

Webinar 2

IBS, SIBO, SIFO
GI problems in Diabetes
Case discussion

Irritable Bowel Syndrome (IBS)

IBS-DGBl Disorders Of Gut-Brain Interaction

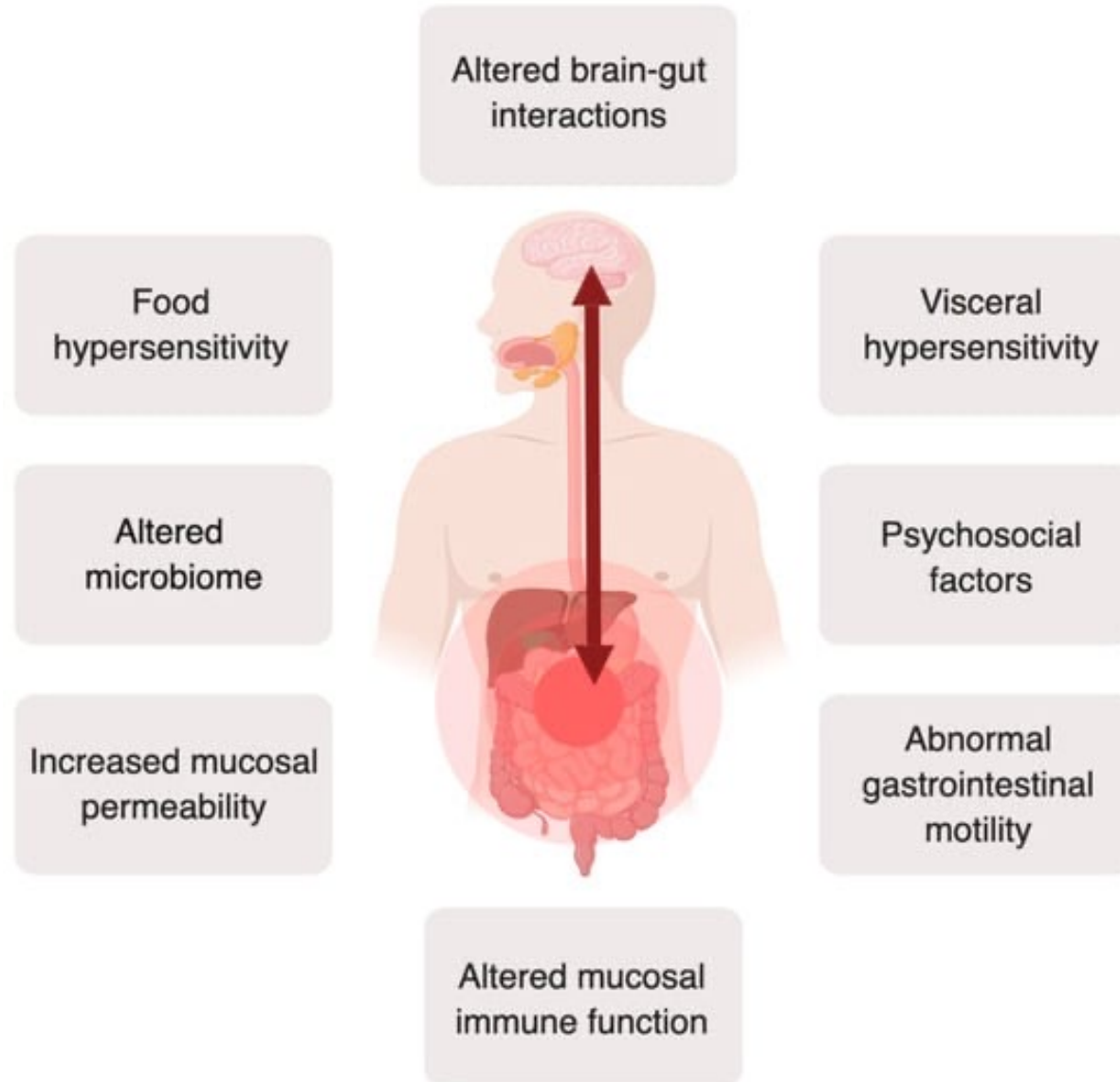
Rome IV Criteria

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

An overview of important pathophysiological factors in IBS



Alarming features

Blood in stools

More than 10% unintentional weight loss

Disease that wakes the patient up during the night

Fever

New onset of signs and symptoms after the 50th year of age Indians 45 years?

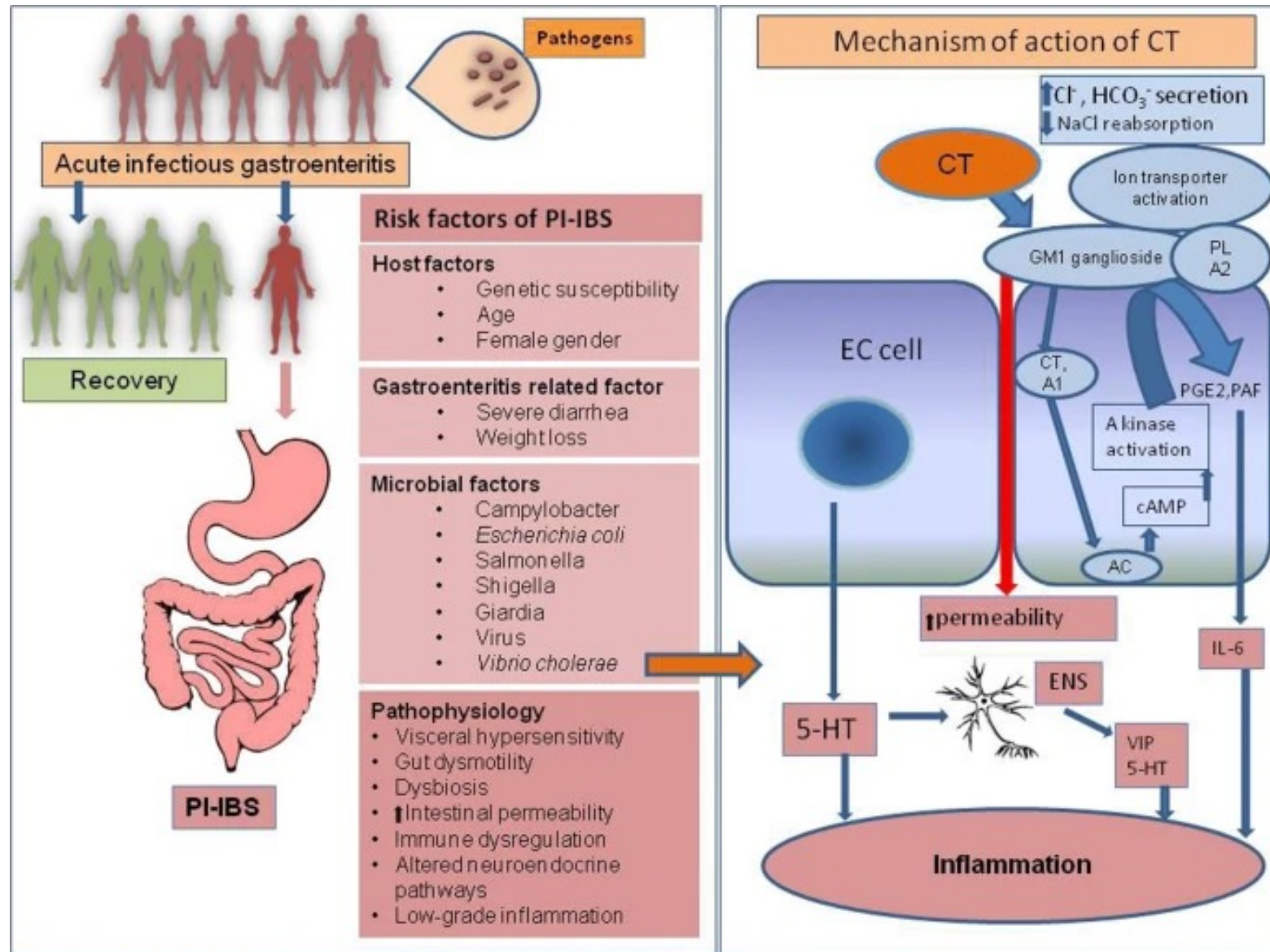
Family history of colorectal cancer, inflammatory bowel disease, or celiac disease

Indian Consensus on IBS in Adults

- Etiopathogenesis of IBS is multi-dimensional including gut-specific mechanisms, altered gut-brain interaction, food intolerance, psychosocial and genetic factors.
- Patients with IBS, particularly those with diarrhea-predominant IBS (IBS-D), are more likely to have SIBO and gut dysbiosis.
- Excessive methane production slows gut transit and is associated with constipation-predominant IBS (IBS-C).
- Gastrointestinal infection with varied pathogens may result in post-infection IBS (PI-IBS)
- COVID-19 may lead to post-COVID-19 IBS
- Probiotics may be helpful but more studies are needed.

Risk factors and pathophysiology of post-infection irritable bowel syndrome (PI-IBS)

Ghoshal, U. C., & Rahman, M. M. (2019). Post-infection irritable bowel syndrome in the tropical and subtropical regions: *Vibrio cholerae* is a new cause of this well-known condition. *Indian Journal of Gastroenterology*, 38, 87-94.



CT Cholera Toxin

Tropical Sprue

- Tropical sprue is a chronic diarrheal disease, possibly of infectious origin, that involves the small intestine and is characterized by malabsorption of nutrients, especially folic acid and vitamin B12.
- Tropical Sprue or post-infectious malabsorption (PI-MAS) has epidemiologic, clinical, and pathophysiological similarities with PI-IBS.

1. Singh, Prashant, and J. Thomas Lamont. "Tropical sprue."
2. Ghoshal, Uday C., et al. "Indian consensus statements on irritable bowel syndrome in adults: A guideline by the Indian Neurogastroenterology and Motility Association and jointly supported by the Indian Society of Gastroenterology." *Indian Journal of Gastroenterology* (2023): 1-25.

Table 6: Current symptom based management of IBS			
Symptom	First Line	Second Line	Future
Constipation	Fiber Osmotic laxative including polyethylene glycol Lactulose/Lactitol Stool softner eg, docusate	Bisacodyl Sodium picosulfate Tegaserod (withdrwan) Lubiprostone Linaclotide Prucalopride (5-HT4 agonist)	Elobixibat (ileal bile acid transporter inhibitor)
Diarrhea	Loperamide Diphenoxylate	Alosetron Ramosetron Ondasetron Bile acid sequestrant (cholestyramine, cholestipol) Rifaximin Clonidine	
Bloating	Treat constipation	Probiotic Antibiotic (rifaximin)	
Pain		Antispasmodics Anticholinergics Mebeverine Pinnaverium Otilonium bromide Antidepressant • Tricyclic anti-depressants • SSRI SNRI	

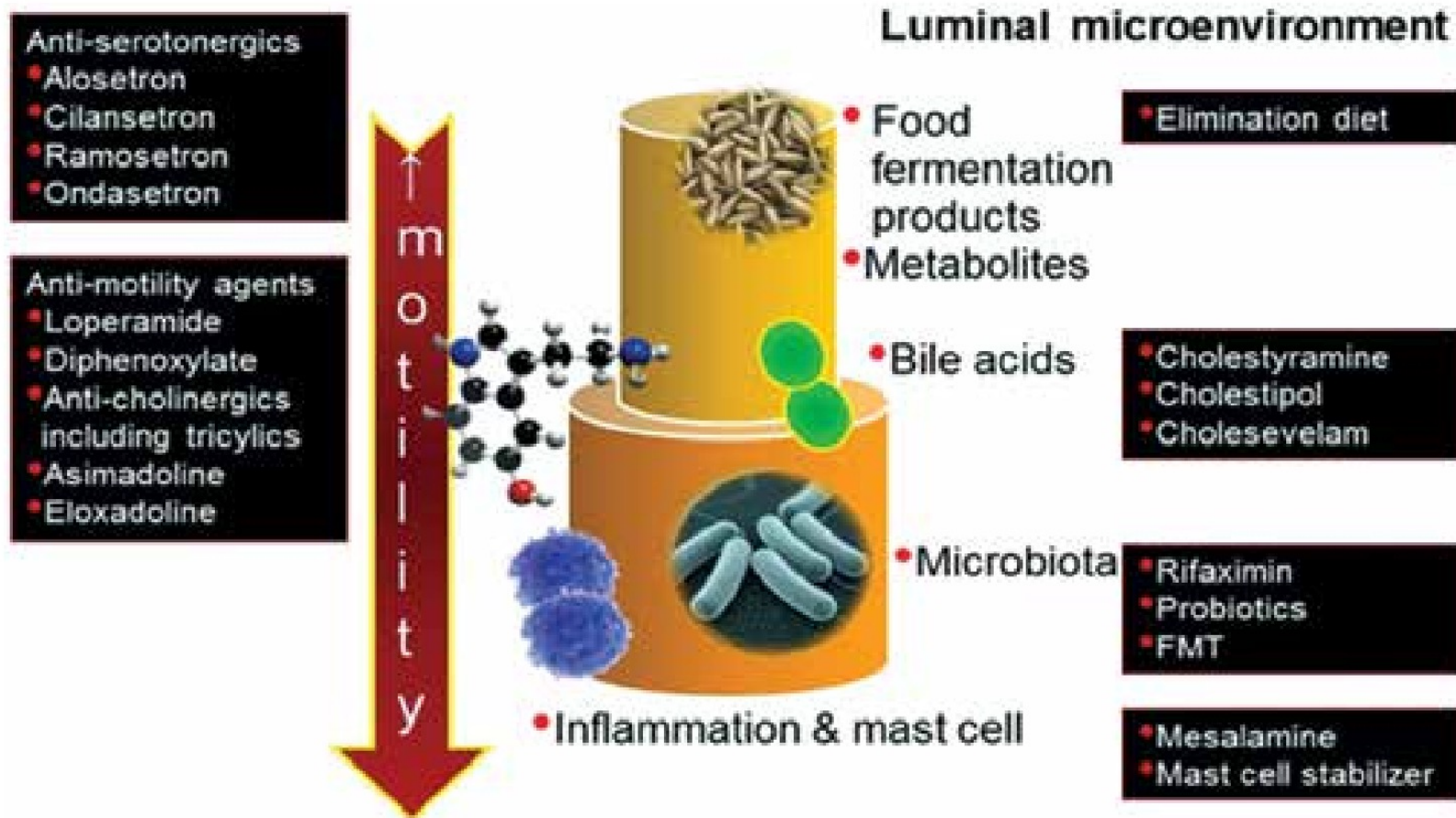
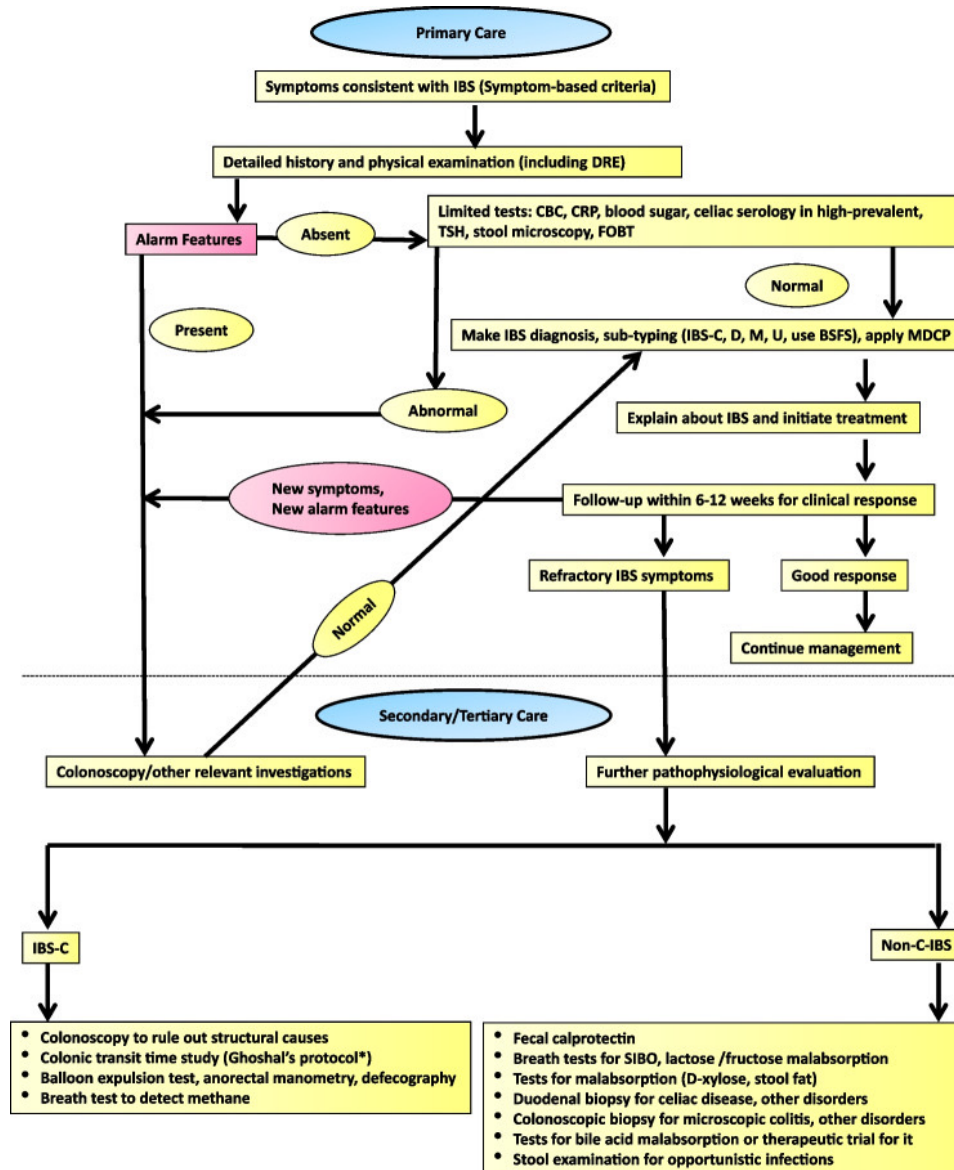


Fig. 2: Abnormalities in luminal micro-environment in diarrhea-predominant IBS, that are used as therapeutic targets with different pharmacological agents. Abbreviation used: FMT: fecal microbiota transplant (currently in experimental stage)

Algorithm of investigation of patients with irritable bowel syndrome.



How Are IBS And Small Intestinal Bacterial Overgrowth (SIBO) Related

SIBO is the presence of $\geq 10^3$ colony forming units per millilitre (CFU/mL) of **jejunal aspirate** on culture (or a positive hydrogen lactulose or glucose breath test.)

4-78 % of people with IBS have SIBO

Similar symptoms:

- ✓ Bloating
- ✓ Abdominal pain
- ✓ Nausea
- ✓ Constipation
- ✓ Diarrhea

How are IBS and SIBO related

- A positive hydrogen breath test is diagnostic of SIBO, which has been associated with diarrhea-predominant IBS (IBS-D) and IBS with mixed bowel habits (IBS-M).
- A positive methane breath test is indicative of methanogen overgrowth, which has been associated with constipation predominant IBS.

Migrating Motor Complex(MMC) and SIBO

- The feeding phase
- The fasting phase. Housekeeping waves. MMC. Occurs after digestion is complete, every 90-120 minutes. (Small frequent meals?)
- SIBO can increase gut transit time because of gasotransmitters like methane from methane-producing bacteria.

Conditions that may contribute to SIBO

- Scleroderma, diabetes mellitus, hypothyroidism, opioids, Parkinson's disease, multiple sclerosis can reduce gut transit time.
- Medications like PPIs, anticholinergics, antidiarrheals, and tricyclic antidepressants, NSAIDs.

Gasotransmitters

- Hydrogen, methane and hydrogen sulfide.
- IBS-C subjects had higher breath methane that correlated with higher gut microbial diversity and higher relative abundance of stool methanogens, predominantly *Methanobrevibacter*, as well as higher absolute abundance of *Methanobrevibacter smithii* in stool.
- IBS-D subjects had higher breath hydrogen that correlated with lower microbial diversity and higher breath hydrogen sulfide that correlated with hydrogen sulphide-producing bacteria, like *Fusobacterium* and *Desulfovibrio* species.

Methanogens

From SIBO to IMO.

- Intestinal Methanogen Overgrowth (IMO)
- Methanogens in excess in the intestine, not just small bowel.
- Methanogens are archea, not bacteria.

Should you do a breath test?

Breath Test	Treatment	Dosage	Symptoms
Hydrogen	Rifaximin	400 mg three times or 550 mg twice daily for two weeks	Bloating
Hydrogen Sulphide	Rifaximin + Bismuth	Bismuth 524 mg four times a day	Diarrhea, pain, and urgency.
Methane	Rifaximin + Neomycin/ Metronidazole	Neomycin 500 mg twice a day for 14 days. Metronidazole: 250 mg three times a day after food. 10-14 days.	Constipation

Is IBS An Autoimmune Problem?

Post infection IBS

1. Antibodies against Cytolethal Distending Toxin B
2. Anti Vinculin Antibody

Good to differentiate IBS-D and IBD

High Anti-vinculin antibody, more difficult to treat

Good to know “it’s not all in your head”

Small Intestinal Fungal Overgrowth (SIFO)

SIFO

- Small intestinal fungal overgrowth (SIFO) is characterized by the presence of excessive number of fungal organisms (mostly Candida) in the small intestine associated with gastrointestinal (GI) symptoms.
- Diagnosed by small bowel aspirate.
- The most common symptoms observed in these patients were belching, bloating, indigestion, nausea, diarrhea and gas.
- Treatment: Fluconazole or nystatin for 2-3 weeks.
- Higher in the immunocompromised and PPI users.
- SIBO and SIFO may be present at the same time.

MAST CELL ACTIVATION SYNDROME (MCAS)

Mast Cell Activation Syndrome (MCAS)

Table 1 Gastrointestinal symptoms in mast cell activation syndrome

Gastrointestinal symptom	Frequency (%)
Nausea ± vomiting	57
Heartburn	50
Abdominal pain	48
Atypical chest pain	40
Alternating diarrhea and constipation	36
Esophageal dysphagia	35
Oral symptoms or sores	30
Diarrhea	27
Constipation	14

Data adapted from reference 1

Weinstock, Leonard B., et al. "Mast cell activation syndrome: a primer for the gastroenterologist." *Digestive Diseases and Sciences* 66 (2021): 965-982.

ORGAN AND SYSTEM INVOLVEMENT IN MAST CELL ACTIVATION SYNDROME

Organ/system	Symptom/finding
Constitutional	Fatigue, fevers, weight loss or gain
Eyes, ears, nose, throat	Conjunctivitis, tinnitus, hearing loss, rhinitis, sinusitis, sore throat
Neurologic	Headaches, migraines, brain fog, anxiety, flushing, nausea
Cardiovascular	Chest pain, palpitations, hypotension
Urogenital	Frequency, urgency, dysuria
Esophageal	Heartburn, dysphagia, globus, chest pain
Stomach	Dyspepsia
Small and large intestine	Abdominal pain/discomfort, diarrhea, constipation
Hepatic	Elevated transaminases, hepatomegaly
Salivary glands	Swelling
Lymphatics	Lymphadenopathy
Dermatologic	Flushing, pruritus, urticaria, rashes
Musculoskeletal	Myalgia, arthralgia, edema

TREATMENT OF MAST CELL ACTIVATION SYNDROME

Intervention	Timing	Frequency	Examples
Avoidance of known triggers	First line	Daily	Stress, heat, alcohol
Diet interventions	First line	Daily	Low histamine and gluten free
Histamine (H ₁) antagonist levocetirizine, loratadine	First line	BID	Cetirizine, fexofenadine,
Histamine (H ₂) antagonist	First line	BID	Famotidine, ranitidine, cimetidine, nizatidine
Leukotriene receptor antagonist	First line	Daily—BID	Montelukast
Treatment of comorbid conditions	First line	Daily	POTS, EDS
Flavonoid	First line	Daily—BID	Quercetin, luteolin
Mast cell stabilizer	Second line	QID	Cromolyn sodium ^{a, b}
Second-generation H ₁ antagonist	Third line	Daily—BID	Ketotifen ^c
Monoclonal antibody	Fourth line	q4 weeks	Omalizumab ^{d, e}

Diabetes And The Gut

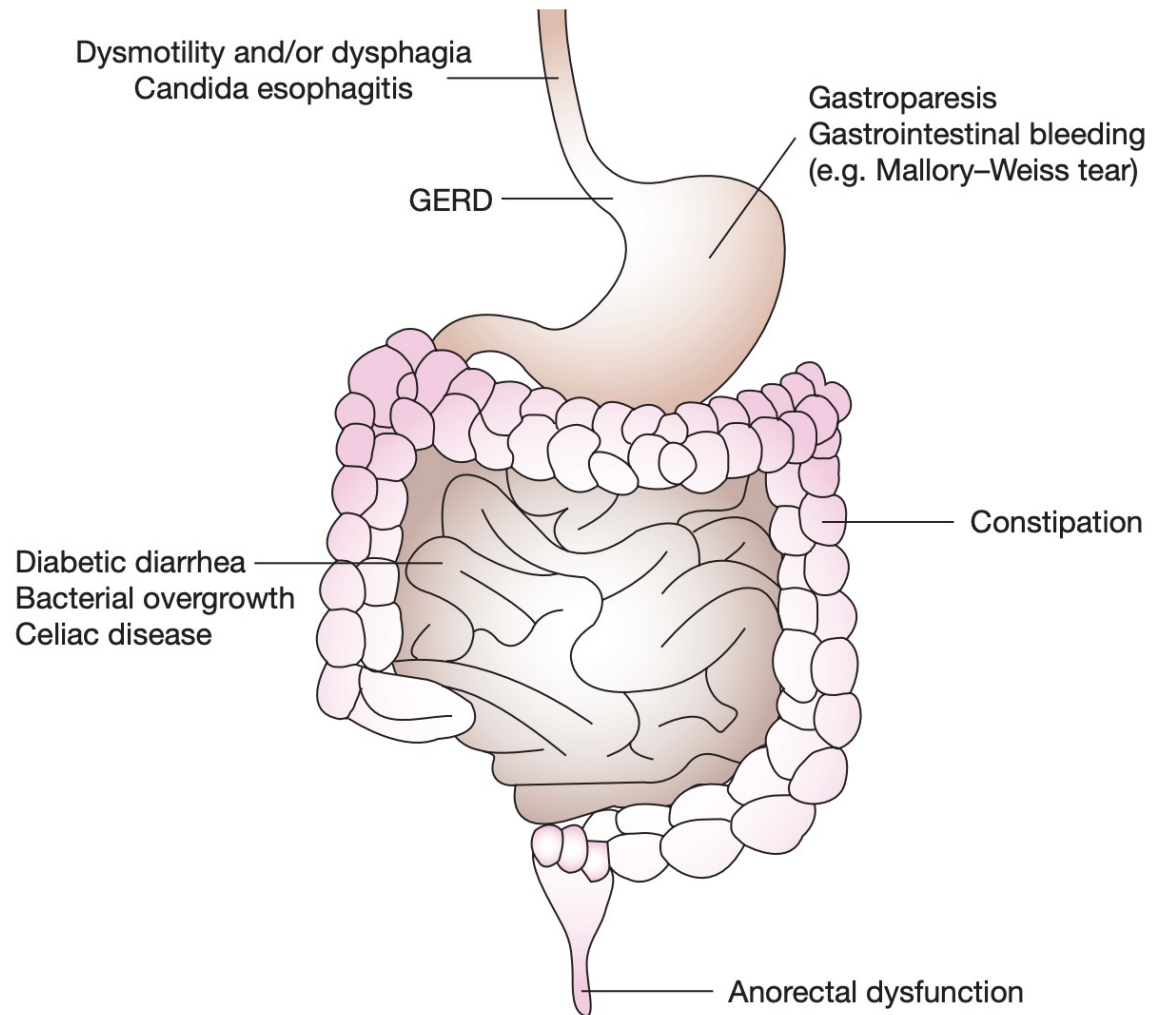


Figure 1 Gastrointestinal complications associated with diabetes.

Diabetes And The Gut

1. Gastroparesis: Delayed gastric emptying.
 - Symptoms: nausea, vomiting, reduced appetite, feeling full after eating small amounts of food, abdominal pain, and heartburn, excessive vomiting.
 - Damage to vagus nerve.
2. Diabetic autonomic neuropathy
3. Medications: Metformin, GLP-1 analogues.
4. Use of artificial sweeteners.
5. Esophageal dysmotility

Why do these changes occur?

- Hypo-and hyper-glycemia
- Autonomic neuropathy
- Not always related to duration of disease
- Enteric myopathy and neuropathy.
- Autoimmune damage
- Metabolic insults that alter critical cellular pathways and essential trophic factor signalling, resulting in smooth muscle atrophy and neural apoptosis
- Possibly trans-differentiation of tissue (i.e. the transformation of one cell type to another).
- Ischemia and hypoxia from microvascular disease of the gastrointestinal tract
- Mitochondrial dysfunction
- Formation of irreversible advanced glycation end products peroxynitrite--mediated endothelial and enteric neuron damage.

Case

Management

- Rule out major disease (Alarm signals)
- Elimination diet. No gluten, no grains
- Low carb food
- Early dinner, TRE.
- Stop snacking
- Sleep
- Correct nutrient depletions
- Rifaximin, Bismuth, Neomycin, Metronidazole, Erythromycin 100 mg
- Probiotics?
- Peppermint Oil
- Melatonin
- Know when to refer

Melatonin in IBS

- Melatonin 6 mg daily (3 mg fasting and 3 mg at bedtime) for 2 months (8 weeks) was compared to placebo.
- Saha, 2007: 3 mg Melatonin at bedtime, small sample size.

1. Faghih Dinevari, M., Jafarzadeh, F., Jabbaripour Sarmadian, A. *et al.* The effect of melatonin on irritable bowel syndrome patients with and without sleep disorders: a randomized double-blinded placebo-controlled trial study. *BMC Gastroenterol* **23**, 135 (2023). <https://doi.org/10.1186/s12876-023-02760-0>
2. Saha, Lekha, et al. "A preliminary study of melatonin in irritable bowel syndrome." *Journal of clinical gastroenterology* 41.1 (2007): 29-32.

References

- Cash, Brooks D., Michael S. Epstein, and Syed M. Shah. "A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms." *Digestive diseases and sciences* 61 (2016): 560-571.
- Suarez, Fabrizis L., et al. "Bismuth subsalicylate markedly decreases hydrogen sulfide release in the human colon." *Gastroenterology* 114.5 (1998): 923-929
- Sellin, Joseph H., and Eugene B. Chang. "Therapy insight: gastrointestinal complications of diabetes—pathophysiology and management." *Nature clinical practice Gastroenterology & hepatology* 5.3 (2008): 162-171.
- Erdogan, Askin, and Satish SC Rao. "Small intestinal fungal overgrowth." *Current gastroenterology reports* 17.4 (2015): 1-7.
- Pimentel, Mark, et al. "Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects." *PLoS One* 10.5 (2015): e0126438.
- Weinstock, Leonard B., et al. "Mast cell activation syndrome: a primer for the gastroenterologist." *Digestive Diseases and Sciences* 66 (2021): 965-982.
- Book *The Microbiome Connection: Your Guide to IBS, SIBO, and Low-Fermentation Eating* by Mark Pimentel, Ali Rezaie
- Book *The Inside Tract Your Good Gut Guide to Great Digestive Health* by Gerard E. Mullin
- <https://tmsforcure.org/what-are-mast-cell-diseases/>