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Workup and Management of Bloating with Diarrhea

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Disclosures

- No relevant financial disclosures

Case presentation

A 34 year old female presented to our institution with 4 weeks of intractable, watery, and non-bloody diarrhea. She described 5-10 bowel movements daily, and described symptoms of abdominal bloating, nausea, early satiety and excessive belching.

Her past medical history included a history of complicated terminal ileitis secondary to Cohn's disease, and she was sp ileocecal resection performed 5 years ago without any post-surgical complications. She was on no maintenance medications for Crohn's disease. She also suffers from chronic GERD and has been on Nexium 20mg QAM for the past 3 years.

Physical exam revealed dry mucous membranes, sunken-appearing eyes, decreased skin turgor. Vital signs were stable although she was a mildly tachycardic with a resting HR of 105.

Case presentation

Laboratories demonstrated electrolyte derangement and pre-renal azotemia. The rest of her laboratories were unremarkable. CRP, TSH were within normal limits. Stool studies were negative for C. Diff and for other bacterial, viral, and parasitic etiologies. Subsequent upper endoscopy with duodenal biopsies along with colonoscopy up to the neo-terminal ileum with random ileal and colonic biopsies for CMV colitis, microscopic colitis and residual Crohn's disease were negative.

After IV fluid resuscitation and medical stabilization, the patient followed up in our outpatient office and a hydrogen breath test was carried out using 75g of glucose. The patient had followed a restricted diet the previous day and fasted overnight.

The results showed an increase in hydrogen to 20 ppm above baseline at 80 minutes.

Case presentation

The patient was subsequently placed on Rifaximin 550mg TID for 14 days for presumed SIBO.

Her symptoms initially showed a drastic improvement. About one week after the Rifaximin course was completed, her symptoms returned.

A repeat breath test was performed, this time with Lactulose 10g, and again, demonstrated an increase in hydrogen to 20 ppm above baseline within 90 minutes.

At this point we determined this could be SIBO with antibiotic resistance -- she was placed on combination of 3 different antibiotics (rifaximin, augmenting and ciprofloxacin) rotated every two weeks to avoid resistance. After 3 cycles her symptoms completely resolved.

She was also taken off her PPI during this time.

Definition of Bloating and Distention

- The term "abdominal bloating" primarily refers to a sensory phenomenon -- a subjective feeling of post-prandial abdominal fullness, pressure, or a sensation of trapped gas -- whereas the term ”abdominal distention" is an objective and measurable increase in abdominal girth.

1. Jiang X, Locke GR, 3rd, Choung RS, Zinsmeister AR, Schleck CD, Talley NJ. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. Gut. 2008;57:756–763.

Bloating and Distention

- Symptoms of abdominal bloating are estimated to affect up to 15-30% of the adult population within the US. [1]
- Women are more likely than men to report abdominal bloating to their physician [1]
  - And are more likely to report interference in their daily life.

1. Jiang X, Locke GR, 3rd, Choung RS, Zinsmeister AR, Schleck CD, Talley NJ. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. Gut. 2008;57:756–763.

Bloating and Distention

- Bloating is more common among patients with food intolerances and IBS (75-90%) [2] -- whereas measurable distention is more common in patients with motility issues, such as those with chronic constipation. [2]

1. Jiang X, Locke GR, 3rd, Choung RS, Zinsmeister AR, Schleck CD, Talley NJ. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. Gut. 2008;57:756–763.
2. Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. Am J Gastroenterol. 2003;98:2454–2459.

Functional vs. Non-functional Abdominal Bloating

- The pathophysiology behind functional abdominal bloating and distention is not completely understood.
  - Some proposed underlying mechanisms include visceral hypersensitivity, abnormal abdominal wall-phrenic reflexes, the effect of poorly absorbed fermentable carbohydrates, and gut dysbiosis. [3]
- Non-functional etiologies each have a different pathogenesis on why they produce this symptom, and can range from malabsorption to bacterial growth to intestinal inflammation.

3. Mari, A., Abu Backer, F., Mahamid, M., Amara, H., Carter, D., Boltin, D., & Dickman, R. (2019). Bloating and Abdominal Distension: Clinical Approach and Management. Advances in therapy, 36(5), 1075–1084.

What forms intestinal gas?

- A study of healthy volunteers found that the average individual produces approximately 700 cc of gas per day, and keeps between 100 to 200 cc of gas within their GI tract at any one time.
- The 5 most common gases within the GI tract are nitrogen, oxygen, hydrogen gas, carbon dioxide, and methane.
- Almost all nitrogen and oxygen within the upper GI tract come from swallowed air.
- CO2 may come from swallowing air, but also from carbonated beverages along with the effect of acid neutralization in the upper GI tract.
    - CO2 is readily absorbed in the small intestine. [4]

4. Tomlin J, Lowis C, Read NW. Investigation of normal flatus production in healthy volunteers. Gut. 1991;32:665–669.

Intestinal Gas

- Food products that are incompletely digested within the small intestine—such as lactose (in patients with lactase deficiency), fructose, sorbitol, legumes, fiber, and complex carbohydrates (ie, wheat)—are broken down within in the colon.
- Therefore, colonic gas production occurs primarily due to the metabolism of food and ingested material by colonic bacteria. [4]
    - As a result, the volume of gas increases and expands post-prandially, primarily within the pelvic colon.

4. Tomlin J, Lowis C, Read NW. Investigation of normal flatus production in healthy volunteers. Gut. 1991;32:665–669.

What causes the symptom of bloating?

- Intraluminal lipids can cause retention of gas, primarily within the proximal small intestine.
- Impaired evacuation, possibly secondary to an abnormal rectal reflex involved in intestinal gas release and propulsion.
- Abnormal viscerosomatic reflex activity, causing abdominal wall muscles relax rather than contract.
- Abnormal sensation or perception to smaller amounts of gas. [4]

4. Tomlin J, Lowis C, Read NW. Investigation of normal flatus production in healthy volunteers. Gut. 1991;32:665–669.

Can there be an abnormal amount of intestinal gas?

- It is difficult to define an "abnormal" amount of intestinal gas for a number of reasons.
- No consensus has been reached on standardized definition.
- Healthy subjects can generally tolerate up to 2,000 cc of intestinal gas quite because they can propel and evacuate gas efficiently.
  - This was confirmed by a study in which gas was infused within the GI tract and abdominal girth was measured. [5]

5. Hernando-Harder AC, Serra J, Azpiroz F, Malagelada JR. Sites of symptomatic gas retention during intestinal lipid perfusion in healthy subjects. Gut. 2004;53:661–665.

Differential diagnosis of bloating and diarrhea

- While abdominal bloating can be a sign of a functional GI disorder, when coupled together with symptoms of chronic diarrhea, other differentials must come to mind.
- The differential diagnosis is broad, but will focus on a few more common etiologies for the purpose of this lecture.

Differential diagnosis of bloating and diarrhea

- **Non-functional etiologies can include:**

  - Celiac disease (gluten-sensitive enteropathy)
  - Crohn's disease
  - Pancreatic insufficiency
  - Gastroparesis
  - Diabetes mellitus
  - Hypothyroidism
  - Scleroderma
  - Bile acid malabsorption
  - Chronic idiopathic pseudo-obstruction
  - Small bowel bacterial overgrowth
  - Acute gastroenteritis / GI infection (Giardiasis)
  - Intrabdominal malignancy - gastric, colon, ovarian.
  - Ascites
  - Disturbances in colonic microflora (gut dysbiosis)
  - Medication side effect (fiber supplements, MV)

6. Lacy, B. E., Gabbard, S. L., & Crowell, M. D. (2011). Pathophysiology, evaluation, and treatment of bloating: hope, hype, or hot air?. Gastroenterology & hepatology, 7(11), 729–739.

Differential diagnosis of bloating and diarrhea

- **Functional Etiologies can include:**
  - Functional abdominal bloating and distention
  - Functional dyspepsia
  - Irritable Bowel Syndrome with Diarrhea
    - Post-infectious IBS

6. Lacy, B. E., Gabbard, S. L., & Crowell, M. D. (2011). Pathophysiology, evaluation, and treatment of bloating: hope, hype, or hot air?. Gastroenterology & hepatology, 7(11), 729–739.

Differential diagnosis of bloating and diarrhea

- **Dietary Intolerances can include:**
  - Lactose intolerance
  - Fructose intolerance
  - Fructan consumption
  - Consumption of sorbitol or other nonabsorbable sugars
  - Carbohydrate intake
  - Non-celiac gluten sensitivity or “non-celiac wheat sensitivity”

6. Lacy, B. E., Gabbard, S. L., & Crowell, M. D. (2011). Pathophysiology, evaluation, and treatment of bloating: hope, hype, or hot air?. Gastroenterology & hepatology, 7(11), 729–739.

Workup for bloating and diarrhea

- Unfortunately, functional etiologies are usually diagnosed only after everything else has been excluded.
- Absence of reliable biomarkers for functional disorders.
- Food intolerance diagnosis are reached after exclusion of reported food intolerances (such as dietary gluten) -- and then re-introduction to confirm temporal association.

Workup for bloating and diarrhea

- Take a good history –
  - How long have symptoms been present for?
  - Is there an association with certain foods?
  - Does it happen every day?
  - Nocturnal symptoms?
  - Extra-intestinal allergy symptoms?
  - New skin rashes? Arthralgias? Vision changes?
- Family history - IBD? Malignancy? Celiac?
- History of pancreatitis?
- Recent GI related infection?
- History of DM or thyroid disorder?
- History of psychological disorders?
- Excessive Burping and belching? (may indicate aerophagia)

Workup for bloating and diarrhea

- Evaluate for alarm features: dysphagia, odynophagia, gastrointestinal bleeding, anemia, and unintentional weight loss.
- This should prompt referral to GI for pan-endoscopy along with cross sectional imaging.

Workup for bloating and diarrhea

- Blood work - CBC with differential, CMP, TSH w/ reflex T4, Hemoglobin A1C, UA, Celiac antibodies, ESR, CRP, Iron Indices, B12, Folate
- Stool studies - gastrointestinal panel to evaluate for bacterial, viral, and parasitic etiologies, fecal calprotectin, fecal lactoferrin, H. Pylori stool antigen, fecal occult blood test.
- Ordered based on clinical suspicion: fecal elastase, SIBO breath testing, urinary histamine.
- Imaging Studies - Abdominal US with or without a KUB, consider cross-sectional imaging if alarm symptoms present.

Celiac Disease

- Celiac disease (CD) is an autoimmune condition and chronic inflammatory disorder provoked by gluten ingestion in genetically susceptible individuals. [7]
- The end result is immune mediated intestinal inflammation which results in enteropathy and subsequent nutrient malabsorption.
- Gluten refers to a family of storage proteins that are naturally found in certain grains including wheat, rye, barley, spelt, and kamut.

7. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. BMC medicine, 17(1), 142.

Celiac Disease

- Reported prevalence of 0.5–1% within the general population. [7]
- The prevalence of CD is higher in first-degree CD relatives (10–15%) and in other high risk groups -- particularly patients with Down syndrome, Type 1 Diabetes, and/or IgA deficiency.
- CD is diagnosed more frequently in women with a female-to-male ratio ranging from 2:1 to 3:1, although more recent studies suggest a 1.5:1 ratio.
- The disease can occur at any age from early childhood to the elderly.
    - There are typically two peaks of onset – within first 2 years of life and within the second or third decades of life.

7. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. BMC medicine, 17(1), 142.

Signs and Symptoms of Celiac Disease

- The intestinal form of CD is more commonly detected in the pediatric population and children younger than 3 years and is characterized by diarrhea, loss of appetite, abdominal distention, and failure to thrive.
- Extraintestinal symptoms can include iron deficiency anemia (present in about 40%), macrocytic anemia due to folic acid and/or vitamin B12 deficiency, osteopenia/osteoporosis, growth retardation/short stature, tooth enamel defects, aphthous stomatitis, dermatitis herpetiformis, elevated transaminases.
- Neurological symptoms include headaches, paresthesia, inflammatory myopathies, gluten encephalopathy.
- Psychiatric symptoms can include both anxiety and depression.
- Reproductive manifestations such as infertility, amenorrhea, late menarche, early menopause, recurrent spontaneous miscarriages, premature birth, and changes in the number and mobility of spermatozoa can also be present.

7. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. BMC medicine, 17(1), 142.

Diagnosis of Celiac Disease

- Screen with autoimmune serological markers - anti-transglutaminase antibodies (tTG), anti-endomysium antibodies (EmA), and deamidated gliadin peptide (DGP) antibodies.
- Anti-tTG antibodies have the highest sensitivity, but no specific antibody test has a sensitivity and specificity of 100%.
    - A tissue transglutaminase IgA (tTg-IgA) test is usually the first screening test ordered, and should always be ordered with a total IgA level -- as low IgA level (2% to 3% of patients with CD) can produce a false negative result. If total IgA is low, order the rest of the antibody tests, specifically DGP-IgG test, which has a better positive predictive value for diagnosing CD than tTg-IgG in this specific context.
- Two important caveats –
    - Antibodies respond to a gluten free diet – so if a patient already placed themselves on a strict GFD, antibody tests may be low.
    - there is a seronegative form of CD, demonstrated by clinical signs of severe malabsorption and atrophy of the intestinal mucosa.
- "Four out of five rule" establish CD diagnosis:
    - (1) typical signs and symptoms (diarrhea and malabsorption);
    - (2) antibody positivity (> 2x the cut off value)
    - (3) HLA-DQ2 and/or HLA-DQ8 positivity (good NPV, particularly useful in patients already on gluten free diet);
    - (4) histological evidence of intestinal damage (i.e., villous atrophy and minor lesions such as isolated increase in IELs)
    - (5) clinical response to GFD.

Treatment of Celiacs

- Strict gluten-free diet [7]
    - A strict GFD is 95% effective at restoring small bowel histology in children within two years, whereas 34% and 66% of adult patients can experience histological recovery at two and five years, respectively. Some studies show no statistically significant recovery in patients 60 years or older. [8]
- Referral to nutritionist for better compliance, to help avoid misinformation and accidental cross-contamination.
- Referral to Rheumatologist to assess for other autoimmune related disorders.
- Follow-up with Gastroenterologist every 3-6 months to assess for CD related complications, the need for cross sectional imaging, and to perform surveillance duodenal biopsies.
- Can monitor progress with symptom surveillance, follow-up blood tests which include trending anti-tTG IgA, surveillance upper endoscopy with biopsies*.
    - Antibodies take at least 2 weeks to appear after initial gluten challenge and can still be elevated at 4 weeks after the last gluten ingnestion.
- Bone density scan should be performed after 12–18 months of a GFD and treatment with calcium, vitamin D, and or bisphosphonates if there is evidence of osteopenia/osteoporosis.
- Anti-pneumococcal and anti-meningococcal vaccinations are recommended due to possible functional hyposplenism.

8. Rubio-Tapia A., Rahim M.W., See J.A., Lahr B.D., Wu T.-T., Murray J.A. Mucosal Recovery and Mortality in Adults With Celiac Disease After Treatment With a Gluten-Free Diet. Am. J. Gastroenterol. 2010;105:1412–1420.

Treatment of Celiacs

- Refractory CD (RCD) is characterized by persistent symptoms along with evidence of villous atrophy after > 12 months of a strict GFD.
    - Up to 1.5% of total cases of CD are classified as refractory.
- A diagnosis of RCD should always be suspected by:
    - Persistent villous atrophy despite a strict, 1-year GFD along with low-titer or negative serologies.
    - Exclusion of other causes of persistent villous atrophy
- Two Types of RCD
    - Type 1 - CD3+ polyclonal T cells comprise the majority of IEL's – this may improve overtime with continuation of strict GFD.
    - Type 2 - aberrant IEL's that do not express surface CD3 or a T-cell receptor - much poorer prognosis, higher mortality and increased likelihood of progressing to enteropathy-associated T-cell lymphoma [9]
- Complications of CD include functional hyposplenism, enteropathy-associated T-cell lymphoma (EATL), non-Hodgkin's lymphoma, small bowel adenocarcinoma, and ulcerative jejunoileitis.

7. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. BMC medicine, 17(1), 142.

9. Smithson, G., Siegelman, J., Oki, T., Maxwell, J. R., & Leffler, D. A. (1AD, January 1). The evolving landscape of biomarkers in celiac disease: Leading the way to clinical development. Frontiers.

SIBO

- Small intestinal bacterial overgrowth refers to a condition resulting in excess and/or imbalance of small intestinal bacteria, resulting in maldigestion and malabsorption. [10]
- Symptoms can include abdominal pain, nausea, bloating, early satiety, loss of appetite, diarrhea, and unintentional weight loss.
- The number of bacteria increases with progression from the proximal small intestine to the large intestine.
- The small intestine is comprised of mainly gram-positive and aerobic bacteria, while the large intestine contains predominantly gram-negative and anaerobic bacteria.
    - SIBO occurs when bacteria that are normally present in the large intestine start to over-grow within the small intestine.

10. Achufusi, T., Sharma, A., Zamora, E. A., & Manocha, D. (2020). Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus, 12(6), e8860.

SIBO

- The prevalence of SIBO among the general population is unknown.
- Risk factors include: [10]
  - Disturbances in the small bowel anatomy (such as small bowel adhesions, blind limbs, ileocecal valve dysfunction (low ileocecal valve pressures).
  - Small bowel dysmotility (including diabetic enteropathy, connective tissue disease such as scleroderma, underlying connective tissue disease, chronic opiate use)
  - Small bowel diverticulum.
  - Hypochloremia caused by chronic PPI use.
  - Reduced pancreaticobiliary secretions caused by chronic pancreatitis.

10. Achufusi, T., Sharma, A., Zamora, E. A., & Manocha, D. (2020). Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus, 12(6), e8860.

Diagnosis of SIBO

- The current gold standard for diagnosis is a quantitative culture of aspirated small bowel fluid (typically defined as bacterial concentration of >10^3 colony forming units/mL in a jejunal aspirate culture).
  - The drawbacks such as high cost of the procedure, invasiveness, technical difficulty, possible contamination by oropharyngeal flora, varying results between different operators has essentially made this an impractical diagnostic utility.
- Breath tests have gained more popularity due to their relatively simple, non-invasive nature.
- High or normal level of folate (upper intestinal tract bacteria are capable of synthesizing folate) with B12 malabsorption.
- Some clinicians may initiate empiric therapy as a diagnostic tool in those with a high level of suspicion for SIBO – although I would not recommend this.
  - Side effects, development of antibiotic-resistant organisms, C. Diff, etc.

10. Achufusi, T., Sharma, A., Zamora, E. A., & Manocha, D. (2020). Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus, 12(6), e8860.

SIBO breath testing

- Breath testing substrates can include glucose, lactulose, lactose, and fructose -- although glucose and lactulose have gained favor.
  - Glucose is more specific, less sensitive while lactulose more sensitive but less specific.
- Breath tests are based on the principle that metabolism of a test dose of the substrate by the bacterial flora leads to the production of hydrogen, methane, and hydrogen sulfide – which is excreted in the breath, analyzed, and quantified.
- In individuals without SIBO, the administration of carbohydrate substrate results in a single late peak in breath hydrogen within two to three hours due to the metabolism of lactulose by colonic flora.
- In patients with SIBO, administration of the same substrate results in an early peak in breath hydrogen levels due to metabolism by small bowel bacteria.

10. Achufusi, T., Sharma, A., Zamora, E. A., & Manocha, D. (2020). Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus, 12(6), e8860.

SIBO breath testing

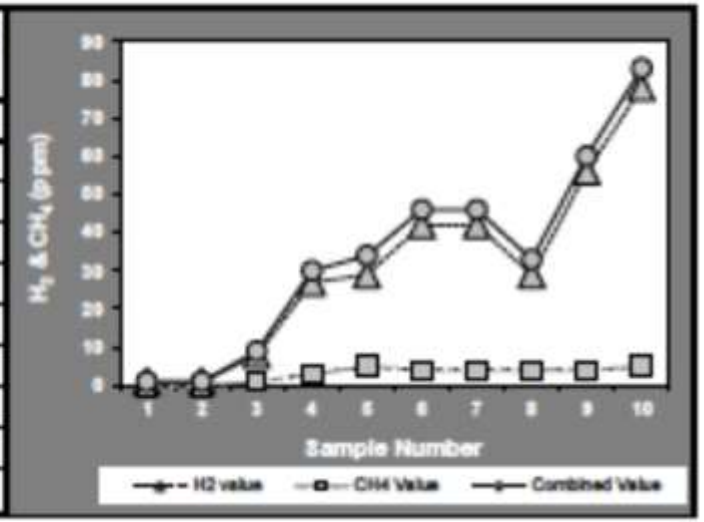
- Hydrogen, carbon dioxide, and methane are sampled and measured at baseline and every 15 minutes following administration of the test substrate (glucose 75 grams or lactulose 10 grams) with or followed by one cup of water.
  - Breath testing should be continued for 120 minutes.
- An absolute increase in hydrogen by ≥20 ppm above baseline within 90 minutes on the lactulose/glucose breath test is diagnostic of SIBO.
- A methane-positive study was defined as a methane level ≥10 ppm at any time.
  - M-SIBO refers to a different overgrowth of organisms that produce methane gas and are part of the part of the Archaea kingdom, which can actually produce symptoms of constipation.

10. Achufusi, T., Sharma, A., Zamora, E. A., & Manocha, D. (2020). Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods. Cureus, 12(6), e8860.

SIBO breath testing

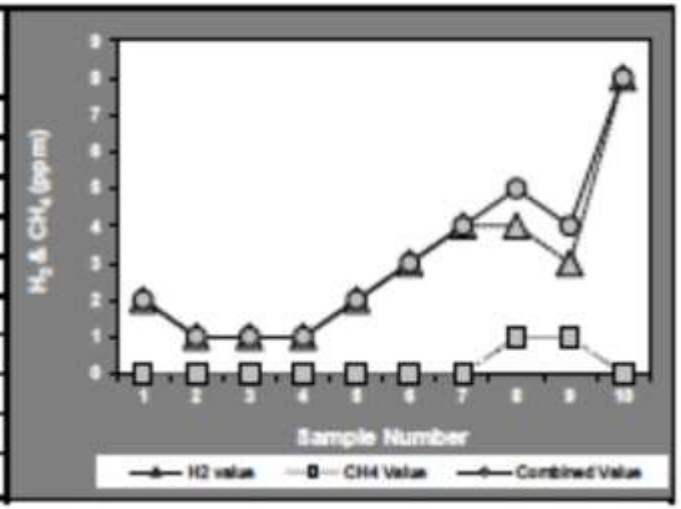
Double Peak

Sample	ppm H_2	ppm CH_4	Total H2 + CH4
1 Baseline	1	0	1
2 20 min	1	0	1
3 40 min	8	1	9
4 60 min	27	3	30
5 80 min	29	5	34
6 100 min	42	4	46
7 120 min	42	4	46
8 140 min	29	4	33
9 160 min	56	4	60
10 180 min	78	5	83



Negative Test

Sample	ppm H_2	ppm CH_4	Total H2 + CH4
1 Baseline	2	0	2
2 20 min	1	0	1
3 40 min	1	0	1
4 60 min	1	0	1
5 80 min	2	0	2
6 100 min	3	0	3
7 120 min	4	0	4
8 140 min	4	1	5
9 160 min	3	1	4
10 180 min	8	0	8



Breath testing can be falsely negative in the setting of distal SIBO – if the glucose substrate is completely reabsorbed in the proximal small bowel, it may not reach the site of bacterial overgrowth if it's more distal.

Similarly, in patients increased gut transit time, hydrogen breath tests may yield a false-positive result -- due to early substrate delivery to the colon and subsequent early detection. [11]

11. Simrén, M., & Stotzer, P. O. (2006). Use and abuse of hydrogen breath tests. Gut, 55(3), 297–303. https://doi.org/10.1136/gut.2005.075127

Treatment of SIBO

- The treatment of choice is antibiotic therapy, aimed at reducing and rebalancing gut dysbiosis.
- The treatment of choice is Rifaximin- a nonabsorbable antibiotic which acts against Gram-positive and Gram-negative aerobic and anaerobic bacteria with a reduced toxicity profile and its utility in irritable bowel syndrome.
  - The dose is 550 mg three times daily for 14 days.
  - A meta-analysis in 2017 investigated the effectiveness of rifaximin in SIBO, and demonstrated that the efficacy of rifaximin in eradicating SIBO was 64%, as compared to 41% with other systemic antibiotics. [12]
- Other antibiotic choices can include Augmentin, tetracyclines, fluoroquinolones, and co-trimoxazole, although with reduced efficacy.

12. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Gatta L, Scarpignato C. Aliment Pharmacol Ther. 2017;45:604–616.

Treatment of SIBO

- Dietary interventions can be helpful at reducing symptoms [12]
  - Low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet - select bacteria inhabiting the small bowel thrive by consuming FODMAPS, therefore, limiting their number deprives bacteria of the much-needed nutrition required for growth and proliferation.
  - Vegan and vegetarian diets rich in fiber may aid in proliferation of less pathogenic bacteria.
  - Elemental diet consisting of predigested micronutrients - proposed benefit of the diet stems from the high amount of predigested micronutrients that are mostly absorbed within the proximal small bowel, thus limiting the delivery of nutrients to the distal portion of the small bowel.
- Other treatments that require more clinical trials include probiotic supplementation (thus far conflicting results as adjunct treatment with Rifaximin), herbal supplementation (berberine complex).
- Those who fail standard therapy should undergo evaluation for other overlapping diagnoses and may need confirmation with jejunal aspirate and culture.

12. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Gatta L, Scarpignato C. Aliment Pharmacol Ther. 2017;45:604–616.

Exocrine Pancreatic Insufficiency

- The pancreas secretes about 1.5 liters of enzyme-rich concentrate (includes trypsinogen, chymotrypsinogen, elastase, carboxypeptidase, pancreatic lipase, and amylase) every day to aid in the digestion of fats, starch, and protein. [13]
- Stimulation of the pancreas after a meal increases the flow bicarbonate-rich juices to help neutralize the acidic gastric acid -- allowing for effective enzymatic digestion.
- This secretory pathway is mediated by both hormonal and neuronal mechanisms.
    - Secretin and CCK are the principle regulatory hormones and are tightly regulated by negative feedback mechanisms.

13. Ketwaroo, G. A., & Graham, D. Y. (2019). Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain. Advances in experimental medicine and biology, 1148, 323–343.

Pancreatic Insufficiency

- Secretin is secreted by the duodenal mucosa in response to the presence of gastric acid.
  - It subsequently stimulates the release of bicarbonate + water from the interlobular pancreatic duct cells. [13]
- CCK is released from gut endocrine cells in response to fat and protein once it reaches the proximal intestine.
  - CCK acts both directly and through vagal afferents to signal pancreatic acinar cells to release digestive proenzymes as part of the pancreatic fluid. [13]

13. Ketwaroo, G. A., & Graham, D. Y. (2019). Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain. Advances in experimental medicine and biology, 1148, 323–343.

Causes of Pancreatic Insufficiency

- Chronic pancreatitis, the most common cause, can result in progressive inflammatory changes and permanent structural damage leading to impaired exocrine function.
- Cystic fibrosis can result in blockage of ductules resulting from inspissated pancreatic secretion.
- Gastric, pancreatic and/or small bowel resection — may lead to secondary exocrine pancreatic insufficiency due to loss of sites of secretin and cholecystokinin-pancreozymin synthesis, reduction of pancreatic glandular tissue, and extensive denervation leading to decreased pancreatic stimulation.

13. Ketwaroo, G. A., & Graham, D. Y. (2019). Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain. Advances in experimental medicine and biology, 1148, 323–343.

Causes of Pancreatic Insufficiency

- Pancreatic/ampullary tumors can result in pancreatic duct obstruction and reduced outflow.
- Hereditary hemochromatosis can cause iron deposition within the pancreas and subsequent organ injury.
- Gastrinoma (ZES) can lead to inactivation of pancreatic enzymes by excessive gastric acid.
- Small intestinal mucosal disease (such celiac disease) can result in decreased CCK release, which reduces pancreatic enzyme secretion.

13. Ketwaroo, G. A., & Graham, D. Y. (2019). Rational Use of Pancreatic Enzymes for Pancreatic Insufficiency and Pancreatic Pain. Advances in experimental medicine and biology, 1148, 323–343.

Causes of Pancreatic Insufficiency

- Clinical manifestations can be mild with abdominal discomfort, bloating, cramping, and increased flatulence.
- Moderate to severe symptoms can result in result in overt steatorrhea (does not occur until approximately 90 percent of glandular function has been lost). [14]
- Complications can include maldigestion of fat and protein resulting in significant weight loss. Deficiencies of the fat soluble vitamins A, D, E, and K can also occur.

14. Capurso, G., Traini, M., Piciucchi, M., Signoretti, M., & Arcidiacono, P. G. (2019). Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clinical and experimental gastroenterology, 12, 129–139.

Diagnosis of Pancreatic Insufficiency

- Workup begins with a full history and review of the patient's past medical history.
- Indirect tests measure the consequence of maldigestion.
  - Simpler, easier to perform, and less expensive as compared with direct pancreas function tests.
- If suspicion remains high, can begin with an indirect test of pancreas function, such as a fecal elastase-1.
  - Elastase is a component of pancreatic fluid that remains relatively intact within the stool.
- Fecal elastase in the most sensitive and specific indirect test of pancreatic function. [15]
  - Watery stools will result in low elastase values, so formed stool needs to be analyzed.
  - Lower sensitivity in mild to moderate EPI -- but has a useful NPV.

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

Diagnosis of Pancreatic Insufficiency

- The cut-off value for a normal result is >200 µg/g feces.
  - Negative predictive value of 86.0%. [15]
  - Values between 100 and 200 µg/g feces are indeterminate and difficult to interpret.
  - Values below 100 µg/g feces are highly suggestive of pancreatic insufficiency.
- The sensitivity of fecal elastase-1 for mild, moderate, and severe exocrine pancreatic insufficiency in patients with chronic pancreatitis are 63, 100, and 100 percent, respectively. [16]
  - Fecal elastase has a specificity of 93 percent in patients with exocrine pancreatic insufficiency.
- Other indirect tests include fecal chymotrypsin (also an enzymatic product of pancreatic secretion but with a lower sensitivity and specificity) and serum trypsinogen (high sensitivity for advanced disease, low sensitivity for less severe disease).

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

16. Löser, C., Möllgaard, A., & Fölsch, U. R. (1996). Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut, 39(4), 580–586.

Diagnosis of Pancreatic Insufficiency

- In patients in whom indirect tests are inconclusive, but the clinical suspicion of exocrine pancreatic insufficiency remains high, can be sent for an endoscopic secretin test, a more of a direct test of pancreatic function.
- The protocol for the secretin endoscopic pancreatic function test is similar to the traditional secretin test protocol. [15]
  - Duodenal aspirates of pancreatic fluid are obtained at 0, 15, 30, 45, and 60 minutes after administration of secretin to stimulate bicarbonate secretion.
  - A peak bicarbonate concentration <80 mEq/L is considered abnormal for the one-hour method.

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

Diagnosis of Pancreatic Insufficiency

- In patients with chronic pancreatitis, abdominal imaging (transabdominal ultrasonography, CT scan, or MRI) may show pancreatic atrophy, calcifications, ductal dilatation, enlargement of the pancreas, and peripancreatic fluid collections.
- More recently, there has been a focus on secretin-enhanced magnetic resonance cholangiopancreatography that allows timed assessments of duodenal filling -- using diffusion weighted magnetic resonance imaging to calculate a diffusion coefficient that can provide a estimation of pancreatic exocrine function. [15]

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

Treatment of Pancreatic Insufficiency

Nutritional assessment should begin with laboratory evaluation of the following:

- Serum retinol and retinol-binding protein (to assess Vitamin A)
- Serum 25-hydroxyvitamin D (25[OH]D)
- Serum alpha-tocopherol levels (to assess Vitamin E)
- International normalized ratio (INR) (to assess Vitamin K)
- Prealbumin
- B12
- Magnesium
- Zinc
- Albumin
- Fasting lipid panel
- HgBA1c annually

Treatment of Pancreatic Insufficiency

- Pancreatic enzyme preparations include Creon, Zenpep, Pancreaze.
- Most drugs have a handy calculator you can use on their website to calculate how many pills are needed, depending on the etiology behind the pancreatic insufficiency.
- Pancreatic enzyme replacement therapy should be started with a reasonable starting dose of 40,000 to 50,000 USP units taken with the first bite of each main meal, and one-half that amount with snacks.
  - There are studies that suggest some patients may need up to 90,000 USP units of lipase with each meal. [15]

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

Treatment of Pancreatic Insufficiency

- If the non-enteric-coated preparation is chosen, suppression of gastric acid with an H2 blocker or PPI is required to avoid denaturation of lipase within the gastric lumen.
- The effectiveness of enzyme supplementation is judged by loss of visible fat in the stool, improvement in fat-soluble vitamin levels, gain in muscle strength and body weight.
- Failure of pancreatic enzyme replacement should prompt dosage adjustment, change in formulation (eg, changing from enteric-coated preparations to non-enteric-coated preparation + PPI), assessment for non-compliance, and/or searching for an alternative cause of symptoms. [17]

17. Shandro, B. M., Nagarajah, R., & Poullis, A. (2018). Challenges in the management of pancreatic exocrine insufficiency. World journal of gastrointestinal pharmacology and therapeutics, 9(5), 39–46.

Treatment of Pancreatic Insufficiency

- Dietary interventions should include eating smaller, more frequent meals.
- High-protein, high-calorie foods consumed in five to six small meals per day, while avoiding diets very high in fiber, as fiber can absorb or block the action of pancreatic lipase.
- Only restrict dietary fat unless steatorrhea can't be controlled.

15. Struyvenberg, M. R., Martin, C. R., & Freedman, S. D. (2017). Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine, 15(1), 29.

Functional Disorders

- For functional disorders related to bloating and diarrhea, the treatment is aimed at lifestyle interventions along with symptom control.

- Treatment Options can include:
  - Dietary changes
  - Abdominal Biofeedback Therapy
  - Exercise and posture
  - Over-the-counter medications
  - Smooth muscle antispasmodics
  - Probiotics
  - Antibiotics
  - Anti-diarhheals

Functional Disorders – Symptom Control

- Dietary changed include Low FODMAP, lactose avoidance, gluten avoidance.
- Low FODMAP Diet
  - FODMAP is an acronym for a certain class of carbohydrates, called fermentable short-chain carbohydrates.
  - Temporarily restricts these carbohydrates in order to relieve symptoms of bloating.
  - Studies verifying the effects of low FODMAP diets in functional disorders are conflicting and randomized double-blind placebo-controlled studies almost impossible to apply in dietary interventions. [18]
  - Restrictive diets are notoriously difficult to adhere to, so food re-introduction should be part of the protocol.
  - Handouts and food diaries help patients organize and list culprit foods.
- Consider nutritionist referral - may increase the patient's compliance and reduce the risk of nutritional deficiencies

18. Nanayakkara, W. S., Skidmore, P. M., O'Brien, L., Wilkinson, T. J., & Gearry, R. B. (2016). Efficacy of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date. Clinical and experimental gastroenterology, 9, 131–142.

Functional Disorders – Symptom Control

- **Exercise and Posture**
  - Exercise - mild physical activity enhances intestinal gas clearance and reduces symptoms in patients complaining of abdominal bloating. [19]
  - Yoga - a randomized trial of yoga for adolescents with irritable bowel syndrome demonstrated an improvement in global GI symptoms after 4 weeks of daily yoga instruction. [20]

19. Villoria A, Serra J, Azpiroz F, Malagelada JR. Physical activity and intestinal gas clearance in patients with bloating. Am J Gastroenterol. 2006 Nov;101(11):2552-7.

20. Kuttner, L., Chambers, C. T., Hardial, J., Israel, D. M., Jacobson, K., & Evans, K. (2006). A randomized trial of yoga for adolescents with irritable bowel syndrome. Pain research & management, 11(4), 217–223.

Functional Disorders – Symptom Control

- **Over the counter medications**
  - Simethicone - good safety profile, over the counter, works by dispersing and preventing the formation of gas pockets along the gastrointestinal tract. [21]
  - Digest enzyme replacement – such as beano and other formulations that contain "digestive enzymes".
    - Intriguing therapeutic option, no great studies verifying it's effectiveness.

21. Martínez-Vázquez MA, Vázquez-Elizondo G, González-González JA, et al. Effect of antispasmodic agents, alone or in combination, in the treatment of irritable bowel syndrome: systematic review and meta-analysis. Rev Gastroenterol Mex 2012;77:82-90.

Functional Disorders – Symptom Control

- **Abdominal Biofeedback Therapy**
  - Most efficacious in patients with pelvic dyssynergia and pelvic outlet obstruction.
  - Uses real-time visual and/or auditory feedback to help correct maladaptive reflexes and behaviors involving the abdominal wall, puborectalis, and anal sphincter.
    - Can also employ rectal sensory balloon training improve rectal sensory abnormalities that can help with gas expulsion [23]
  - A randomized control trial in 2017 demonstrated improvement in abdominal distention with biofeedback compared to placebo. [22]

22. Barba E, Accarino A, Azpiroz F. Correction of Abdominal Distention by Biofeedback-Guided Control of Abdominothoracic Muscular Activity in a Randomized, Placebo-Controlled Trial. Clin Gastroenterol Hepatol. 2017 Dec;15(12):1922-1929.

23. Rao SS. Biofeedback therapy for constipation in adults. Best Pract Res Clin Gastroenterol 2011; 25: 159–166.

Functional Disorders – Symptom Control

- **Antispasmodics**
  - A meta-analysis performed 2017 demonstrated that anti-spasmodics (agents such as hyoscine, dicyclomine) were superior over placebo in treating complaints of abdominal bloating, and the addition of simethicone improved their performance. [24]
  - Anti-spasmodics have been studied extensively in IBS but results regarding it's effectiveness have been inconsistent.
    - Worth consideration as a trial.

24. Martínez-Vázquez MA, Vázquez-Elizondo G, González-González JA, Gutiérrez-Udave R, Maldonado-Garza HJ, Bosques-Padilla FJ. Effect of antispasmodic agents, alone or in combination, in the treatment of Irritable Bowel Syndrome: systematic review and meta-analysis. Rev Gastroenterol Mex. 2012 Apr-Jun;77(2):82-90.

Functional Disorders – Symptom Control

- **Probiotics**
- Although probiotics are commonly used, most formulations have not been adequately evaluated in randomized, placebo-controlled trials.
- A double-blind, placebo-control clinical trial in 2011 studied the effect Lactobacillus acidophilus and Bifidobacterium lactis in patients with nonconstipated functional bowel disorders and did conclude that there was a statically significant improvement in bloating severity during an 8-week trial period. [25]
- In 2006 a large-scale, multicenter, clinical trial of women with IBS given B. infantis 35624 demonstrated improvement in bloating, bowel dysfunction, incomplete evacuation, straining, and the passage of gas with a dose of 1×10^8 CFU/mL the end of the 4-wk study compared to placebo. [26]
- 2 randomized placebo controlled studies, one in children and one in adults, confirmed a statistically significant reduction in bloating in patients with diarrhea-predominant IBS in those given VSL3, a proprietary probiotic blend available as a prescription and over the counter. [27][28]

25. Ringel-Kulka T, Palsson OS, Maier D, et al. Probiotic bacteria Lactobacillus acidophilus NCFM and *Bifidobacterium lactis* Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. *J Clin Gastroenterol.* 2011;45:518–525.

26. Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, Kiely B, Shanahan F, Quigley EM. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol. 2006 Jul;101(7):1581-90.

27. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2003;17:895–904.

28. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL#3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil. 2005;17:687–696.

In Summary

- Abdominal bloating and diarrhea can be a symptom of both functional and non-functional GI disorders
- Taking an adequate history is just as important as the workup involved.
- The care involved should have a multidisciplinary approach
- Careful evaluation for alarm symptoms should prompt urgent GI referral.
- Any questions?