Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by **December 31, 2021** in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after **March 1, 2022** for this activity.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 24, 2021
Intestinal Failure and Short Bowel Syndrome
Dejan Micic, MD
June 17, 2021 at Noon Eastern

Week 25, 2021
ACG 2021 Clinical Guideline: Management of Irritable Bowel Syndrome
Brian E. Lacy, MD, PhD, FACP
June 24, 2021 at Noon Eastern

Visit gi.org/ACGVGR to Register

Disclosures:
Speaker:
Baha Moshiree, MD, MSc, FACP
Speaker: Alnylam Pharmaceuticals, Salix/Bausch Pharmaceuticals
Advisory Board: Alnylam, Alnylam Pharmaceuticals, Progenity, Salix/Bausch Pharmaceuticals, Takeda Pharmaceuticals
Grant Support: Allergan, EndoFLIP (Medtronic), Progenity, Salix/Bausch Pharmaceuticals, Takeda Pharmaceuticals
Patent Pending (Smurf/Cake) – University of Miami and Atrium Health – Co-inventor with Dr. Julia Dallman (University of Miami) Ingestible Capsule Device (Small Bowel Aspiration Capsule): PCT/US17/20728 (Univ Miami- Moshiree Inventor)

Moderator:
Rita M. Knotts, MD, MS
Dr. Knotts, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

*All of the relevant financial relationships listed for these individuals have been mitigated
Tackling Small Bowel Malabsorptive Disorders: The Masqueraders of IBS

Baha Moshiree MD, MSc
FACG, FAGA, ANMS Council Member
Professor of Medicine
Director of Motility
Atrium Health

Objectives:

- Recognizing IBS Masqueraders
- Discussion of Carbohydrate malabsorption syndromes and their diagnosis
- What’s new in SIBO as it pertains to patients with small bowel dysmotility from systemic conditions
- Systemic conditions causing small bowel pseudo-obstruction will be addressed

Symptom overlaps of IBS with of small bowel malabsorptive disorders
Real Patient Case 1:

**HISTORY & PE**

- **HPI**
  - Has periumbilical pain with meals and BMs only (pain lasts < 10 minutes and is usually associated with meals)
  - Diarrhea bouts with Bristol Stool Scale (BSS) type range 6-7 with flares and goes 4-6 times a day
  - Last year or so has lost 5 lbs.
  - Other GI complaints: Bloating, distension
  - Symptom triggers: Stress, high carbohydrate foods. Has tried Low FODMAP diet, gluten free diet and takes loperamide when she has diarrhea.
  - No nocturnal diarrhea

- **PMHX**
  - **IBS**
  - Anxiety disorder
  - Migraine
  - Fhx: IBS (mother)

- **SH**
  - No illicit drug use
  - No hx abuse or eating disorder

**PE**

- Thin female, BMI 18
- Normal vitals otherwise
- Abdomen: + Loud bowel sounds, nontender, distended diffusely, no masses, no HSM, no rebound

**Labs**

- CBC and iron panel (normal)
- Fecal testing for parasites
- NI fecal calprotectin (normal)

**Medications**

- Loperamide prn helps
- Probiotics
- Fiber supplementation up to 15 grams

---

**PE and Meds**

- Thin female, BMI 18
- Normal vitals otherwise
- Abdomen: + Loud bowel sounds, nontender, distended diffusely, no masses, no HSM, no rebound

- CBC and iron panel (normal)
- Fecal testing for parasites
- NI fecal calprotectin (normal)
Searching for IBS-D: Differential Diagnoses

IBS-D

SIBO/SIFO/IMO

Bile acid diarrhea

Microscopic colitis

Pancreatic insufficiency

Celiac disease

Disaccharidase deficiency

Non-celiac wheat intolerance

Autoimmune enteropathy

Food allergy

Eating disorders or food intolerance

Carbohydrate Malabsorption

Modified from GIHF

Diagnostic Testing for IBS Without Alarm Features

All IBS Subtypes

IBS-D

IBS-C

CBC

Age-appropriate CRC screening

- Fecal calprotectin or Lactoferrin & CRP
- IgA TtG ± quantitative IgA
- Rule out Giardiasis- if high risk factors exist
- Routine testing for parasitic infections not needed
- When colonoscopy performed, obtain random biopsies (Age 45 and up)

- Stool diary/ abdominal plain film to assess for fecal loading
- Rule out Celiac disease

Anorectal physiology testing:

We suggest that anorectal physiology testing be performed in patients with IBS and symptoms suggestive of a pelvic floor disorder and/or refractory constipation not responsive to standard medical therapy. Consensus recommendation, unable to assess using GRADE methodology.


Moshiree B. Satish SS. Journal of Family Practice. 2021
What Are More Common Diagnoses Than Celiac Disease?

Giardiasis as a cause of small bowel malabsorption - Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors for Giardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children in childcare settings, in particular, diaper-aged children</td>
</tr>
<tr>
<td>Close contacts of people with giardiasis (for example, people living in the same household or people who care for those ill with giardiasis)</td>
</tr>
<tr>
<td>People who drink water or use ice made from places where Giardia may live (for example, untreated or improperly treated water from lakes, streams, or wells)</td>
</tr>
<tr>
<td>Backpackers, hikers, and campers who drink unsafe water or who do not practice good hygiene (for example, proper handwashing)</td>
</tr>
<tr>
<td>People who swallow water while swimming and playing in recreational water,</td>
</tr>
<tr>
<td>People exposed to human feces (poop) through sexual contact</td>
</tr>
<tr>
<td>International travelers where Giardia may live, especially in lakes, rivers, springs, ponds, and streams</td>
</tr>
</tbody>
</table>

Modified from Centers for Disease Control and Prevention. National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). 2015.

How Common Is BAD?

- Common, but frequently underdiagnosed cause of chronic diarrhea
- Reported in 25-38% of patients presenting with chronic diarrhea or IBS-D
  - Higher prevalence in patients with history of terminal ileal disease resection, cholecystectomy, or abdominal radiotherapy

<table>
<thead>
<tr>
<th>BAD subtypes</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Terminal ileal disease (eg, CD, resection) Radiation injury resulting in impaired reabsorption of bile acids</td>
</tr>
<tr>
<td>Type 2</td>
<td>Idiopathic or primary</td>
</tr>
<tr>
<td>Type 3</td>
<td>Secondary to other conditions that alter intestinal motility or bile acid absorption (eg, celiac disease, cholecystectomy, SIBO, radiation enteritis)</td>
</tr>
</tbody>
</table>


Virtual Grand Rounds

IS BAD the issue here?

Enterohepatic circulation of bile acids

FGF19 provides negative feedback inhibition of BA synthesis

Colonic motility and transit

Visceral sensation

Fluid secretion

Mucosal permeability

Bile acids in colon

Bile acid reabsorption in small intestine

Adapted from Camilleri M. Gut Liver. 2015;9:332-339. Courtesy GIHF

Bile acid diarrhea (BAD) is more common than IBD and Celiac Disease amongst those with IBS.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated population prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>0.1-0.2%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0.2-0.3%</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>0.7-1%</td>
</tr>
<tr>
<td>Primary bile acid diarrhea</td>
<td>~1%</td>
</tr>
</tbody>
</table>

Prevalence of BAD in IBS-D or functional bowel disorders with diarrhea ranged from 17-35%.
Pooled rate = 28% (95% CI: 23-34%)

Is this a carbohydrate malabsorption?
How Common Is Disaccharidase Deficiency in IBS?

Lactose Intolerance By Lactose Breath Testing

- Patients with lactose intolerance, %
  - IBS patients (n=251): 38
  - Controls (n=174): 26
- OR=2.57 (95% CI: 1.27-5.22)

Key Intestinal Disaccharidases

- **Maltase**: Used to approximate glucoamylase; Not explicit to maltase, more related to SI (75%) than MGAM (only 25%)
- **Palatinase**: Used to approximate isomaltase; SI responsible for most isomaltase activity (>70%)
- **Lactase**: Specific to lactose, but lactase deficiency can be as high as 50% after 5 years of age
- **Sucrase**: ≥85% specific to sucrose

MGAM, maltase-glucoamylase; SI, sucrase-isomaltase.
Courtesy of GIHF

American College of Gastroenterology
Potential Etiologies of Key Disaccharidase Deficiencies

**Genetic**
- Congenital lactase deficiency
- Genetic Sucrase-Isomaltase Deficiency (GSID)
  - Autosomal recessive (CSID)
  - Symptomatic heterozygous carriers
  - Compound heterozygotes

**Secondary causes**
- Celiac disease
- Bacterial overgrowth
- IBD
- Allergic enteropathy
- Acute gastroenteritis
- Giardiasis
- Other (eg, mucositis, autoimmune enteropathy?)

CISD, congenital sucrase isomaltase deficiency; IBD, inflammatory bowel disease.

Prevalence of Disaccharidase Deficiency in Adults with Unexplained GI Symptoms

**Analysis of Duodenal Biopsies (N=120)**

- Normal disaccharidase levels: 53.3%
- Maltase deficiency: 0.8%
- Maltase/sucrase/palatinase deficiency: 0.8%
- Pan-disaccharidase deficiency: 46.7%
- Lactase deficiency: 35.8%
- Baseline GI symptoms or severity did not predict enzyme deficiency

Courtesy of GHF
Do carbs matter?

- **Almost** all dietary carbs **become** FODMAPs when proximal carb digestion and/or absorption is abnormal...
  - Lactose intolerance
  - Carb intolerance secondary to celiac, cystic fibrosis, chemotherapy, etc.
  - Congenital sucrase-isomaltase deficiency – primary or genetic sugar/starch intolerance

- FODMAPs (undigested and fermented carbs) arriving to the colon from small bowel causing gas, bloating, and diarrhea

**Courtesy of GIHF**

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American College of Gastroenterology

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Should we consider Carbohydrate enzyme deficiencies in our Differential Diagnosis?

- **Lactose Intolerance**
  - But, lactose consumption is steadily declining¹...

- **Low FODMAP Diet (LFD)**
  - Can be helpful in ~50% of IBS cases
  - But LFD does **NOT** eliminate sucrose...

---

- http://www.ncc.umn.edu/products/
Consider CSID in Low FODMAP Diet Failures

**Adequate relief of IBS-D symptoms with LFD**

<table>
<thead>
<tr>
<th>Symptom Relief, %</th>
<th>All patients</th>
<th>Non-carriers</th>
<th>Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=46</td>
<td>n=23</td>
<td>n=23</td>
</tr>
<tr>
<td>Adequate relief</td>
<td>52.2</td>
<td>60.9</td>
<td>45.5</td>
</tr>
</tbody>
</table>

P=0.031

**Response rate by number of SI hypomorphic genes (N=39)**

<table>
<thead>
<tr>
<th>Number of Hypomorphic SI variants</th>
<th>Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>56.1</td>
</tr>
<tr>
<td>1 (heterozygous)</td>
<td>42.1</td>
</tr>
<tr>
<td>2 (homozygous)</td>
<td>16.7</td>
</tr>
</tbody>
</table>

P=0.0039

---

Sucrase-Isomaltase Deficiency as a Potential Masquerader in IBS

- **N= 31 patients,** mean age 46, 69% Female (IQR 30-60), were recruited from GI clinic with presumed diagnosis of IBS-D/M (abdominal pain, diarrhea, and/or bloating)
  - Patients with history of IBD, GI malignancy, or celiac disease excluded
  - All patients underwent EGD with duodenal biopsies and testing for disaccharidase deficiency
  - Patients with SID were less likely than controls to have abdominal pain (OR 0.16, 95% CI 0.03–0.81, P = 0.04)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
<th>n (%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (45.5)</td>
<td>17 (85)</td>
<td>0.16</td>
<td>0.0037</td>
</tr>
<tr>
<td>Bloating</td>
<td>4 (36.3)</td>
<td>12 (60)</td>
<td>0.39</td>
<td>0.2734</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (63.6)</td>
<td>8 (40)</td>
<td>2.54</td>
<td>0.2734</td>
</tr>
</tbody>
</table>

SID was present in **35%** of patients
100% were also lactase deficient

Kim SB, Moonhwa B et al. DDS 2019.
EGD, esophagogastroduodenoscopy; IBD, inflammatory bowel disease; OR, odds ratio.
Enzyme Function via Disaccharidase Assay Is the Gold Standard for SID Diagnosis

**COLLECT**
- First biopsies
- 2-3 biopsies obtained from distal duodenum/proximal jejunum
- Disaccharidase levels decreased by ≥33% in proximal duodenum
- Place samples in empty eppendorf tube
- Do not place tissue on gauze, filter paper, or use any type of support medium, not even saline

**FREEZE**
- Place eppendorf tube with collected sample immediately on ice (dry or wet ice)
- Freeze within 2 hours of collection at -20°C to -70°C

**SHIP**
- Ship frozen on dry ice; forward to appropriate lab promptly on same day
- Turn around time typically 3 to 7 days

*Genetic test* – rule in, not out - large gene, many SNPs not investigated. NOTE: The genetic test is not a validated diagnostic test for CSID

Assay measures activity of all four sugars: Lactase (lactose), Sucrase (Sucrose), Maltose and Palatinase (Starch sugars)


2. Courtesy GIHF

USH Carbohydrate Consumption is high

~ 46% of 2,000 calorie western diet\(^1,2\)

- Fats & Proteins, 54%
- Carbs, 46%

What do we do with high sucrase levels on biopsies?

Developing mRNAs for inhibition of SI enzyme to block postprandial hyperglycemia as a mechanism for DMII?


Diet plans for patients with SID should be developed in conjunction with a dietitian!!

Back to Our Patient

- Endoscopy was normal- including biopsies for celiac dz
- Biopsies done for SID showed the following:
  - Low sucrase (<25 µM/min/g/prot)
  - Maltase enzyme activity (<50 µM/min/g/prot)
  - Normal lactase
- Treatment
  - She first tried the Low FODMAP diet and had some relief.
  - Avoidance of sucrose containing foods helped the most- with help of dietitian
  - Peppermint oil for pain with fecal urgency
  - Send for genetic testing for CSID-heterozygous mutation
### Real Patient Case 2:

#### History & PE

**26-year-old female with either intermittent diarrhea or constipation, has fecal urgency. Has had abdominal pain all her life**

- **HPI**
  - Notes diffuse pain asst with meals and BMs only – can last hours though and also occurs outside of meals
  - BMs once a week with help of laxatives then has diarrhea BSS 6-7 or 1.
  - Takes PEG tid at times.
  - Many cleanouts with golytely
  - Last year or so has lost 20+ lbs.
  - Other GI complaints: Bloating, distension, satiety and fullness.
  - Distension and pain limits her PO intake
  - Symptom triggers: Stress

- **PMHX**
  - Cystic fibrosis related lung dz (Delta F508) homozygote (hx recurrent pneumonias)
  - Pancreatic insufficiency
  - Cholecystectomy (gallstones)
  - Pyloroplasty for gastroparesis
  - Nissen fundoplication
  - Autism spectrum disorder –High functioning (ASD) with ADD features
  - Recurrent rhinosinusitis with multiple antibiotics
  - Nonautoimmune myopathy
  - Hx DIOS- but no surgery
  - Hx Rectal prolapse and dyssynergia s/p ileostomy 8 months ago

#### Physical Exam (PE)

- Thin female, BMI 18
- Normal vitals otherwise
- Abdomen: + Loud bowel sounds, tenderness LUQ and LLQ, distended diffusely, no masses, no HSM, no rebound
- Solid stool present in ileostomy

#### Labs

- CBC and iron panel (normal)
- Fecal testing for parasites and fecal calprotectin (normal)
- B12 normal, high folate
- Fecal elastase < 50

#### Medications

- Azithromycin Tabs –CF
- Probiotics
- Pancreatic enzyme supplements – with compliance
- Laxatives for constipation: PEG, senna, sorbitol, lactulose, stool softeners and golytely for constipation episodes
- Vitamin D supplements, b12
- Iron IV
- MTV (CF MVW)
• Family History
  • Twin sister without CF or ASD- has IBS

• Social History
  • No Etoh, drug use or tobacco use
  • ?ARFID

Dysfunctional CFTR leads to high prevalence of GI Symptoms in CF- Not IBS

- Decreased fluid secretion in the intestinal lumen
- Bicarbonate deficiency increases acid content
- Mucus accumulation (DIOS)
- Dysbiosis (SIBO)
- Inflammation
- Dysmotility (Constipation)

Lisle et al. Cold Harbor Perspect Med 2013
Xue et al. Scientific Reports 2016
Tabori et al. PLoS ONE 2017
Small bowel transit (small bowel dysmotility) is delayed in CF

- N=10
- Age matched controls
- Age>18

**Undefined GI symptomatology in this study

Whole gut motility testing done with WMC

WMC study showing isolated small bowel dysmotility
Current transit testing and labs:

- Gastric emptying (Post pyloromyotomy):
  - **FINDINGS:**
    - % Empty at 1/2 hour: 11%
    - % Empty at 1 hour: 17% (NI >10%, <70%)
    - % Empty at 2 hours: 62% (NI >=40%)
    - % Empty at 3 hours: 86% (NI >=70%)
    - % Empty at 4 hours: 94% (NI >=90%)

- Labs: Folate > 24.8 ng/ml, RBC folate: 1130 ng/ml (normal >498), b12 normal
- Vitamin D nil
- Ferritin 9 (low)
- Several CT scans- Stool in ileal segments. No transit point
- ROM study- > 15 markers in rectosigmoid colon- one in right colon.
- SBFT- transit from stomach to ileostomy was 8 hours (< 4-6 hours normal for barium studies), Fecal material seen close to ostomy site but no stenosis seen with ileoscopy
- Op Note: Dilated, atonic-appearing colon. Chronically, partially dilated TI.

---

Does this patient have small bowel dysmotility or Pseudo-obstruction (CIPO) from CF?
Is this SIBO?
How do we treat her-prokinetics first or treat for SIBO?
How can we diagnose it?
Symptoms and signs of small intestinal dysmotility

- CIPO is sporadic usually but can be familial (visceral myopathy, neuropathies)
- Idiopathic or due to systemic etiologies (60% cases are secondary):
  - **Neuropathic**: DM, paraneoplastic, amyloidosis (myopathic too), Parkinson’s disease,
    post-viral infections
  - **Myopathic**: eg Connective tissue diseases, Ehlers Danlos Syndrome (α- actin deficiency in a subset)
  - **Mesenchymal** (ICC abnormalities)
- Symptoms:
  - Too slow: Gas, fullness, bloating, cramps, constipation or diarrhea
  - Too Rapid: Gas, fullness, bloating, cramps and diarrhea
- History: Repeated imaging showing small bowel dilation often with air fluid levels. Patient may have had operations without a source of obstruction found is KEY
- Remember: Can have dysmotility and obstruction at same time!!!

Causes of CIPO

<table>
<thead>
<tr>
<th>Myopathic and Neuropathic causes of pseudo-obstruction</th>
<th>Causes</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary visceral myopathy and neuropathy</td>
<td>Autosomal recessive</td>
<td>Familial visceral myopathy</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant</td>
<td>Non-familial visceral myopathy</td>
</tr>
<tr>
<td>Secondary visceral myopathies</td>
<td>Connective tissue disease</td>
<td>CREST, Progressive systemic sclerosis, dermatomyositis, lupus, mixed connective tissue diseases</td>
</tr>
<tr>
<td>Inflammatory diseases</td>
<td>Sarcoidosis, diffuse lymphoid infiltration, amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Muscle dystrophies</td>
<td>Duchenne's dystrophy, myotonic dystrophy</td>
<td></td>
</tr>
<tr>
<td>Secondary visceral neuropathies</td>
<td>Neurologic diseases</td>
<td>Parkinson’s disease, Multiple sclerosis, diabetic neuropathy (also myopathic), post-infectious (viral infections such as CMV, EBV, herpes, other enteroviruses), Chagas’ disease, amyotrophy, amyotroph lateral, paraneoplastic disease (malappetite)</td>
</tr>
</tbody>
</table>
Antroduodenal Manometry indications

- Chronic intestinal pseudo-obstruction
- Provocative testing
- Functional versus organic intestinal disorders
- Refractory Gastroparesis
- Recurrent bacterial overgrowth
- Preoperative motility testing (GES)
- Occasionally in mechanical obstruction

Antroduodenal Manometry (Conventional)

- Phase I: Absence of measurable phasic pressures-low motor activity (3 pressure waves per 5-10min) (40-60%)
- Phase II: Random/irregular pressure waves
  - Resembles fed pattern (20-30%)
- Phase III: Large-amplitude propulsive contractions, coordinated and rhythmic propagating along the GI tract.
  - Few of the MMCs reach the ileum.
  - The MMC lasts 90-120 minutes
  - Most begin in the stomach and travel at speed of 5 cm/min distally
  - This is how we get rid of undigested products—the intestinal housekeeper

High Resolution Antroduodenal Manometry

- Antrograde Coupling
- Retrograde Coupling

Courtesy of Bill Hasler MD and Jason Baker PhD

Antral Peristalsis
Pylorus
Retrograde Duodenal Peristalsis

Courtesy of Mark Fox MD

Cine-MRI for studying CIPO and PanGI Dysmotility

- Study Motility patterns via Cine-MRI was studied in 8 subjects with CIPO in comparison to healthy controls
- Small bowel motility is hyperactive in ½ of patients with CIPO
- Wide variation in motility patterns was seen (higher, lower and similar to healthy subjects).
- In CIPO however, the change in fed state were not seen as compared to healthy subjects (p <.001)

- Courtesy of Mark Fox MD

Rijn KL et al. NGM 2021;33:e14062.
Relationship of Clinical Entities and histophathologic phenotypes: London Classification of GI neuromuscular pathology 2009

No clinical Guidelines define who should get a full thickness biopsy

Lymphocytic ganglionitis & Lymphocytic leiomyositis in CF


Diagnostic testing in suspected CIPO or small Intestinal dysmotility

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td>CBC, CMP, TSH, Hgb A1c, Vitamin B12, Folate, CRP, CK, ANA, Anti-scl-70, anti-ds DNA, aldolase, celiac serology, IGA level, ANNA-1 or anti-Hu SPP3/SPP (if indicated) AChR, Genetic testing for some diseases (MELAS, MNGIES, EDS, amyloid)</td>
<td>Precise diagnosis may be difficult, ruling out all secondary causes depends on clinical history and findings on exam</td>
</tr>
<tr>
<td>Radiology</td>
<td>Plain x ray Barium with small bowel follow through (SBFT) Computed tomography (CT) - CTE Cine-MRI</td>
<td>Radiation exposure for Cine-MRI — Validation of clinical utility pending (Cost?)</td>
</tr>
<tr>
<td>Conventional/High Resolution Manometry</td>
<td>Multi-lumen catheter (Water perfused or solid state) Determines if neurogenic or myogenic Can determine obstruction from motility disorder</td>
<td>Low specificity and invasive Not standardised Requires trained expertise in motility Poor correlation with histopathology Picks up artifacts (cardiac or pulmonary)</td>
</tr>
<tr>
<td>Wireless motility capsule</td>
<td>Determines intraluminal pressure and pH (transit) — Whole gut transit and small bowel transit • 15%-30% of patients with gastroparesis have colonic transit or small bowel transit abnormalities</td>
<td>Risk of capsule retention Contraindicated if Crohns or hx obstruction or dysphagia High Cost</td>
</tr>
<tr>
<td>Breath testing</td>
<td>Indicative of SIBO not necessarily CIPO Determining oral-cecal transit (Lactulose BT)</td>
<td>Not gold standard and high false positive rates for SIBO</td>
</tr>
<tr>
<td>Radiopaque markers</td>
<td>Not validated for small bowel transit</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Full thickness small bowel biopsy necessary with special staining (Amyloid, inflammatory enteropathies, ICC per HPF)</td>
<td>London Classification only. No clinical consensus reached but evolving technique can differentiate myopathy, neuropathy from loss of ganglion or decrease and ICC loss Invasive</td>
</tr>
</tbody>
</table>

Small bowel dysmotility and symptom correlation – Only diarrhea correlated with SBT delay

Normal gastric emptying times (GET) (≤5 and >1:45 hours)  
Small bowel transit times (SBTT) (≤6 and >2:15 hours)  
Colon transit times (CTT) (≤58:45 and >4:30 hours)  
WGTT <73 hours

NIDDK GP consortium data:  
N=209 patients with gastroparesis:  
Prevalence of transit delays in patients with Gastroparesis 15.5% by transit and 13.7% SB Motility Index  

Zebrfish and ‘Smurf cakes’ link autism gene mutation to digestive woes

Compher C. & Metz, JPNEN 2007; 31, no2, P240
Blue poo: impact of gut transit time on the gut microbiome using a novel marker

Findings:
- Gut microbiome taxonomic composition accurately discriminated between gut transit time and longer gut transit time was linked with specific microbial species (Akkermansia muciniphila, Bacteroides spp and Alistipes spp (P value <0.01))
- The blue dye measure of gut transit time had the strongest association with the gut microbiome over stool consistency by BSS and Stool frequency.


Is this all just SIBO?

Based on a survey of gastroenterologists (N=90) from academic or community hospitals, responses to the question: “When working up patients for SIBO or IBS, what percent of your patients receive each of the following? “

Moshiree B & Khan A. Adv Ther Gastroenterology (Submitted)
### Expert Guideline recommendations on SIBO

<table>
<thead>
<tr>
<th>Best Practice Advice 1:</th>
<th>Definition of SIBO lacks consistency and precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Practice Advice 2:</td>
<td>Symptoms: Bloating, Diarrhea, abdominal pain/discomfort and steatorrhea in severe cases</td>
</tr>
<tr>
<td>Best Practice Advice 3:</td>
<td>Insufficient evidence to check any inflammatory markers in SIBO (Fcal)</td>
</tr>
<tr>
<td>Best Practice Advice 4:</td>
<td>Lab findings such as elevated folate and less commonly B12 may be helpful</td>
</tr>
<tr>
<td>Best Practice Advice 5:</td>
<td>Limited understanding of SIBO exists and inability to adequately sample</td>
</tr>
<tr>
<td>Best Practice Advice 6:</td>
<td>Controversy regarding role of SIBO in functional GI diseases exists</td>
</tr>
<tr>
<td>Best Practice Advice 7:</td>
<td>Management: correct underlying causes and administer antibiotics and nutritional deficiencies correction</td>
</tr>
<tr>
<td>Best Practice Advice 8:</td>
<td>Role of SIBO in IBS is unclear</td>
</tr>
</tbody>
</table>

### Is Breath Testing necessary?
Or should we do small bowel aspiration?

- Hydrogen: Indicative of SIBO
- Methane: Indicative of intestinal methanogenic overgrowth and correlated with constipation
- H2S: Indicative of SIBO

Breath testing has not been validated in CF (or any lung dz) as it is dependent on CO2.

Exhalation from lungs

Small bowel aspirates are still the gold standard for SIBO diagnosis

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart Capsule Bacterial Detection System 17</td>
<td>Ingestible capsule which automatically tracks its own progress through the upper gastrointestinal tract with an LED-based sensor array, capturing a sample when localized in the jejunum. The total live bacteria count for the small intestine is determined via a fluorescent signal, which is converted in the wearables receiver to a gas-bacterial concentration and positive or negative SIBO indication. Results are communicated wirelessly from the receiver to a Physician Medical Application (PMA) on a smartphone or computer.</td>
</tr>
<tr>
<td>Metabonomic technology 18</td>
<td>Proton nuclear magnetic resonance (1H-NMR) spectroscopy detects differences in metabolite patterns (metabolic fingerprints) produced by bacteria in small bowel aspirates from healthy subjects and patients with SIBO. Potential for future diagnostic use upon discovery of biomarker prognostic factors.</td>
</tr>
<tr>
<td>Microbiome profiling 22</td>
<td>16S rRNA sequencing is used to compare the duodenal microbiome composition between subjects with and without SIBO. Higher or lower populations of particular bacteria may distinguish SIBO patients from healthy subjects.</td>
</tr>
<tr>
<td>Gas Chromatography 1,2</td>
<td>Gas chromatography of volatile fatty acids, produced by anaerobic bacterial metabolism in the segments of jejunum fluid may distinguish SIBO from normal.</td>
</tr>
</tbody>
</table>

Performance result of SCBDS assay in patients with suspected SIBO

94% Overall Agreement between SCBDS assay vs Reference Standard (TBC): Interim Performance Results

<table>
<thead>
<tr>
<th>Site</th>
<th>Assay vs TBC (10^5 CFU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>Augusta: 36/39 (92%)</td>
</tr>
<tr>
<td>305</td>
<td>Atrium: 15/15 (100%)</td>
</tr>
<tr>
<td></td>
<td>MARG: 11/12 (92%)</td>
</tr>
<tr>
<td>Total</td>
<td>62/66 (94%)</td>
</tr>
</tbody>
</table>

- Controls performed consistently across multiple sites
- 94% Overall agreement of SCBDS assay to TBC across multiple sites
- Overall agreement with different cut-off in PM-301
  - 10^5 CFU/mL: 92%
  - 10^4 CFU/mL: 95%
  - 10^3 CFU/mL: slightly drop off at 90%.

Presented at ACG 2020: Presidential Award
• Of 79 patients, 25 were affected by SIBO (31.6%) (by glucose BT) with a significant correlation with lower BMI, (p<0.05) and serum albumin levels (p<0.05) independently from pancreas insufficiency.

• Eradication rate of SIBO was 9/10 (90%) in rifaximin group and 2/6 (33.3%) in control group (p<0.05).

• In the rifaximin group, gastrointestinal symptom improvement was observed in 4/5 patients aged - 14 years and in 0/5 patients aged 14 years (p<0.05); in 2/6 patients in the control group.


Treating complications of small bowel dysmotility

<diagram>

Treating SIBO

- Start with Diet- Get a dietician, start low processed carbohydrate, sugars and low residue

- Rotating Antibiotics q1-2 weeks with breaks
  - Tetracycline: 250mg QID or TMP 200mg BID (can use doxycycline too)
  - Ciprofloxacin 250mg BID
  - Amoxicillin-clavulanate 500mg TID
  - Metronidazole x 5-7d if breakthrough (500 mg TID)
  - Rifaximin 550mg mg TID x 14 days or alternative dosing

Prokinetics available for Treatment of CIPO and small bowel dysmotility (none FDA approved)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Considerations</th>
<th>Reference</th>
</tr>
</thead>
</table>
- Effects of motilin agonists and octreotide on small bowel motility

**Table 1. Baseline characteristics of study population (n = 21).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>49 yrs (12)</td>
</tr>
<tr>
<td>Age range</td>
<td>20-65 yrs</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Gastroesophage (%) diagnosed by</td>
<td>44</td>
</tr>
<tr>
<td>Gastric emptying scintigraphy (n = 16)</td>
<td>100</td>
</tr>
<tr>
<td>Motilinoma</td>
<td>100</td>
</tr>
<tr>
<td>Motilinoma (%) not diagnosed by</td>
<td>100</td>
</tr>
<tr>
<td>Patient symptoms (%)</td>
<td>86</td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>86</td>
</tr>
<tr>
<td>Nausea/vomiting (%)</td>
<td>63</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>14</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Abbreviation: SD = standard deviation.*

**Octreotide (OCT) delays gastric antral activity**

**Figure 2. Effect of erythromycin (ERY), azithromycin (AZI) and octreotide (OCT) on mean number of migrating motor complexes (MMC) in antral manometry (p-values listed in comparing each medication with AZI).**

**Serotonin agonists improve whole gut transit**

**Figure 2. Small bowel transit with and without tegaserod in 40 healthy subjects (23 males, 17 females). Data are mean ± SEM.**

**Figure 3. Box plot diagrams showing the distributions of small bowel transit time in the three study periods. Control, first period (October 2013 to March 2014); the period of prucalopride use (from March 2014 to December 2015); control, second period (December 2015 to September 2016).**


New possible therapies Renzapride as a highly selective - 5HT4 agonist

* Mechanism of action is also validated by pharmacologically-related molecules, eg cisapride, prucalopride

CIPO/Small bowel dysmotility Algorithm

- Peristalsis- (“Gold standard” is still manometry)
- WMC/MRI may be helpful
- Exclude reversible causes and work with multidisciplinary team
- Imaging showing stasis/dilation and air fluid levels but no obstruction or transition
- Malnutrition
- Confirm presence of SIBO = empiric treatment
- Prokinetics and correction of macro and micro-nutrient depletions
- Start elemental nutrition (PEJ) or TPN
- Small Bowel Transplantation (specialized centers only)
- Cyclic antibiotics ± Prokinetics
- ?Fecal transplantation?
### Other treatments for CIPO

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Source</th>
</tr>
</thead>
</table>


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### Back to patient’s case

- Smurfcake transit study- 12 hours (prolonged given she has an ileostomy)
- Dietician consultation CF clinic (iron IV, tube feedings with many water flushes), SIBO-diet initiated
- Cycled Antibiotics (ciprofloxacin, doxycycline, and metronidazole) or rifaximin for bacterial overgrowth (1 week a month)
- Prokinetic agents: Azithromycin elixir thru G tube, oral pyridostigmine, prucalopride
- Constipation: Linaclotide, golytely as needed
- Venting gastrostomy and PEG-J tube for elemental diet (avoiding TPN)
- Social work support/behavioral health: Address ARFID
- Considerations: Full thickness biopsy of small bowel (J tube placement)

Next plan Pathology to look for Lymphocytic ganglionitis or Lymphocytic Leiomyositis – Per London Classification
Multidisciplinary effort needed!

Dedicated Gastroenterologist (any subspecialty)
Small bowel is everyone’s turf!!

Nutrition: Dietician/TPN team of Pharmacists

Financial support: Social Worker/Medical Authorization Liaison

Coping and anxiety: GI psychologists and behavioral health specialists, Genetic counselor

Other Medical Disciplines involved: Pulmonary, Endocrinology, Genetics, Oncology, Neurology, Surgery, GI pathologist, Nursing

Wake Forest School of Medicine
Charlotte Joins Atrium Health 2024
Questions?

Speaker:
Baha Moshiree, MD, MSc, FACG

Moderator:
Rita M. Knotts, MD, MS