NATIONAL CSID APP LEADERSHIP SUMMITS

A CME Proceedings Newsletter for Advanced Practice Providers

SEPTEMBER 2023

INSIDE THIS ISSUE

Two CSID APP Leadership Summit meetings

were held on September 9, 2023 at the GHAPP Fifth Annual Meeting in National Harbor, MD to discuss current evidence and understanding of CSID. A total of 48 APPs and 5 faculty participated in these 2 events. The key messages from these discussions are summarized in this issue.

GHAPP Gastroenterology & Hepatology Advanced Practice Providers

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 joint providership estimates the initiative will attract an audience of 5,000 participants, including physicians, nurse practitioners, nurses, and physician assistants. A comprehensive reach optimization effort will be driven by the Gi Health Foundation (GiHF) and Gastroenterology & Hepatology Advanced Practice Providers (GHAPP) proprietary databases and educational portals. Outreach will focus on health care professionals who have opted-in for educational updates from GiHF and GHAPP.

Program Overview
The joint providership of Medical Education Resources (MER) and 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
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://hcp-education.org/education.ghapp.org/content/csid-app-leadership-summits-cme-proceedings-newsletter-advanced-practice-providers to complete the posttest and evaluation.

Media
Internet, print

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Fee Information
There is no fee for this educational activity.

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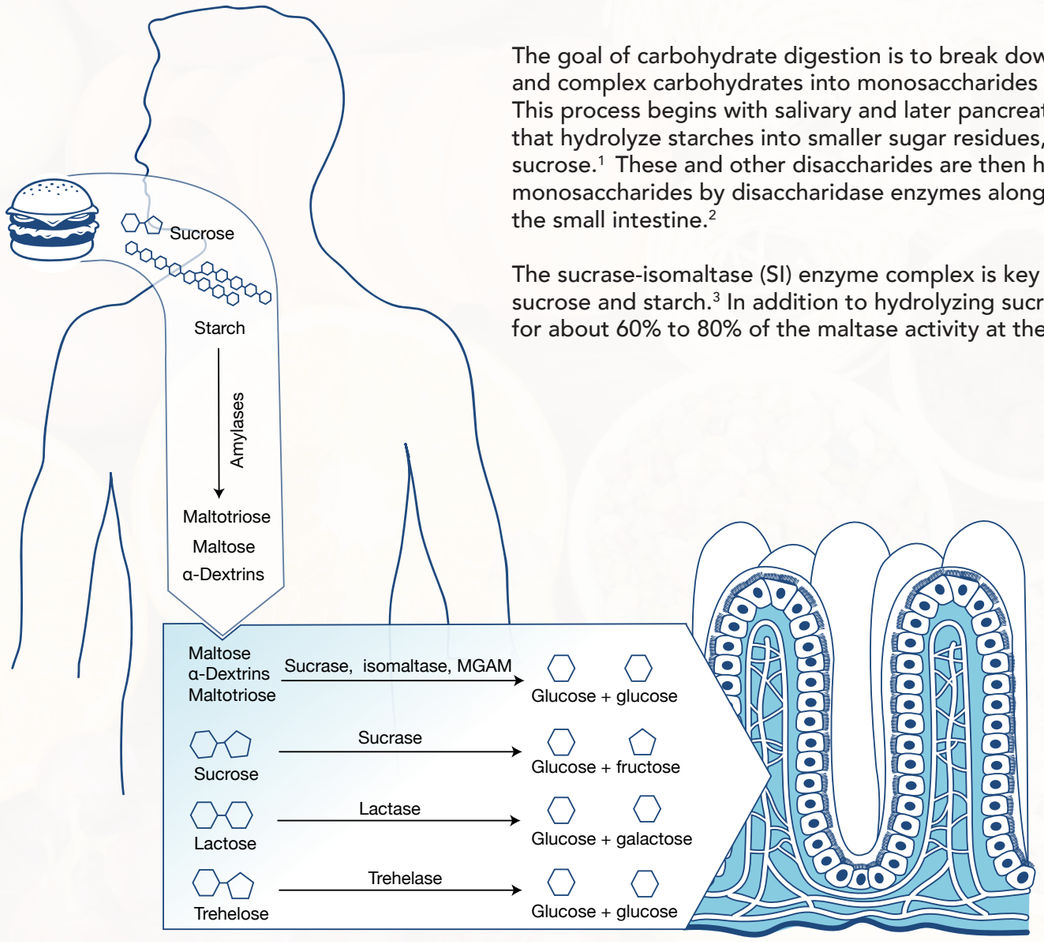
CARBOHYDRATE DIGESTION

Back to the basics



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

The goal of carbohydrate digestion is to break down all disaccharides and complex carbohydrates into monosaccharides for absorption. This process begins with salivary and later pancreatic α-amylases that hydrolyze starches into smaller sugar residues, maltose and sucrose.[1] These and other disaccharides are then hydrolyzed into monosaccharides by disaccharidase enzymes along the brush border of the small intestine.[2]

The sucrase-isomaltase (SI) enzyme complex is key to the digestion of sucrose and starch.[3] In addition to hydrolyzing sucrose, SI is responsible for about 60% to 80% of the maltase activity at the brush border.

Carbohydrates make up nearly half of the average Western diet.[4]

Most of these are table sugars (sucrose) and starches that are composed of different α-linked sugars.[1] Sugars are intrinsic in fruit and milk products, whereas starches are found in many vegetables, legumes, and grains.[5] Added, or extrinsic sugars, are used to improve palatability or the functional properties or food or beverages. Sugar and starches are the main source of glucose for the brain, central nervous system, and red blood cells, and as such their proper digestion and absorption are essential for health.

CSID 101

Congenital sucrase-isomaltase deficiency (CSID) was first recognized as a deficiency of "sugar-splitting enzymes" in 1960.[6]

This condition results when patients inherit 2 defective copies of the *SI* gene due to either recessive homozygous or compound heterozygous mutations that reduce or abolish enzymatic activity.[7] The nature and position of the mutations influences enzyme activity in patients with CSID, with sucrase ranging from completely absent to low residual activity and isomaltase ranging from absent to normal.[8] Maltase activity is also reduced significantly in most patients with CSID.[8,9]

In addition to congenital forms of the disorder, acquired or secondary forms of sucrase-isomaltase deficiency have been observed in patients with chronic diarrhea from other causes.[10] Secondary or acquired SID can result from conditions that damage the brush border of the small intestine, including 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). The faculty speculate that secondary cases of SID are seen more commonly in adult patients than congenital cases, and may even contribute to symptoms in patients who have been diagnosed with post-infectious IBS.

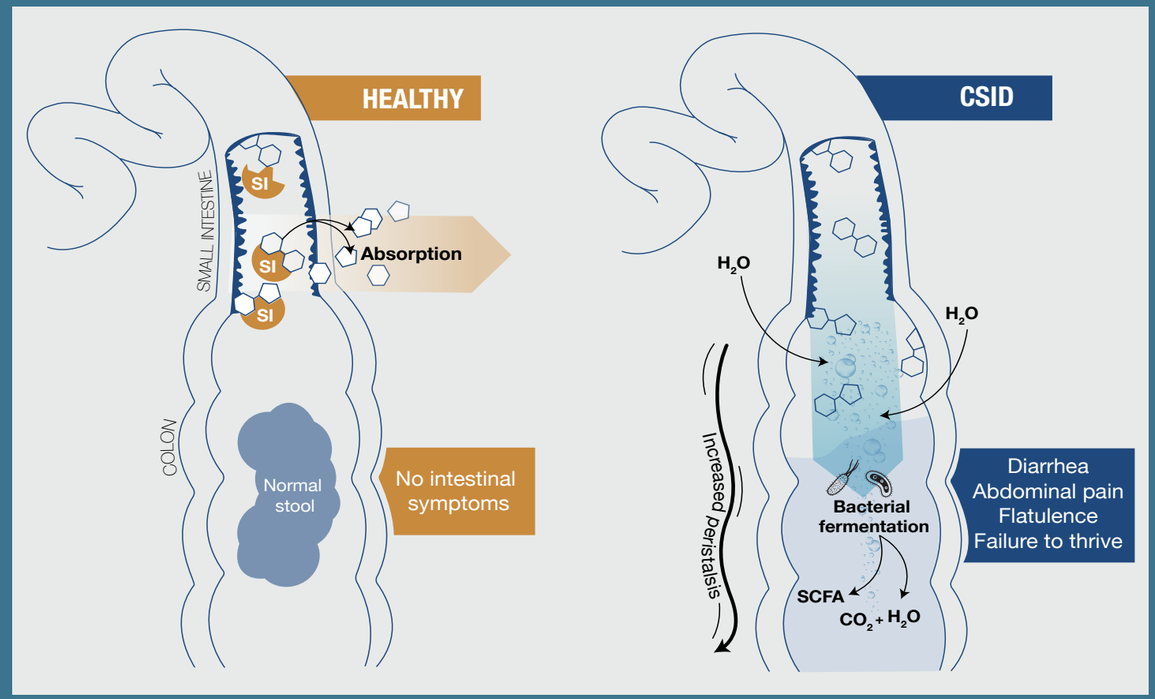
Clinical features that are characteristic of CSID in adults typically include symptoms that are lifelong, frequent (usually multiple events per day and multiple days per week), and occur postprandially.[2,3] Patients may report avoiding carbohydrates or sweet foods, as well as a family history of close relatives with similar symptoms. Symptom severity can vary based on the amount of dietary sugar and starch intake, as well as with gastric and small bowel transit.[2]

These are the people who have the typical IBS story:

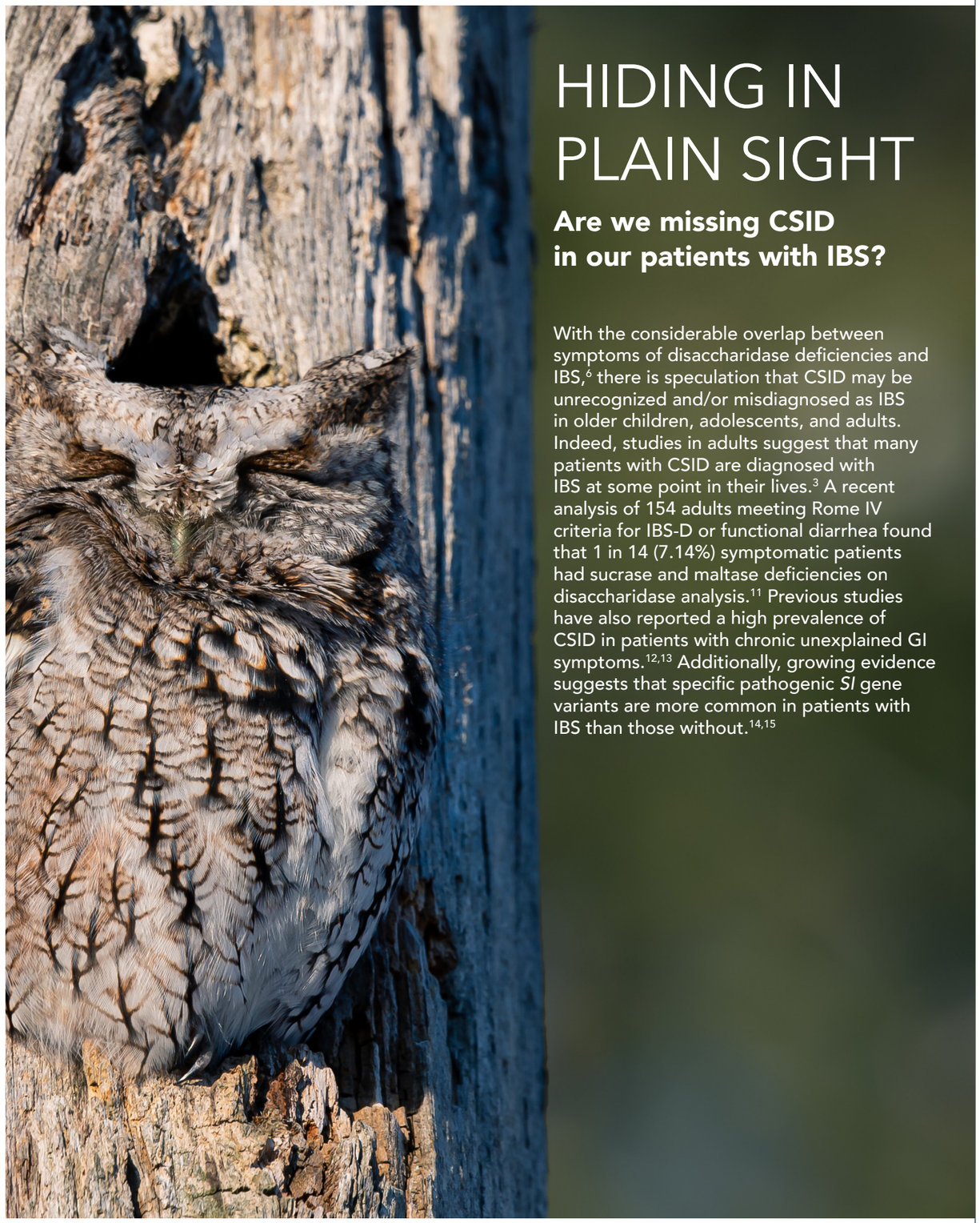
'I know where the clean bathrooms are. I know that food exacerbates my symptoms. I can count on when I will have symptoms. It starts as some crampy discomfort and bloating, and I feel better when I defecate.'

Brooks Cash, MD

The pathophysiologic basis of symptoms in CSID



When the SI enzyme is deficient or absent, non-absorbed carbohydrates enter the colon causing excess bacterial fermentation and increased production of short-chain fatty acids and gases.[2,3] This in turn leads to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea.



HIDING IN PLAIN SIGHT

Are we missing CSID in our patients with IBS?

With the considerable overlap between symptoms of disaccharidase deficiencies and IBS,[6] there is speculation that CSID may be unrecognized and/or misdiagnosed as IBS in older children, adolescents, and adults. Indeed, studies in adults suggest that many patients with CSID are diagnosed with IBS at some point in their lives.[3] 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.[11] Previous studies have also reported a high prevalence of CSID in patients with chronic unexplained GI symptoms.[12,13] Additionally, growing evidence suggests that specific pathogenic *SI* gene variants are more common in patients with IBS than those without.[14,15]

CSID BY THE NUMBERS

Although historically considered a rare disease, studies demonstrating that heterozygous carriers of *SI* variants also experience symptoms suggest that CSID may be more common than once believed.[10-12,15-17] In a 6-year retrospective study involving disaccharidase assay of 27,875 mucosal biopsy tissue samples in symptomatic children, at least one disaccharidase deficiency was present in 45% of samples, with 9.3% deficient in sucrase and maltase.[16] A subsequent systematic review of 30 observational studies in children undergoing esophagogastroduodenoscopy (EGD) found similar results, with an overall prevalence of lactase, sucrase, and maltase deficiencies noted to be 39.2%, 9.0%, and 9.1%, respectively.[18]

Reported prevalence of sucrase deficiency in adults with IBS-like symptoms

via disaccharidase assay

7.1% among 152 adults with IBS-D or functional diarrhea who underwent duodenal biopsy and disaccharidase assay at the University of Michigan or University of Texas Health Science Center at Houston[11]

35% among 31 adults with presumed IBS-D or IBS-M who underwent duodenal biopsy and disaccharidase assay at the University of Miami[12]

9.2% among 120 adults with unexplained GI symptoms who underwent duodenal biopsy and disaccharidase assay at the Digestive Health Center at Augusta University Medical Center[19]

via ^{13}C-sucrose breath test

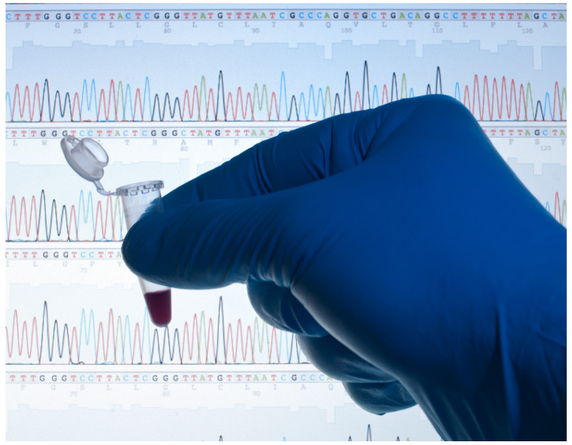
26.5% among 147 adults with chronic unexplained GI symptoms[13]

> We have a lot of female college students with IBS, diarrhea. It would be interesting if this is actually what they had and if I could catch it, I would feel really excited.
>
> APP Participant

TESTING FOR CSID

Searching for answers

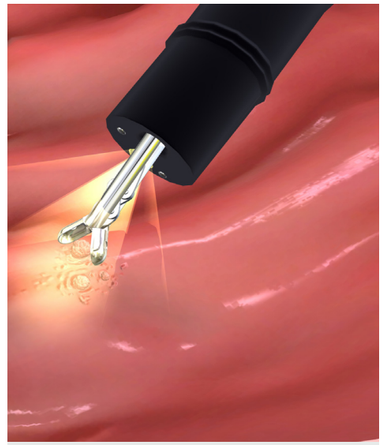
The gold standard for diagnosing intestinal disorders associated with carbohydrate metabolism is endoscopic **small bowel biopsies assayed for disaccharidase** (lactase, sucrase, isomaltase, and maltase) activities.[1,3,8] Disaccharidase assay allows for the evaluation of other disaccharidases as well as causes of secondary disaccharidase deficiencies. However, specimens require special handling (ie, immediate freezing), leaving significant room for error, and assay variability is considerable.[2]



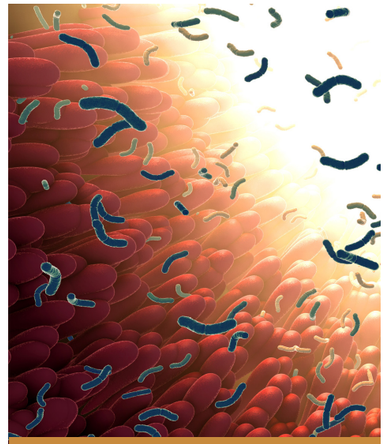
Genetic tests are available for CSID, although they currently test for only a small number of common pathogenic variants.[2] Accordingly, a negative test does not rule out the condition. Additionally, the results do not provide reliable information regarding the clinical phenotype. Despite these limitations, however, the faculty noted that some payers request genetic testing for CSID for approval of enzyme replacement therapy.

The **^{13}C-sucrose breath test** is a simple, noninvasive option[20] that can be stocked in the office or sent directly to patients. Although a direct measure of sucrase activity, the sucrose breath test has not been validated for use in clinical practice.

The **sucrose-hydrogen-methane breath test** requires more pre-test restrictions than the ^{13}C-sucrose breath test and does not differentiate CSID from small intestinal bacterial overgrowth (SIBO) or transit disorders.[2,3] Additionally, the hydrogen breath test requires a 50-g sucrose load and can cause significant symptoms in those who do have CSID.



Using proper technique for obtaining and transporting biopsy samples for disaccharidase assays is imperative for ensuring accurate results. The faculty emphasized that samples should be collected distal to the ampulla since disaccharide levels in the proximal duodenum can be decreased over 30%.[21] Two samples should be collected, with the first used to determine disaccharide levels and the other used to study the architecture of the mucosa.[2]



In response to questions around the relationship of SIBO and CSID, the faculty noted that differentiating between the 2 conditions with breath testing can be challenging. While SIBO can cause acquired SID, CSID can also lead to false-positive testing for SIBO. Additionally, CSID and SIBO could coexist in the same patient for unrelated reasons.

The 4-4-4 test is a simple method for testing based on having the patient drink a solution of 4 tablespoons of sugar mixed in 4 ounces of water, and waiting 4 hours to assess symptoms. Preliminary data suggest high sensitivity of this method, but studies are need to validate its use in practice. Additionally, ingesting a sucrose load of this quantity can provoke significant symptoms in those with the condition.

> I'm a big believer that the numbers I'm seeing firsthand, as well as what the trials are showing, that this is a disease state that is insanely prevalent. It is out there. So I am not looking for this as the last thing. If patients are coming in with bloating and loose stools and there's no reason for me to do an upper endoscopy, then I will do a breath test. If they have dysphagia or concerns with peptic ulcer disease, weight loss, some other reason to do an upper endoscopy, then I'll do that with the disaccharidase assay.
>
> Dak Patel, DO

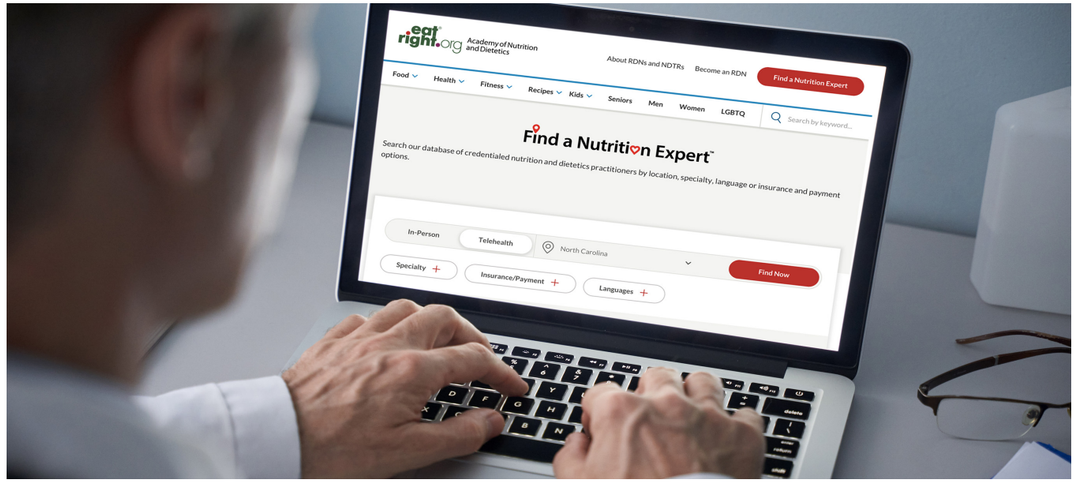
DIETARY MANAGEMENT OF CSID

Easier said than done

Dietary restriction of sucrose and starch plays a pivotal role in managing patients with CSID.[3] 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. The faculty commented that starch restriction may be more of a priority in patients with low maltose, often causing upper GI symptoms such as nausea rather than the diarrhea typically seen with CSID. However, most patients can tolerate up to 120 g of starch when spread throughout the day. 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.[3]

Although dietary restriction should theoretically be effective, follow-up 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 patients are typically compliant with the prescribed diet.[8, 22,23]

In light of the prevalence of disordered eating in patients with FGIDs, a primary goal is to work with patients to allow for the most liberal diet possible that will manage symptoms. However, the faculty cautioned against diagnosing eating disorders in patients with functional GI disorders who have tried to alleviate their symptoms with various diets. Such patients know that food is contributing to their symptoms, but they have not yet been diagnosed



Finding a GI dietitian

Access to a dietitian who is knowledgeable about CSID is essential for optimizing management. 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.[26] The faculty noted that although many dietitians do accept private insurance, Medicare currently only covers dietetics for patients with diabetes or renal disease.

Although the availability of GI-trained dietitians remains limited, the AGA is currently developing a list of such professionals. Additionally, several websites such as the Academy of Nutrition and Dietetics provide listings of dietitians.

Dietary clues to CSID

Experts are increasingly considering sucrase deficiency in patients with IBS symptoms who fail to respond to usual dietary and medical therapies.[3]

Patients' history in tolerating various foods can provide useful information when suspecting CSID. Mrs. Scarlata noted that she is suspicious of CSID when patients describe intolerance to starchy food such as rice, since this is not a FODMAP and is typically well tolerated by patients with IBS.

These differences in response to dietary modification have been documented in clinical trials as well. One study found that patients with IBS-D and pathogenic *SI* variants are 3 to 4 times less likely to experience symptom relief with a low FODMAP diet than patients without such variants.[24] Conversely, a recent retrospective pilot study in 50 patients with IBS-D demonstrated significantly better response to a starch and sucrose-reduced diet among adults carrying 2 *SI* variants than those carrying single or no variants.[25]

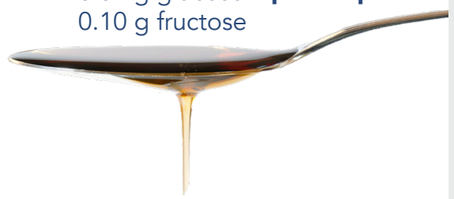
Honey

0.19 g sucrose
7.5 g glucose **per tbsp**
8.6 g fructose

High FODMAP, low sucrose

Maple syrup

11.7 g sucrose
0.32 g glucose **per tbsp**
0.10 g fructose



Low FODMAP, high sucrose

A low FODMAP diet is not a low-sucrose diet.

ENZYME REPLACEMENT

Tips for use in the real world

Treatment of CSID has improved considerably with the availability of enzyme replacement therapy (sacrosidase), which allows liberalization of the previously sucrose-restrictive diet.[8,13] In long-term, randomized, double-blind trials, 81% of patients using sacrosidase were able to remain asymptomatic while consuming an unrestricted diet compared with 78% untreated during the baseline, diet-restricted period.[8,27] 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.[13]

Because sacrosidase hydrolyzes sucrose only, dietary starch restriction may also be needed to manage symptoms of CSID. Although sacrosidase allows patients to follow a more liberal diet, the optimal combination of enzyme supplementation and dietary management needs to be tailored to individual patients. The recent availability of the individual sacrosidase containers[28] offers some practical advantages (eg, travel, eating in restaurants) over the multidose bottle. However, some of the participants have encountered insurance coverage issues with the single-use containers that were encountered with the multidose bottle.

Although sacrosidase is the only FDA-approved treatment for CSID, nonprescription options such as Starchway, a combination of sucrase and glucoamylase, are available.[2]

Enzyme replacement therapy and dietary restriction of sucrose and starch are the cornerstones of CSID management.[1,3]

> If you look at the IBS data, patients are willing to give up 25% of their remaining lives to feel better. Some of these patients are really desperate for something. So if 60% of patients in the Frissora study improved with sacrosidase, this is another tool in our toolbox and we should be careful about gate-keeping something that can help these patients.
>
> APP participant

Q&A

How should enzyme replacement be administered?

Patients should be instructed to take sacrosidase 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.[28]

Is sacrosidase the only enzyme replacement product available for CSID?

Although sacrosidase (Sucraid®) is the only FDA-approved enzyme replacement available for treating CSID, nonprescription enzyme replacements are available, including invertase and Starchway, a combination of invertase and glucoamylase.[2,9] However, the faculty cautioned that the nonprescription enzyme products have not been subjected to the rigorous testing and quality control as Sucraid has, nor have they been evaluated in clinical trials in patients with CSID.

Are there any risks of sacrosidase therapy?

Sacrosidase is usually well tolerated, with constipation, insomnia, and headaches being the most common adverse events. [8] 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.

Should patients be retested after enzyme replacement is initiated to evaluate if any secondary causes of SID have been resolved?

Most experts do not retest patients after initiating enzyme replacement therapy to determine if the deficiency was secondary. Although there are no data informing practice in this regard, the faculty believe it is reasonable to assess patient response to a trial of sacrosidase discontinuation, with reinitiation of treatment in those whose symptoms recur off therapy.

CSID LEADERSHIP SUMMIT

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