A CME Proceedings Newsletter for Advanced Practice Providers

DECEMBER 2023

INSIDE THIS ISSUE

A series of regional CSID APP Leadership Summit meetings

was held in Scottsdale, Denver, Boston, and Chicago in 2023. A total of 31 APPs and 1 gastroenterologist participated in these 4 events. The key messages from these discussions are summarized in this issue.

GHAPP Gastroenterology & Hepatology Advanced Practice Providers

Regional CSID APP Leadership Summits:
A CME Proceedings Newsletter for Advanced Practice Providers

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Release date: March 1, 2024
Expiration date: March 1, 2025

Target Audience
The initiative's total targeted reach is 5,000 health care professionals. including nurse practitioners, nurses, and physician assistants.

Program Overview
The joint providership of Medical Education Resources (MER) and the GI Health Foundation (GiHF) proposes to develop an accredited proceedings e-Newsletter on the management of patients with CSID. In addition to the content discussed during the CSID leadership summits and virtual mentorship sessions, additional expert opinions, recent publications, abstracts, and presentations from congress meetings will be reviewed as part of the e-Newsletter development process.

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

- Describe the prevalence of CSID in patients with common GI disorders
- Incorporate current diagnostic strategies to differentiate CSID from other causes of persistent diarrhea seen in clinical practice, particularly among patients with suspected IBS
- Summarize benefits and limitations of current treatment strategies for CSID

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Accreditation Statement
JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by Medical Education Resources (MER) and GiHF. MER is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Disclosures

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Method of Participation
There are no fees for participating in and receiving credit for this activity. During the period March 1, 2024 through March 1, 2025, participants must 1) read the learning objectives and faculty disclosures, 2) study the educational activity, 3) complete the posttest by recording the best answer to each question, and 4) complete the evaluation form. A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 75% or better.

Please visit https://education.gihealthfoundation.org/content/cme-proceedings-newsletter-advanced-practice-providers-regional-csid-app-leadership-summits to complete the posttest and evaluation.

Media
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Fee Information
There is no fee for this educational activity.

This activity is jointly provided by Medical Education Resources and the Gi Health Foundation.

MEDICAL EDUCATION RESOURCES

GI Health Foundation

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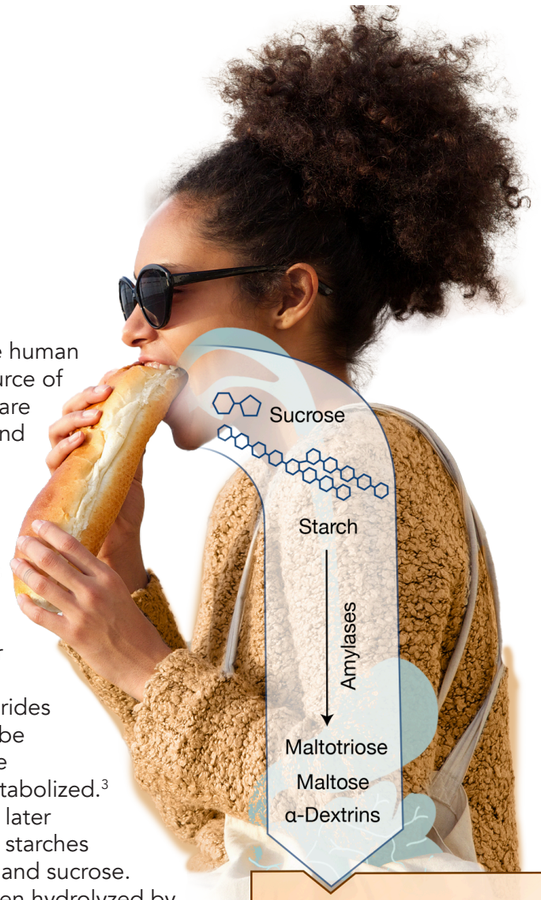
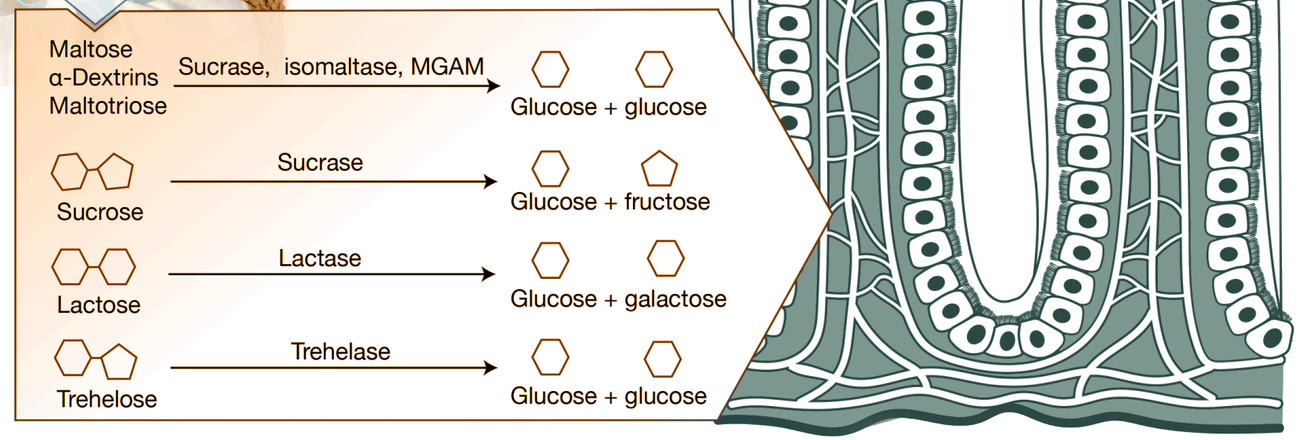
Digesting and absorbing carbohydrates

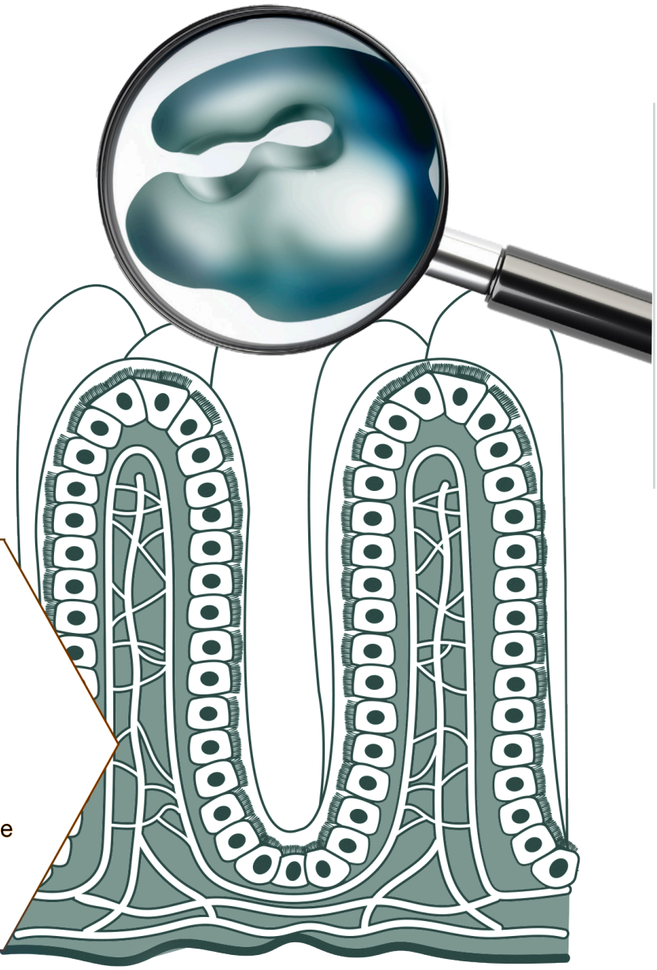
The SI enzyme is key to the digestion of sucrose and starch.

As one of the 3 macronutrients in the human diet, carbohydrates are a primary source of energy.[1] Most dietary carbohydrates are derived from table sugars (sucrose) and plant starches that are composed of different α-linked sugars.[2]

The glucose and fructose found in fruit and honey are monosaccharides (ie, simple sugars) that require no further digestion and are absorbed as they are.[1] However, because sugar transporters in the intestine can only transport monosaccharides, disaccharides (sucrose, lactose, and maltose) must be hydrolyzed into their monosaccharide components to be absorbed and metabolized.[3] This process begins with salivary and later pancreatic α-amylases that hydrolyze starches into smaller sugar residues, maltose, and sucrose. These and other disaccharides are then hydrolyzed by disaccharidase enzymes bound to cells along the brush border of the small intestine.[4] Sucrase-isomaltase (SI), lactase, maltase-glucoamylase (MGAM), and trehalase are the main intestinal brush border enzymes responsible for hydrolyzing lactose, sucrose, maltose, and trehelose.[5]



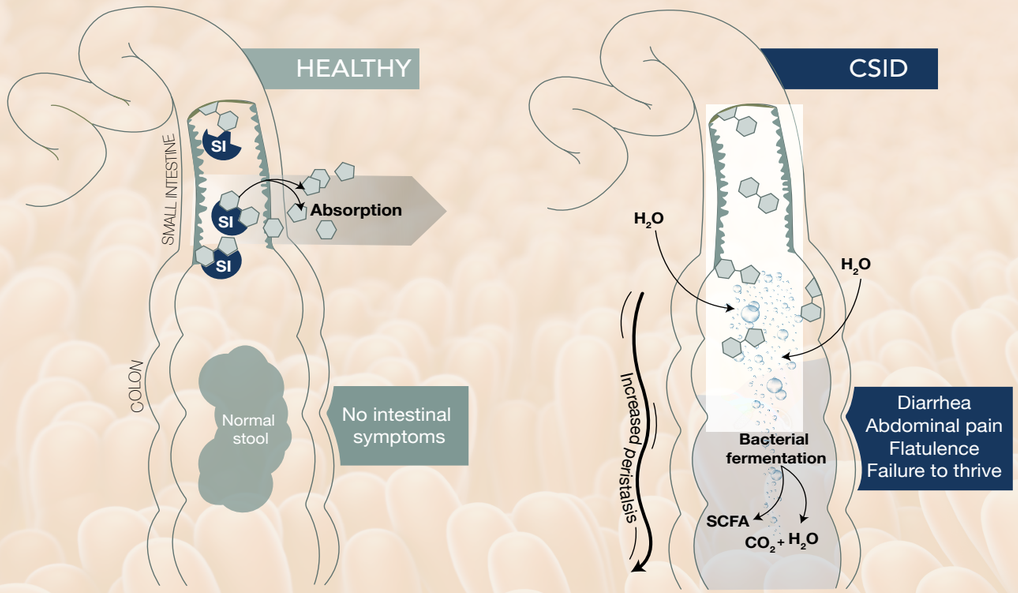




A closer look at the SI enzyme

The SI enzyme is made up of 2 domains, sucrase and isomaltase, that are anchored to the brush border membrane in the small intestinal villi.[6] Together, the 2 domains of the enzyme are responsible for hydrolyzing sucrose, maltose, isomaltose, and oligosaccharides in starch and glycogen into monosaccharides.[3,6]

Congenital sucrase-isomaltase deficiency (CSID) was first described in 1960 as a deficiency "sugar-splitting enzymes"in children presenting with osmotic diarrhea.[7] Over 2 decades later, the condition was linked to mutations in the SI gene causing abnormal synthesis or transport of the SI enzyme.[8] Since that time, more than 1000 variants in the *SI* gene have been identified,[9] with some showing classical autosomal recessive homozygous mutations and others compound heterozygous mutations.[3] Mutations can affect either the sucrase or isomaltase subunit of the enzyme, leading to variable effects on enzyme activity.[2,3] Despite the large number of identified mutations, however, most of the clinical symptoms associated with CSID have been attributed to 4 variants.[10]



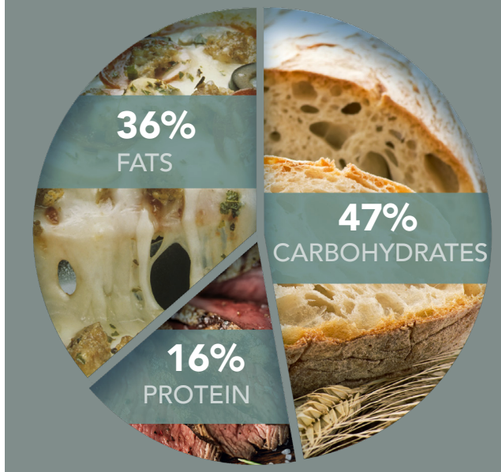
Under normal conditions, most of an ingested carbohydrate load is completely absorbed before reaching the colon.[11]

The presence of unabsorbed carbohydrates in the intestinal lumen and colon leads to an increased osmotic load, excess bacterial fermentation and increased production of short-chain fatty acids and gases.[12,13] This in turn leads to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea. The faculty emphasized that these symptoms are very similar to those of IBS, most notably IBS-D or mixed IBS.

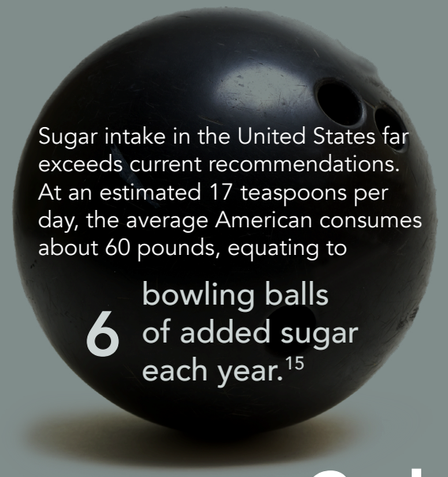
Inherited or acquired?

The faculty suspect that most cases of CSID that they see in clinical practice are acquired rather than congenital. Acquired, or secondary, forms of sucrase-isomaltase deficiency can occur in patients with chronic diarrhea from other tcauses such as include villous atrophy or alteration (eg, celiac disease, Crohn's disease); infection (eg, acute gastroenteritis, HIV enteropathy, small intestinal bacterial overgrowth); and rapid transit (eg, dumping syndrome, colitis).[3] The clinical impact of sucrase-isomaltase deficiency in these disorders may be transient, with enzymatic activity returning to normal with resolution of the underlying disorder.[3]

Carbohydrate fun facts



Carbohydrates make up nearly half of the average Western diet.[14]



Commercially known as cane sugar or table sugar,[11] sucrose is the source of about 30% of carbohydrate calories.[13]

Also known as milk sugar, lactose has less sweetening effects than other sugars and does not cause rewarding effects on the CNS.[16,17] Only 50% of normal lactase activity is needed for adequate lactose digestion.[17]

Fructose, found naturally in honey and most fruits, is the sweetest of all naturally occurring carbohydrates.[18,19] Due to its unique metabolic properties, fructose may be a particularly harmful component of sugar, and studies have linked high fructose consumption to an increased risk for metabolic syndrome and fatty liver disease.[18–21]

Recognizing CSID in clinical practice

Are we missing the forest for the trees?

The clinical presentation and severity of CSID vary depending on the nature and position of the *SI* mutations, as well as their homozygous or heterozygous combinations.[22,23] Accordingly, sucrase activity in patients with CSID can range from completely absent to low residual activity, while isomaltase activity can range from absent to normal.[13] Maltase activity is also reduced significantly in most patients with CSID.[6,13]

In contrast to the classic, severe presentation of CSID in patients with homozygous SI mutations,[13] a broad range of phenotypes has been observed in adults with CSID. Many of the symptoms of CSID overlap with those of IBS, particularly IBS-D.[5] Like IBS, CSID symptoms often occur postprandially, but patients with CSID may be likely to associate symptoms with sweets and other high-sucrose foods. Patients with CSID may report a lifelong history of symptoms, potentially with avoidance of carbohydrates or sweet foods, as well as family members with similar symptoms.

Key factors other than residual enzyme activity that can affect the onset and symptoms of CSID include the amount of dietary sugar and starch consumed, the rate of gastric emptying, activity of other intestinal disaccharidases, and the metabolic activity of fermenting bacteria.[2,3,13]

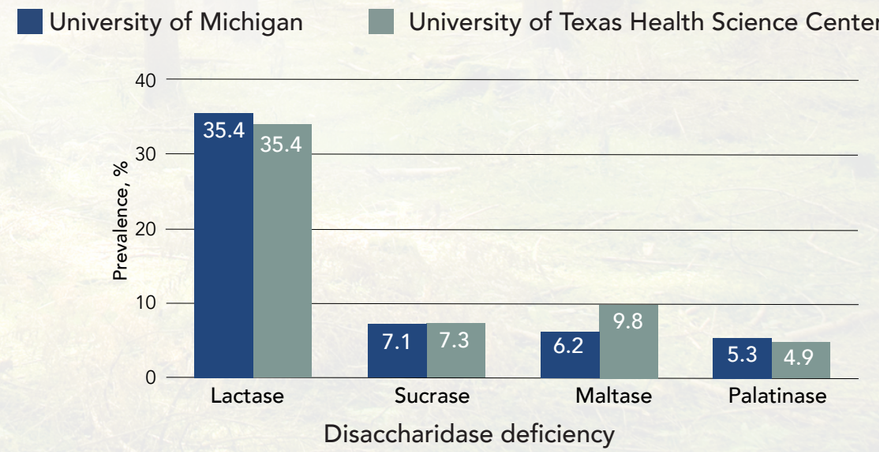
With the overlap in symptoms, there is speculation that CSID may be unrecognized and/or misdiagnosed as IBD in older children and adults.

Although historically considered to be a rare autosomal recessive disorder,[13] both clinical and genetic data indicate that CSID is more common than previously believed.[4,22,24–26] This is increasingly apparent in patients with unexplained functional GI symptoms, particularly with presumed IBS. Indeed, studies in adults suggest that many patients with CSID are diagnosed with IBS at some point in their lives.[5] A recent analysis of 154 adults meeting Rome IV criteria for IBS-D or functional diarrhea found that 1 in 14 (7.14%) symptomatic patients had sucrase and maltase deficiencies on disaccharidase analysis.[24] Previous studies have also reported a high prevalence of CSID in patients with chronic unexplained GI symptoms.[27,28]

Growing evidence also suggests that specific pathogenic SI gene variants are more common in patients with IBS than those without.[22,23] In a study involving 1031 patients with IBS, patients with IBS were nearly twice as likely to have a genetic *SI* mutation compared with controls.[23] In a larger study involving 2207 patients with IBS, 4.2% of patients with IBS-D were found to carry rare SI pathogenic variants, a higher frequency relative to a large matched reference population.[22]

In another study, patients with IBS-D and pathogenic *SI* variants were 3 to 4 times less likely to experience symptom relief with a low FODMAP (fermentable, oligo-, di-, mono-saccharides, and polyols) diet than patients without such variants.[29] Additionally, a recent pilot study demonstrated better response to a starch and sucrose-reduced diet among adults carrying 2 *SI* variants than those carrying single or no variants.[30]

Prevalence of disaccharidase deficiency in adults with Rome IV-defined IBS-D or functional diarrhea (N=154)[24]

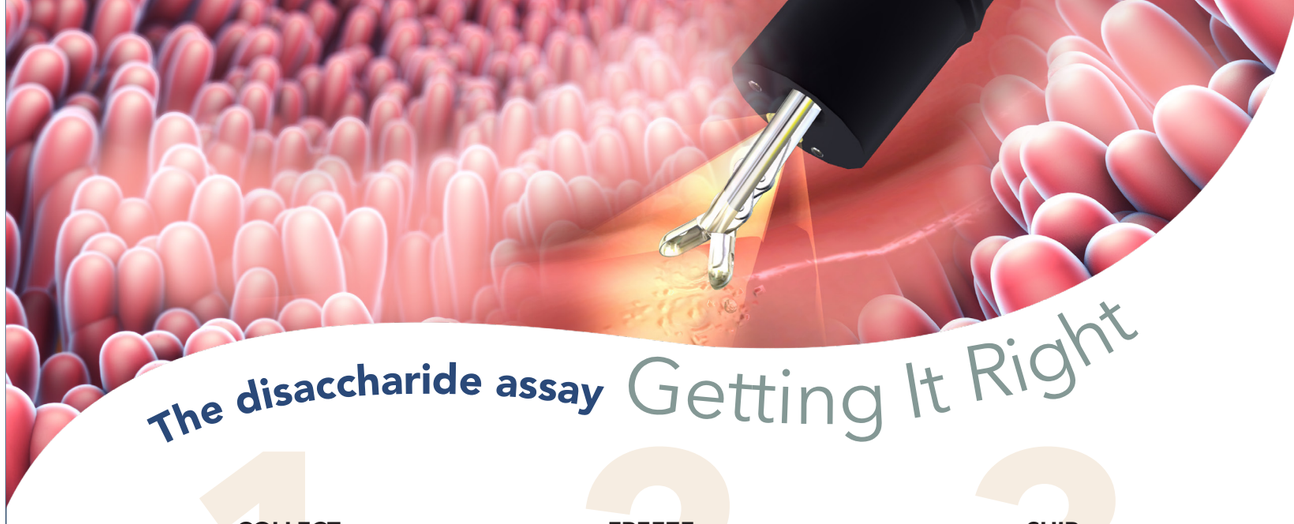


Diagnosing CSID

Small intestinal mucosal biopsy assayed for disaccharidase activities is the gold standard for diagnosing CSID.[2,13] Although invasive, this method allows for the evaluation of all disaccharidases (ie, lactase, sucrase, isomaltase, and maltase) and can help distinguish between congenital and secondary deficiencies. However, assay results vary considerably as their accuracy depends on proper specimen collection and handling.[4] Breath tests and a sucrose challenge are noninvasive options for diagnosing CSID, but the clinical utility of these methods has not been validated. However, several clinical trials are underway to characterize the role of these tests in clinical practice.[31] Although genetic testing is available for CSID, the available test has not been useful clinically as it identifies only a small number of *SI* mutations.[2]

Who should be tested?

Although there are insufficient data to inform recommendations for CSID testing, the faculty believe that testing is reasonable in patients with chronic, unexplained GI symptoms, particularly bloating. Additionally, increasing evidence suggest that CSID should be considered in patients with IBS symptoms who fail to usual dietary and medical therapies.[5,29,30]

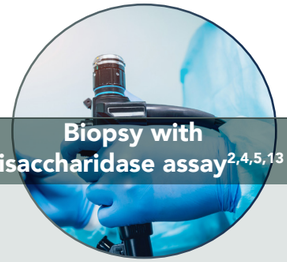


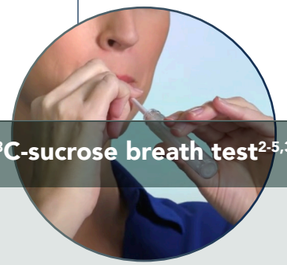
The disaccharide assay Getting It Right

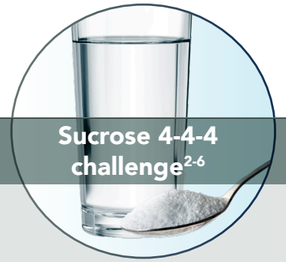
COLLECT
First biopsies should be obtained from the distal duodenum or proximal jejunum and the samples placed in a empty eppendorf tube. Do not place the tissue on gauze, filter paper, or use any type of support medium, not even saline.

FREEZE
Place eppendorf tube with collected sample immediately on dry or wet ice and freeze within 2 hours of collection at -20° C to -70° C.

SHIP
Samples should be shipped frozen on dry ice to appropriate lab promptly on the day of collection.







	Biopsy with disaccharidase assay[2,4,5,13]	Sucrose-hydrogen-methane breath test[2,3,5,33]	^{13}C-sucrose breath test[2-5,34]	Genetic test[2-6]	Sucrose 4-4-4 challenge[2-6]
DESCRIPTION	• Disaccharidase analysis performed by specialty laboratory on biopsy samples per the Dahlquist method • Samples are collected distal to the ampulla • First sample is used to determine disaccharide levels and the other to study the architecture of the mucosa	• Measures exhaled hydrogen and/or methane levels produced by bacterial fermentation of a test carbohydrate	• Measures exhaled ^{13}C-CO_2 levels produced by bacterial fermentation of a test sucrose load	• Identifies 37 mutations in the *SI* gene using saliva, buccal swab, or blood	• Patient is monitored for the presence of symptoms (bloating, gas, diarrhea) for a 4 to 8-hour period after drinking 4 ounces of water with 4 tablespoons of dissolved table sugar
BENEFITS	• Can differentiate between congenital and acquired causes of SID • Determines activities of all disaccharidases (lactase, sucrase, isomaltase, maltase)	• Simple, noninvasive • Can be performed by patients at home	• Simple, noninvasive • Can be performed by patients at home	• Positive result confirms diagnosis	• Simple • Noninvasive
KEY LIMITATIONS	• Invasive • Specimens require special handling (ie, immediate freezing) • Significant room for error due to sample collection and handling • Considerable assay variability	• Numerous pre-test restrictions required • Cannot differentiate between small intestinal bacterial overgrowth (SIBO) from CSID • Required 50-g sucrose load can cause significant symptoms in patients with CSID	• Pre-test restrictions required • Not validated	• Currently tests for only a small number of common pathogenic variants • Negative test does not exclude CSID • Does not provide information regarding the clinical phenotype	• Can cause severe symptoms in patients with CSID • Not validated

Managing CSID

Combining diet and enzyme replacement therapy

Given that all patients with CSID are sucrose intolerant, a sucrose-free diet should be started before starch intake is modified. If symptoms persist after institution of a sucrose-free diet, starch consumption can be reduced. Dietary adjustment in patients who require both sucrose and starch modification is accomplished on a trial and error basis, adjusting specific foods as needed based on symptoms. This process can be complex, involving several weeks of elimination of dietary sucrose and starch, followed by gradual reintroduction of foods int o the diet.[5] With this in mind, the faculty emphasized the importance of engaging a dietitian to help patients with this process. In addition to working with patients to determine their individual tolerance of sucrose- and starch-containing foods, dietitians can teach patients to understand food labels so they better recognize sucrose and starch in foods.[36]

Although dietary restriction should be theoretically effective, studies indicate that only a minority of patients remain consistently asymptomatic with this approach, with up to 75% of patients continuing to experience diarrhea, gas, and/or abdominal pain. Further, only half of children are typically compliant with the prescribed diet.[13,37,38]

Enzyme replacement therapy and dietary restriction of starch and sucrose are the cornerstones of CSID management.[2,5]

Treatment of CSID with enzyme replacement therapy can improve symptoms while allowing patients to consume a more liberal diet.[5,13,27] Sacrosidase, which is sucrose enzyme derived from *Saccharomyces cerevisiae*, was approved by the FDA for treatment of CSID in 1998.[4] In long-term, randomized, double-blind trials, 81% of patients using full-strength sacrosidase were able to remain asymptomatic while consuming an unrestricted diet compared with 78% untreated during the baseline, diet-restricted period.[13,39] More recently, a chart review of 258 adults with chronic unexplained GI symptoms demonstrated that dietary counseling and/or enzyme replacement improved symptoms in the 60% of patients who had positive breath tests for sucrose malabsorption.[27] However, because sacrosidase does not provide specific replacement for deficient isomaltase, restricting starch in the diet may still be necessary in some patients.[35]

Sacrosidase is usually well tolerated, with constipation, insomnia, and headaches being the most common adverse events. Patients with a known hypersensitivity to yeast or yeast products, papain, or glycerin should not take sacrosidase. Additionally, caution is warranted in patients with poorly-controlled diabetes because sacrosidase can raise blood glucose levels by hydrolyzing sucrose.

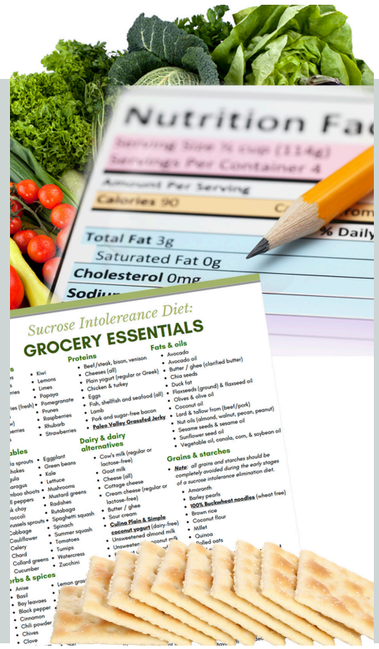
Although sacrosidase is the only FDA-approved treatment for CSID, nonprescription options such as Starchway, a combination of sucrase and glucoamylase, are available.[4]

Educating patients

Tips & tricks

Provide examples of low-sucrose diets.
Recognizing the importance of fostering positive relationships with food, clinicians are encouraged to help patients understand what foods they can have rather than focus solely on foods that should be restricted. Providing patients with examples of low-sucrose, low-starch diets can be a helpful tool.

Teach patients how to read food labels.
The starch content of a food can be determined by subtracting the amount of fiber and sugar listed on the label from the total carbohydrates.



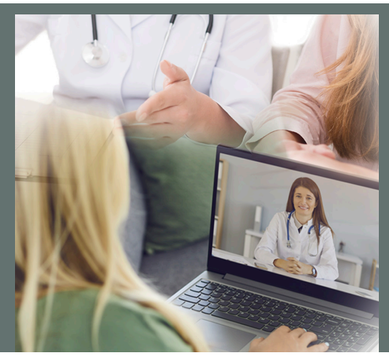
Help patients estimate their starch tolerance.
The amount of starch can be personalized based tolerance threshold. Saltines can be used to increment and determine a patient's starch threshold, as each cracker contains ~2 g.

Help patients recognize the various terms for sugar.
Many terms for sucrose can be listed on food labels, including brown sugar, sucrose, granulated sugar, maple syrup, cane juice, molasses, table sugar, and confectioner's sugar.

Instruct patients on the proper use of enzyme replacement therapy.
Sacrosidase should be taken with meals or snacks, with half the dosage taken at the beginning of each meal or snack and the remainder taken during the meal or snack. Unlike pancreatic enzymes, the dose of sacrosidase does not require titration based on the quantity of food consumed.

Set realistic expectations.
Although clinical response with sacrosidase tends to occur rapidly, it may vary based on the type and severity of symptoms.

Engage dietitians.
The faculty consider referral to a dietitian, where available, as an important first step in managing CSID.



Think out of the box.
Even in areas with limited access to dietitans or other providers with expertise in CSID, patients can learn about the disease and its management from multiple websites and from their peers in CSID Facebook groups. Group nutritional visits, typically conducted via Zoom meetings, can be used to educate patients who are prescribed similar diets.

Regional CSID Summits

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