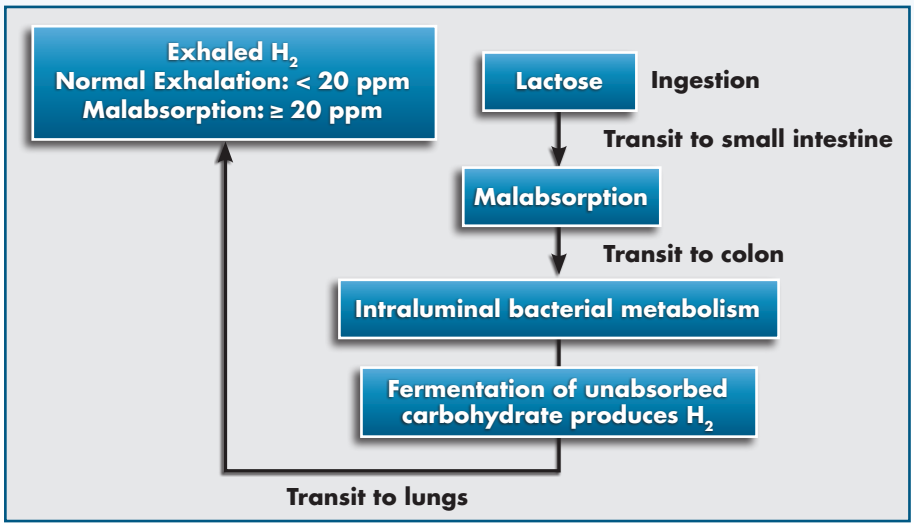
Other stool testing, including occult blood, leukocyte analysis, and/or calprotectin, may also be required if intestinal inflammation is in the differential diagnosis.[53]

Though testing for stool reducing substances and pH are often used in the diagnosis of patients with suspected CSID and GGM, they are not specific enough for use in cases of potential lactose malabsorption. In the case of functional diarrhea, or Toddler's diarrhea, stool pH should be normal and there should be an absence of sugar. Visible mucus and undigested food are typically indicative.[28]

Breath Testing

When dietary sugars escape small intestinal absorption, they become available for fermentation by bacteria and result in the production of H_2.[63] Specifically, when H_2 is produced by bacterial carbohydrate metabolism, it is absorbed into the portal circulation of the colonic mucosa and excreted in the breath (**Figure 1**).[53,63] In breath H_2 testing, patients are administered a weight-specific load of a carbohydrate and changes in breath H_2 excretion are measured over a period of time.[31,53] Malabsorption is defined as a specific rise in the ppm of breath H_2 over the baseline (0 time) value.

Figure 1. *Production of breath H2 following lactose ingestion*



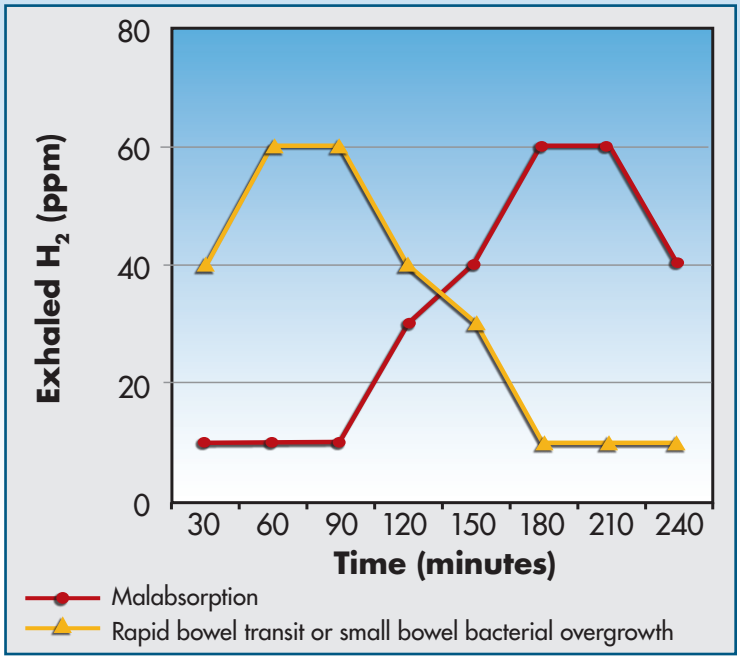
Recent guidelines have been published on the performance of lactose H_2 breath tests in adults and children.[64] For lactose, a dose of 1 g/kg up to 25 g is recommended with a test duration of 3 h and a sample frequency of 30 min. A cut-off value of a rise in breath H_2 of 15-20 ppm is recommended.[65] Evaluation of symptoms of abdominal pain, bloating, flatulence, and diarrhea using a visual analogue scale during and for 8 h after the test is suggested. Others have recommended that, if the breath test is negative but symptoms are present, a lactulose breath test be carried out to determine if the patient is a non-hydrogen producer (patients who fail to show elevated breath hydrogen excretion, despite deficient enzyme activity).[66] Other reasons for false negative tests include taking antibiotics or the inability to perform the test properly because of age.[53,67]

False-positive measurements can be seen with rapid intestinal transit, which reduces the amount of time available for proper carbohydrate absorption and metabolism.[53,68] An example of an abnormal breath H_2 test, due to rapid transit or small bowel bacterial overgrowth as opposed to lactase deficiency, is shown in **Figure 2**.

It should be noted that, while breath H_2 testing is often used to test for carbohydrate malabsorption, it is unreliable for predicting lactose malabsorption in infants recovering from diarrhea.[53,65,69]

Breath H_2 testing for fructose malabsorption is problematic, because up to 40% of adults may have symptoms after a fructose breath test, depending on the fructose dose, and the level of breath H_2 produced does not correlate with symptoms.[70,71] Further, in children,

FIGURE 2. *Normal breath test results of lactose malabsorption compared to abnormal results*



the proportion of those with fructose malabsorption appears to decrease with age.[72] Current data support the use of a 0.5 g/kg dose of fructose to a maximum of 15 g and using 15-20 ppm as a cutoff for breath H_2 excretion.[65,70–72]

Breath H_2 testing also has been used in the diagnosis of SI deficiency.[73] The appropriate dose and cutoff value has not been well studied, but doses of 1-2 g/kg (max 50 g) with a cutoff value of 10 ppm have been used.[31,73] More recently, a ^{13}C-sucrose breath test has been employed for diagnosis in a small study. Although preliminary results were encouraging, normal values have not been defined.[21]

Breath H_2 testing has proven useful in the diagnosis of GGM.[74] A rise in breath H_2 above 10 ppm after administration of 1 g/kg of glucose (up to 25 g) and development of watery, acid stools positive for glucose support the diagnosis. Similar findings should result from the administration of galactose, but not fructose. A rise in breath H_2 (≥ 12 ppm) after glucose administration also may occur in small bowel bacterial overgrowth.[75] However, in practice, the rise in breath H_2 in GGM can be into the hundreds of ppm, whereas in small bowel bacterial overgrowth, it is modest.

Duodenal Biopsy With Disaccharide Analysis

Standard disaccharidase analysis in duodenal biopsies typically includes lactase, maltase, sucrase, and palatinase. Biopsies provide material for both enzyme activity determination and histological examination and may be obtained by endoscopic biopsy in the second or third portion of the duodenum.[33] At least 2 specimens should be obtained via standard upper endoscopy and 3 specimens obtained via pediatric upper endoscope for proper determination of disaccharidase activity. The location of the specimens also should be documented when interpreting intestinal disaccharidase levels, as simultaneous biopsies obtained from the duodenum and jejunum have shown a 30%-40% reduction in lactase, sucrase, and maltase activity in the duodenum compared to the jejunum in patients with known normal disaccharidase activity.[31,76,77] While biopsies are considered standard diagnostic procedures in most malabsorption disorders, in practice they are not commonly used to diagnose lactase deficiency and fructose malabsorption.[31,53,54] Biopsies are not essential in GGM if other diagnostic modalities, such as stool testing, breath testing, and dietary exclusion, are properly administered and the results demonstrate indisputable and selective glucose intolerance.[54]

Treatment of Carbohydrate Malabsorption Disorders

In children of any age, intake of appropriate dietary nutrients is critical for appropriate nutrition and growth. Problems in carbohydrate digestion and/or absorption can result in barriers to appropriate development, including chronic gastrointestinal complaints, decreased weight for height and age, increased risk of osteoporosis later in life, and long-term risk of abnormal bone density and fractures.[31,49,53,78–81] Treatment of carbohydrate-induced diarrhea usually consists of elimination or reduction of the malabsorbed carbohydrate; however, in sucrase or lactase deficiency, supplementation may be more acceptable to the patient and/or family. Treatment options for carbohydrate-induced diarrhea are listed below and summarized in **Table 2**.

Dietary Exclusion of Malabsorbed Carbohydrates

Once diagnosis has confirmed which carbohydrate is being malabsorbed, elimination or reduction of the corresponding carbohydrate may be required. Avoidance of foods containing the specific malabsorbed carbohydrate should resolve the symptoms,[12,31,53] but adherence to such diets often requires a life-long commitment and an in-depth knowledge of the sugar content of most foods.[31,53]

Lactose. Children who avoid milk have been documented to ingest less-than-recommended amounts of calcium for normal bone calcium accretion and mineralization, so complete milk restriction should be carefully managed, and the recommended intake of calcium must be supplied by calcium supplements, calcium-fortified fruit juices, and vegetables.[53,90–92] According to the Institute of Medicine of the National Academies, the recommended intake of calcium for pediatric patients is 200 mg/day for infants aged 0-6 months, 260 mg/day for children aged 6-12 months, 700 mg/day for children aged 1-3 years, 1000 mg/day for children aged 4-8 years, and 1300 mg/day for children aged 9-18 years.[93] However, many lactose malabsorbers may be able to tolerate small amounts of milk without complaints, so small portions of 4-8 oz. can be spaced throughout the day and consumed with other foods to avoid symptoms.[2,82–86] Patients may also be able to tolerate hard cheeses (many soft cheeses have lactose) and plain yogurt, as the bacteria

TABLE 2. *Treatment Recommendations for Specific Malabsorption Types*[2,15,28,31,53,82–89]

Malabsorption Type	Treatment	Recommendation
Lactose	Dietary elimination	• If possible, avoid complete elimination from diet • Milk may be tolerated in small quantities spaced out through the day • Ensure pediatric patients receive adequate intake of calcium through supplementation and/or calcium-fortified juices
	Supplementation	• Available over-the-counter • Proven effective for improved absorption of lactose in children
Fructose	Dietary elimination	• Regimen of incrementally increasing amounts of fructose may resolve malabsorption • Generally limited to infants, so fructose should be reintroduced at school age
Si Deficiency	Dietary elimination	• Avoid beetroot, peas, honey, soybean flour, and onions; care must be taken with glucose polymer formulas and medications • Avoidance of starches (wheat and potatoes) may also be necessary during infancy, but may be tolerated after age 3-4 years
	Supplementation	• Lypholized baker's yeast is effective, but its bad taste is often rejected by children • Sacrosidase is more palatable and FDA approved
Glucose-Galatose	Dietary elimination	• Usually resolves symptoms • Carbohydrate-free formula is also available for infants
Functional Diarrhea (Toddler's Diarrhea)	Monitoring	• Restrict juices rich in fructose • Avoid restrictive diets that deprive calories • Daily diet and defecation diary will help document that specific foods are not responsible

in the yogurt may digest the lactose.[53,94–96] Milk substitutes, like rice milk, almond milk, and soy milk, are generally free from lactose, but have less protein than cow's milk.[2] Most milk substitutes have added calcium to amounts similar to cow's milk. Lactose-free and lactose-reduced milks may also be considered, and sweet acidophilus milk possesses lactase activity and has a taste similar to milk.[2,53,97]

Oral lactase replacement often allows patients to consume some or all milk-based products freely.[2,87] In a study of 18 lactose intolerant children aged ≈ 11 years and with no underlying gastrointestinal disease, lactase-containing tablets (β-galactosidase) and a subsequent lactose load resulted in significantly lower breath H_2 test results than placebo (7 ppm vs. 60 ppm, respectively).[87] The patients who were given the lactase-containing tablets also had reduced abdominal pain, bloating, diarrhea, and flatulence in comparison to those who were given the placebo. Lactase enzymes are also available in liquid form, with both the tablet and liquid forms available over-the-counter.

Fructose. Reduction or elimination of dietary fructose results in improved symptoms in 81% of patients after 1 month and 67% of patients at 12 months, with 50% of patients seeing complete symptom resolution after 12 months.[12,54,98] GLUT5 promotes uptake of fructose; however, GLUT5 levels in rodent models have been shown to depend on a chronic load of dietary fructose and sucrose, so malabsorption may be improved by incrementally increasing fructose in the diet.[54] As malabsorption is typically limited to infants, reintroduction of fructose in the diet should be considered in patients as they reach their school-age years. Combined sugar malabsorption patterns, specifically fructose and fermentable oligosaccharides and polyols, may persist and may contribute to symptoms in patients with functional gastrointestinal disorders.[12,99–101]

Sucrose/maltose. In patients with CSID, dietary restrictions often require life-long adherence to a strict sucrose-free diet.[31,53] The degree of restriction is dependent on the patient's individual complaints, but foods with high concentrations of sucrose, including beetroot, peas, honey, soybean flour, and onion, should be avoided, and care must be taken with glucose polymer formulas and medications that contain sucrose as sweeteners.[53] Due to their effect on isomaltase activity, foods with high amylopectin content (e.g., cereals, breads, and pastas) and potatoes should also be excluded, especially during the first years of a patient's life; however, starch tolerance generally improves in the first 3-4 years, and rice starch and maize starch are easier to digest.[31,53,102]

Lyophilized baker's yeast (*Saccharomyces cerevisiae*) possesses sucrase activity, low isomaltase and maltase activity, and almost no lactase activity.[53] Enzyme replacement with small amounts of lyophilized baker's yeast, when administered with an oral sucrose load, has shown encouraging results, with reductions in breath H_2 test results by up to 70% and reduction or elimination of diarrhea, cramping, and bloating.[31,53,89] However, baker's yeast is not very palatable and, as a result, is poorly accepted in young children.[31]

An alternative to traditional baker's yeast is sacrosidase, a liquid preparation that contains high concentrations of invertase (sucrase) that is highly potent, stable with refrigeration, and tasteless when mixed with water.[103] In a study of 14 patients with CSID treated with

sacrosidase, breath H_2 was significantly reduced and symptoms of diarrhea, abdominal pain, and gas were either prevented or relieved, allowing children to consume a more normal, sucrose-containing diet. A later study showed significant decreases in breath H_2 in 28 children aged 5 months to 11 years when sacrosidase was compared to placebo.[15] It was also found that higher concentrations of sacrosidase were associated with fewer stools and a greater number of formed or hard stools and fewer symptoms of gas, abdominal cramps, or bloating, with no difference in vomiting. Only 1 adverse event was reported from this study, as 1 child with a history of asthma reported wheezing. Unlike lactase-containing supplements, sacrosidase is only available by prescription.

Glucose/galactose. Diets eliminating glucose and galactose are usually effective in resolving symptoms.[54] Due to the long-term risk of abnormal bone density and fractures, calcium and vitamin D should be supplemented in patients with restricted glucose and galactose intake; however, no long-term renal, bone, or cardiovascular consequences have been reported in patients adhering to life-long glucose- and galactose-free diets. During infancy, carbohydrate-free formulas, to which fructose should be added, are available. Fructose is used at a concentration of 6%-8%. Later in life, limited amounts of glucose (in starches) or sucrose may be added. In some children, use is extended beyond infancy, due to a lack of viable alternatives. It should be noted that prolonged use can become expensive in comparison to an elimination diet.

Educating Parents and Patients

Dietary management of carbohydrate malabsorption disorders poses a distinct challenge, especially in patients who are entering the late stages of infancy, where they begin to exert more independence.[53] However, providing proper and thorough education to these patient's parents and the patient's themselves when they reach an age where they can appropriately understand their limitations may increase confidence in their ability to manage their special needs and reduce anxiety levels over symptom control.[104] In a study of 62 adult patients with breath test–confirmed fructose malabsorption, 74% showed a positive response to dietary education, including proper adherence to elimination diets. These results may also translate to the level of success experienced by parents instituting specialized dietary restrictions in their children.

Education should involve teaching parents the scientific basis of their child's malabsorption and determination of a comprehensive list of foods that may cause digestion problems.[104] Food alternatives, such as sweet acidophilus milk in lactose intolerant patients, should be emphasized. Invaluable advice can be provided from well-trained dietitians, but in cases where this is not an option (e.g., if the parents

Case Study 1: *Follow-up*

Ben's breath H_2 excretion was tested, and a duodenal biopsy was performed. His breath hydrogen rose by 40 ppm after a weight-appropriate sucrose load, and his biopsy results show a complete absence of sucrase activity, with some reduction in isomaltase and maltase activity. The diagnosis of CSID was confirmed and explained to Ben's parents, including an explanation that he should avoid sucrose-containing foods and, if symptoms persist, starches, such as wheat and potatoes. It was also explained that this is a lifelong problem that may require long-term adherence to a restrictive diet. However, Ben also was prescribed sacrosidase for attempted reintroduction of these foods into his diet once his symptoms had resolved.

Case Study 2: *Follow-up*

After oral administration of lactose, Crystal's breath H_2 increased 30 ppm over her baseline and she developed abdominal pain and bloating during posttest monitoring. A 10-day elimination diet of all lactose-containing foods resulted in resolution of her previous symptoms of intermittent abdominal pain, bloating, and diarrhea. Because of her preference to continue consuming dairy products, an over-the-counter lactase supplement was recommended. She also was educated on the possibility of reducing her symptoms by ingesting lactose with meals and spreading out her intake over the day. In the event that neither of these approaches worked, she was instructed on dairy alternatives and the importance of supplementing her calcium intake if milk avoidance was required.

Case Study 3: *Follow-up*

Mary's history showed no previous digestive symptoms, and physical examination results, including growth parameters, were normal. Examination of her stool revealed no pathogens or blood, and serologic testing for celiac disease was negative. A diagnosis of functional diarrhea (Toddler's diarrhea) was made. It was recommended that her mother restrict her juice intake and increase the fat and fiber content of her diet (i.e., provide an appropriate diet for age). Her diarrhea improved, although it did not resolve over the next few months. Her mother was advised to start a daily diet and defecation diary to make sure that Mary's diarrhea did not result from specific foods.

cannot afford it), dietary manuals that list the sugar content of selected foods should be recommended.[53] Parents of children with a carbohydrate malabsorption disorder should be instructed on how to properly read food labels and avoid foods with more than the lowest amounts of specified carbohydrates, including, if needed, the use of sugar-free medications.

Summary

Carbohydrates are a critical component to the dietary intake of people worldwide, but are especially essential in growing children. Malabsorption of these major building blocks to healthy and appropriate growth can cause barriers to a child's development, possibly leading to long-term problems, such as reduced height, weight, and osteoporosis. In severe carbohydrate-induced diarrhea it can lead to life-threatening dehydration. Through carbohydrate-specific diagnosis, the causes of watery diarrhea can be quickly established, and appropriate treatment, including dietary exclusion and supplementation, will reduce these symptoms and ensure patients receive the necessary nutrients for normal growth. At the same time, educating parents on appropriate adjustments to carbohydrate intake enables them to regain control of their child's nutrition and often improves their confidence and relieves anxiety.

Thank you for participating in this activity

To complete the activity posttest and evaluation, please visit http://www.pednutrition.net/carbohydrateCME or review page 2 under "How to Receive CME Credit" for further details.

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