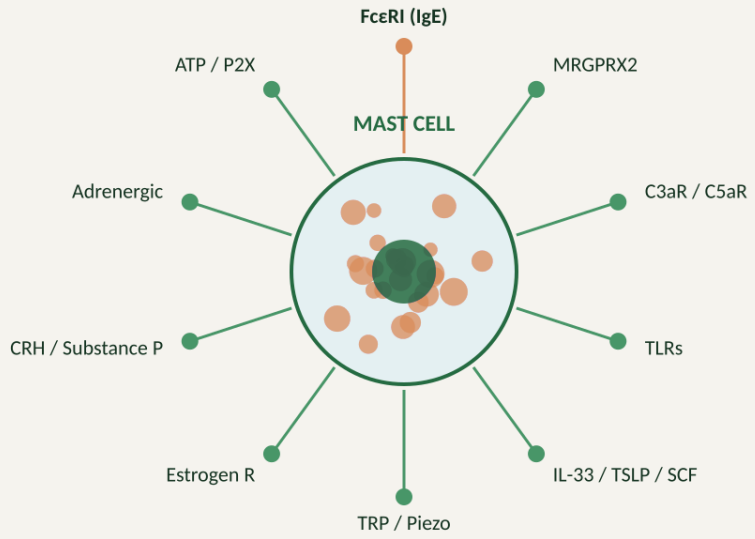
Clinical presentation of MCAS in GI practice

ZACHARY SPIRITOS MD, MPH



ROADMAP

Where we are going

How we got here	What mast cells really are, and the IBS data
Recognize it	Hypermobility first, then the story and symptoms
Diagnosis	The criteria, the tests, and what not to miss
Diet	A personalized approach, and the FODMAP data
Medications	Tailored to what's driving symptoms
Putting it together	Sequencing, and going low and slow

01

How we got here

Why the mast cell belongs in the IBS conversation

THE TRADITIONAL DEFINITION

IBS names the symptoms.

Not the mechanism.

Rome IV

Recurrent abdominal pain ≥ 1 day/week, with a change in stool frequency or form

Biopsies look normal

No structural damage, no biomarker

Visceral hypersensitivity

The defining physiology

So, what turns up the gain?

The window into the mast cell

Lacy BE, et al. Gastroenterology 2016 · Mertz H, et al. Gastroenterology 1995

A QUICK RESET

Mast cells are more than allergy cells

HOW MOST OF US WERE TAUGHT

The allergy cell

- Allergen → IgE → FcεRI → degranulation
- Hives, hay fever, asthma, anaphylaxis
- If IgE and skin testing are normal, it isn’t the mast cell

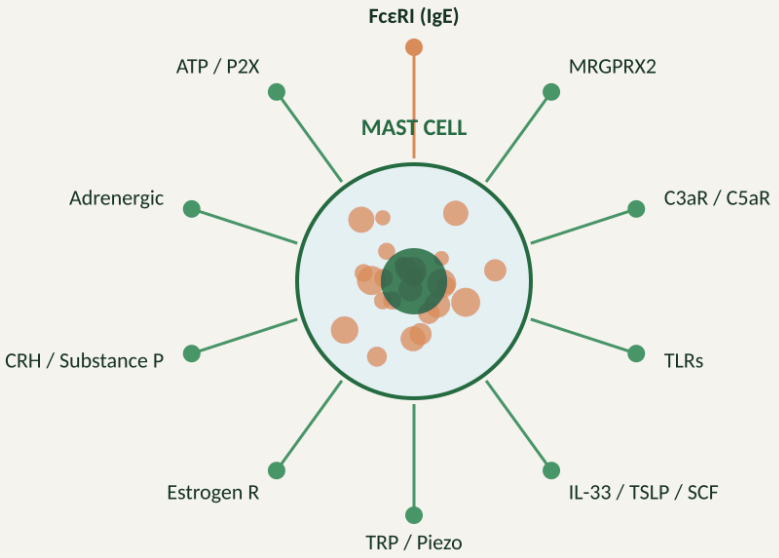
WHAT THEY REALLY ARE

Sentinels at every barrier

- Live in tissue just under the gut, skin and airway lining — not floating in blood
- Coordinate wound healing and the wider immune response
- Sit beside nerves and talk to them constantly
- Fire through a dozen non-IgE pathways

NOT JUST AN IGE STORY

A sensor for the world around it



Stretch	Piezo and TRP channels — a big meal, gas, distension
Temperature	TRP channels — hot showers, cold air, heat
Hormones	Estrogen activates; progesterone calms — cycle flares
Stress	CRH, adrenaline, substance P — a hard week
Drugs and additives	MRGPRX2 — opioids, fillers, dyes
Microbes and damage	TLRs, complement, IL-33 from injured lining

Redegeld FA, et al. Immunol Rev 2018 · Halova I, et al. Immunol Rev 2018

THE PLAIN DATA

More mast cells in IBS — and busier ones

+181%

more colonic mucosa occupied by mast cells

77%

of IBS patients above every healthy control

3.7×

more tryptase released by biopsies

+101%

more histamine released

Barbara G, et al. Gastroenterology 2004;126:693 · Robles A, et al. NGM 2019 · Bashashati M, et al. NGM 2018

WHY THESE THREE STUDIES MATTER

From association to cause to treatment

STUDY	WHAT THEY FOUND	WHY IT MATTERS
Barbara 2004	Mast cells cluster near colonic nerves — the closer they sit, the more severe and frequent the pain	It isn't just how many mast cells — it's where they are
Buhner 2009	Fluid from IBS biopsies fired ~58% of human gut neurons; blocking H1, proteases and 5-HT_3 stopped it	Mast-cell products alone are enough to excite gut nerves
Wouters 2016	Ebastine (an H1 blocker) 20 mg × 12 weeks: relief in 46% vs 13% on placebo, with lower pain scores	Block the mediator and the pain drops — a treatable target

Gastroenterology 2004;126:693 · 2009;137:1425 · 2016;150:875

THE HALLMARK OF IBS

How mast cells create visceral hypersensitivity



Mast cells sit right next to sensory nerves in the gut wall

They release histamine, which binds H1 receptors on the nerve

H1 sensitizes TRPV1, the nerve's heat-and-pain sensor

Normal stretch from food, gas or stool now registers as pain

In plain terms: the gut isn't damaged — the volume is turned up. TRPV1 responses are stronger in IBS nerves, and IBS tissue sensitizes TRPV1 through H1, while healthy tissue does not.

Wouters MM, et al. Gastroenterology 2016;150:875–87

CLOSING THE LOOP

The drugs we've used for years are mast-cell drugs

Amitriptyline

Best-evidenced IBS drug…and a potent H1 antihistamine that also damps stress signaling

Mirtazapine

Strongly antihistaminic at low dose which helps nausea, early satiety, appetite and sleep

Cyproheptadine

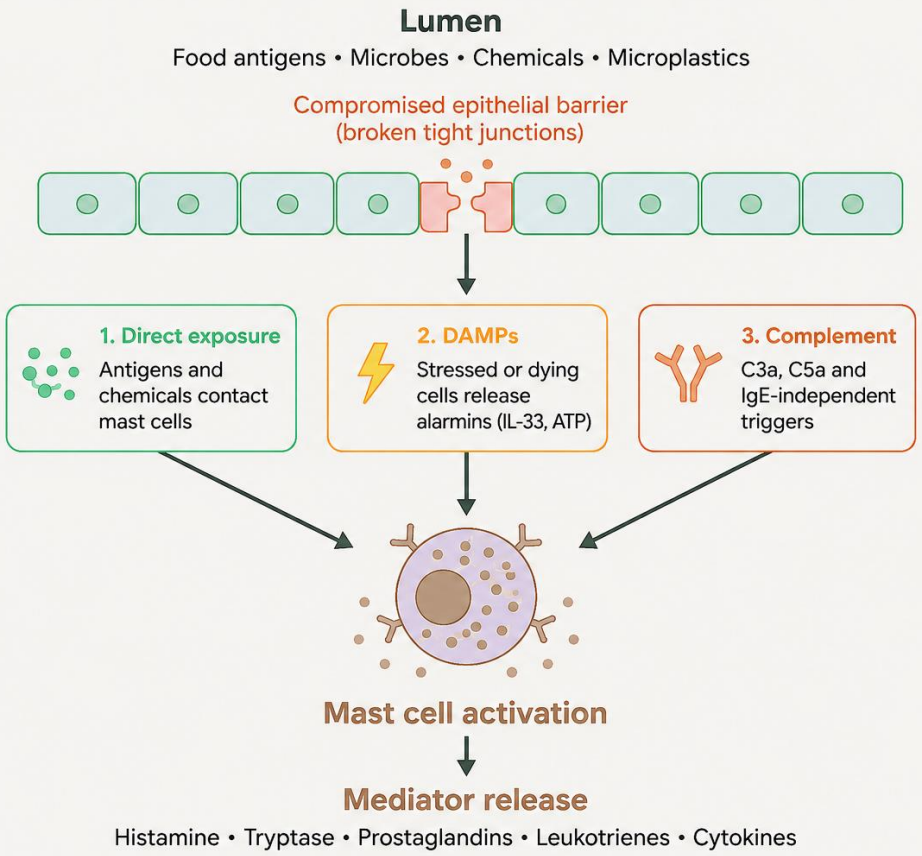
H1 + serotonin blocker — functional abdominal pain, dyspepsia and nausea

H1 antihistamines

Ebastine reduced IBS pain in a randomized trial

Ford AC, et al. Lancet 2023 · Rodriguez L, et al. J Pediatr 2013 · Wouters MM, et al. Gastroenterology 2016

Why they're activated: a leaky barrier



The gut is the largest barrier — and the densest field of mast cells.

When the lining leaks, food proteins, microbes and danger signals reach the mast cell all day.

Once primed, the threshold drops — heat, weather, hormones and stress become triggers.

Akdis CA. Nat Rev Immunol 2021 · Halova I, et al. Immunol Rev 2018

ONE CELL, MANY MEDIATORS

What mast-cell mediators do to the gut

Sensitivity	Gut nerves fire more easily — normal stretch is felt as pain
Motility	Faster or slower transit — urgency, diarrhea, constipation, stasis
Secretion	More acid, fluid and mucus
Barrier	Looser tight junctions — a leakier lining that causes systemic symptoms, too

MEDIATORS INVOLVED

Histamine · tryptase and other proteases · prostaglandin D_2 · leukotrienes · cytokines · nerve growth factor · PAF

Released together, acting together — no one mediator maps to one symptom.

02

Recognize it in clinic

Start with hypermobility — then listen for the pattern

STEP ONE

Consider starting with hypermobility

The Beighton misses many

Problem joints aren’t scored, and patients stiffen with age

Some are “stiff as a board”

Muscles guard what ligaments can’t hold

Look for the guarding

Tight neck, trapezius and jaw · a hypertonic pelvic floor

Ask about the pelvic floor

Incomplete evacuation, straining, dyspareunia, “can’t relax it”

THE COMPANY IT KEEPS

Hypermobility rarely travels alone

~40%

of hEDS patients have POTS

58–100%

have small-fiber neuropathy on skin biopsy

12–22%

have gastroparesis

Cazzato D, et al. Neurology 2016 · Gazit Y, et al. Am J Med 2003 · Nelson AD, et al. NGM 2015

THE ARC WE HEAR

It starts with the story

1

Always sensitive

Foods, meds, scents — often told it's anxiety

2

A tipping event

Postpartum, infection, mold, a hard year

3

Tolerance narrows

Leftovers, heat, smells, fillers

4

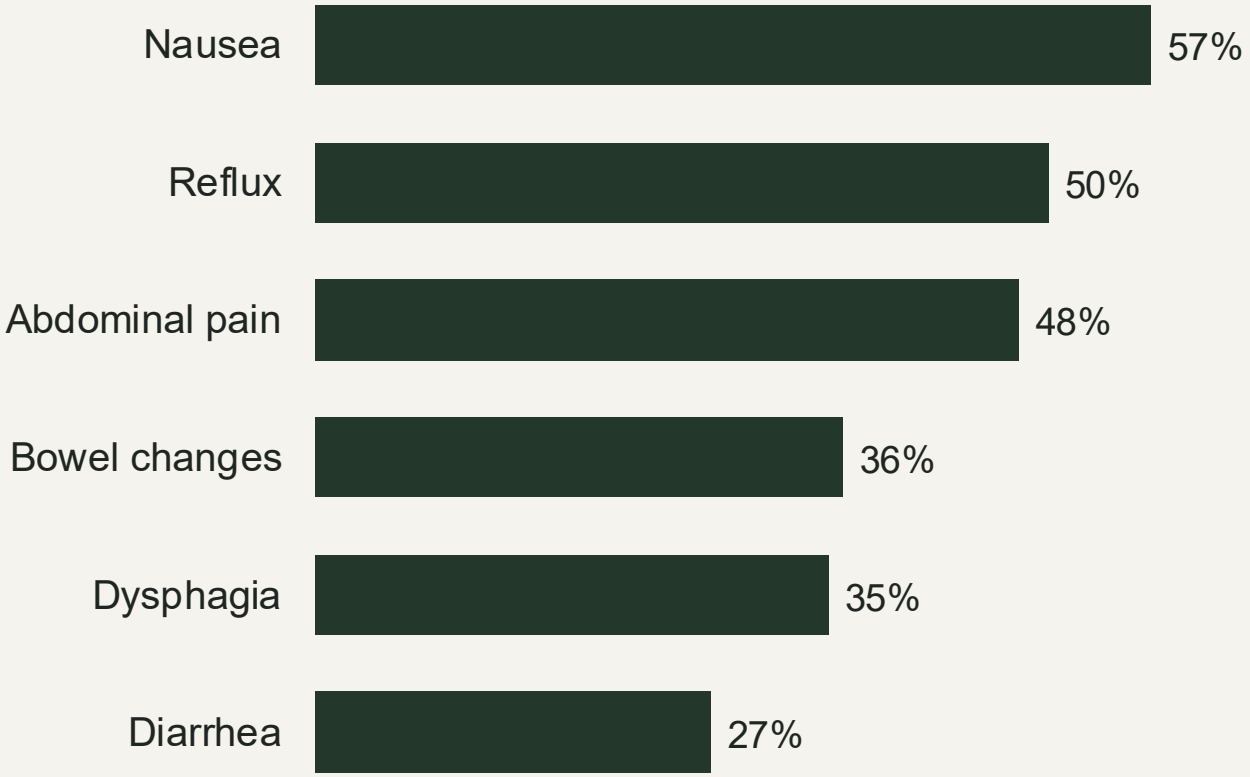
The loop tightens

Anxiety about symptoms creates more symptoms; confidence shrinks and triggers hit harder

"I never used to react to anything — now everything sets me off."

WHAT SHOWS UP IN GI CLINIC

The GI picture



The gut can be the only — or the loudest — expression of mast-cell disease

Some patients have purely GI disease, with no systemic symptoms at all.

Afrin LB, et al. Characterization of mast cell activation syndrome. Am J Med Sci 2017;353:207–15 (n = 413)

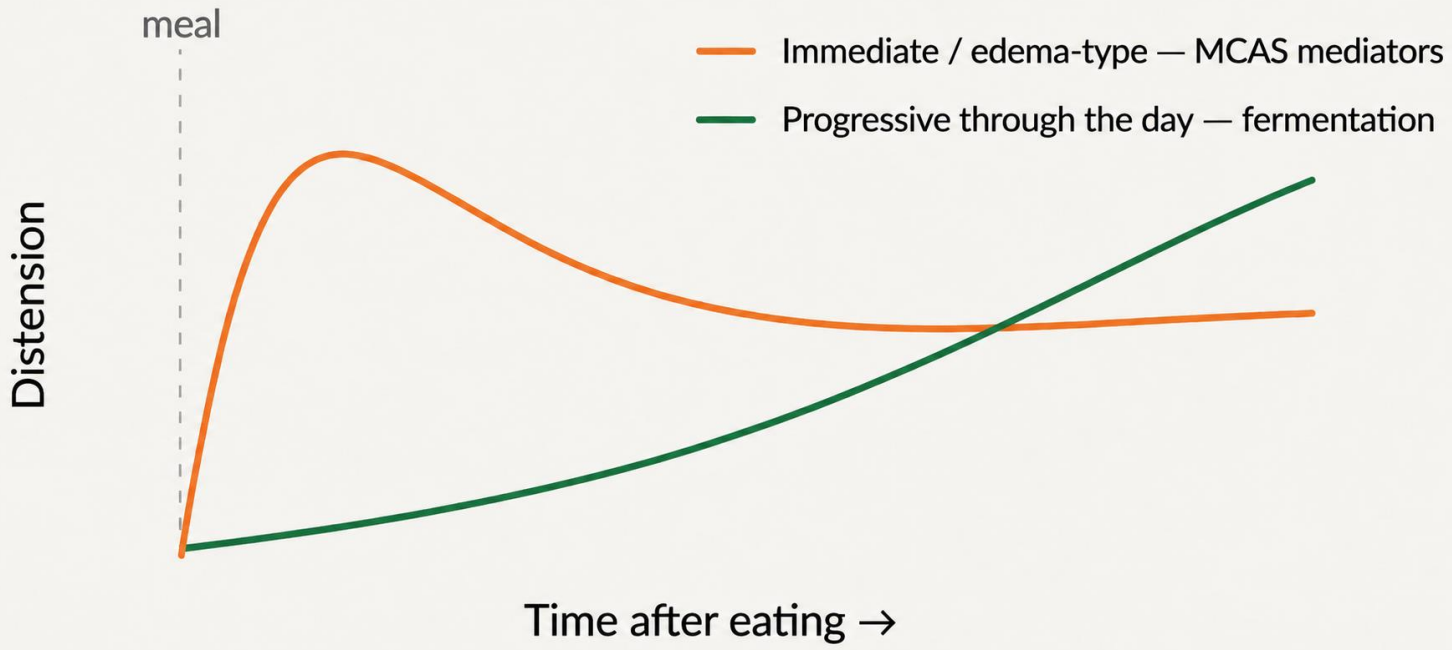
CLINICAL CUES

Five things that should make you think mast cell

PPI-refractory heartburn	Burning that doesn’t track with acid — H2 blockade often beats a bigger PPI
Bloating within minutes	“I look pregnant after I eat,” almost regardless of the food
Nausea apart from meals	Chronic and central — CNS and brainstem mast cells
Bowels that alternate	Diarrhea and constipation, often with pelvic-floor guarding
A shrinking diet	“I can only eat chicken and rice”

READ THE TIME-COURSE

Two very different kinds of bloating



Within minutes

A mediator response, like localized edema — often labeled abdominophrenic dyssynergia

Builds over hours

Fermentation — SIBO, SIFO, fructose or sucrase-isomaltase problems, 4–6 h after the trigger

A RELATIONSHIP TO UNTANGLE

SIBO is common in MCAS — and often downstream

~31%

of MCAS patients were SIBO-positive on lactulose breath testing

Why it happens	Mediators and small-fiber injury slow the small bowel → stasis → overgrowth
What we see	Antibiotics help briefly, then symptoms return within days to weeks
How to discern	Late, progressive bloating favors SIBO; immediate bloating favors mast cells
What to do	Treat it — and treat the motility and mast cells driving it

Weinstock LB, et al. Am J Gastroenterol 2019;114:S675 (abstract) · Weinstock LB, et al. Dig Dis Sci 2021;66:965–82

ASK BEYOND THE GUT

It’s rarely just the gut

Skin	Flushing, itching, hives, dermatographism
Neurologic	Brain fog, headaches, insomnia, anxiety, sensory sensitivity
Cardiovascular / autonomic	Palpitations, presyncope, temperature dysregulation
Respiratory	Throat tightness, air hunger, congestion
Musculoskeletal / pelvic	Migratory joint pain, bladder and pelvic pain
Constitutional	Fatigue; flu-like malaise during flares

The clue is the pattern: symptoms that hop between systems and flare with triggers.

03

Diagnosis

A clinical diagnosis, with honest use of the tests

HOW I DIAGNOSE IT

MCAS is a clinical diagnosis.

The history, hypermobility, the pattern of triggers, and response to treatment outweigh any single lab.

HOW MCAS IS DEFINED

Two consensus frameworks

CONSENSUS-1 · VALENT 2012

Strict and specific

- Episodic symptoms of mediator release in ≥ 2 organ systems
- Objective lab proof during a flare — tryptase rise of ≥ 20% + 2 ng/mL over baseline
- Response to mast-cell-directed therapy
- Endorsed by AAAAI, highly specific, but misses many patients

CONSENSUS-2 · AFRIN / MOLDERINGS 2021

Broader and clinical

- Chronic or recurrent multisystem symptoms of mast-cell activation
- Accepts a wider range of mediators — and tissue evidence — not just tryptase
- Weights the overall picture and therapeutic response
- Requires no better explanation for the symptoms

Valent P, et al. Int Arch Allergy Immunol 2012;157:215–25 · Afrin LB, et al. Diagnosis (Berl) 2021;8:137–52

TESTING

Helpful when positive, silent when negative

Serum tryptase	Best for flagging mastocytosis or HαT; peaks 1–2 h after a flare
Plasma histamine	Half-life of minutes; strict handling
24-h urine N-methylhistamine	A more stable histamine metabolite
24-h urine LTE_4	If high, supports a leukotriene-directed trial
24-h urine PGD_2 metabolite	If high, supports a COX-directed trial

A positive test validates and can guide therapy. A negative test doesn't rule MCAS out — over 1,300 mediators, only a handful measurable.

DON'T MISS

Before you call it MCAS

CONDITION	THINK OF IT WHEN	NEXT STEP
Mastocytosis or HαT	Baseline tryptase ≥ 8, bone pain, skin lesions	KIT D816V in blood; TPSAB1 copy number
Celiac disease	There is an adverse reaction to gluten	tTG-IgA with total IgA
Eosinophilic GI disease	GI symptoms not answering mast-cell therapy	Biopsies, including normal-looking mucosa
Carcinoid	Flushing and diarrhea without other mast-cell features	Chromogranin A, 24-h urine 5-HIAA
Autoinflammatory disease	True fevers, rashes, serositis; CRP up during attacks	Labs during an attack; autoinflammatory gene panel
HAE with normal C1-INH	Deep, non-itchy swelling or abdominal attacks; no antihistamine response	Think bradykinin; HAE gene testing, specialist

04

Diet

Listen first — then match the approach to the story

A PERSONALIZED APPROACH

Listen first, then match the diet to the story

WHAT YOU HEAR	WHAT TO DISCUSS	HOW
“Bread and pasta wreck me”	A gluten-free trial	Celiac serology, and remove gluten
Leftovers, wine, aged cheese, cured meats	A low-histamine trial	2–4 weeks, then reintroduce one food at a time
Gas and distension with onion, garlic, beans	Low-FODMAP Start with fructans + GOS	Elimination trial and always reintroduce
Already down to a few safe foods	No new restriction	Expand with a dietitian; medications to cover reintroduction

Not an algorithm — one change at a time, guided by the patient’s own pattern.

TRIGGER IDENTIFICATION

Low-histamine, done simply

Pull back

Aged cheese, fermented foods, cured and deli meats, smoked or canned fish, alcohol

Watch the liberators

Citrus, tomato, spinach, chocolate, walnuts and cashews

Mind the leftovers

Histamine builds even in the fridge — cook fresh, freeze immediately

Then reintroduce

One food at a time, after 2–4 weeks

Low-FODMAP may calm mast cells, not just gas

THE OLD MODEL

A plumbing problem

- FODMAPs are poorly absorbed and fermented
- Fermentation makes gas and pulls in water
- A sensitive gut feels the stretch

THE MAST-CELL MODEL

An immune trigger

- Stretch itself fires mast cells through Piezo channels
- High-FODMAP intake raises luminal LPS (endotoxin)
- LPS trips TLR4 on mast cells → leaky barrier and primed nerves
- Removing FODMAPs calms the mast cell, not just the gas

THE DATA

What happens to mast cells on low-FODMAP

STUDY	DESIGN	FINDING
McIntosh · Gut 2017	IBS RCT: low vs high FODMAP for 3 weeks	~8-fold lower urinary histamine on low-FODMAP
Hustoft · NGM 2017	IBS, low-FODMAP then blinded re-challenge	Lower IL-6 and IL-8, microbiome shift
Singh · JCI Insight 2021	Mice fed high-FODMAP for 14 days	↑ fecal LPS, mast-cell activation, barrier loss — absent in mast-cell–deficient mice
Singh · Gastroenterology 2025	IBS-D, 4 weeks low-FODMAP (42 completers)	Responders had fewer, calmer colonic mast cells, lower histamine and tryptase, better barrier

THE GUARDRAIL

The goal is a bigger diet, not a smaller one.

Watch for fear-driven restriction (ARFID). Bring in GI psychology and a dietitian early.

05

Medications

Tailored to what’s driving the symptoms

TAILOR IT

Match the medication to what's going on

Reflux, broad mediator symptoms	H2 + H1 antihistamines
Food intolerance, cramping, loose stools	Cromolyn, ketotifen
Distension, food intolerance, brain fog	Low-dose GIP/GLP-1
Bloating with FODMAPs	FODZYME at the meal
Very pain-predominant	Neuromodulators — once compression is excluded
Stress-driven flares	CRH–mast cell axis → stress management, GI psychology

ANTIHISTAMINES

Start with H1 and H2 blockade

Step 1

Famotidine

40 mg BID × 14 days; keep if ≥ 25% better; nizatidine if not

Step 2

Add cetirizine

20 mg BID; fexofenadine by day if sedating

Step 3

Rotate H1s

Levocetirizine, fexofenadine, desloratadine — 14 days each

When needed

First-generation

Hydroxyzine for sleep · cyproheptadine for nausea

Ketotifen and cromolyn

KETOTIFEN · STABILIZER + H1

Cramping, diarrhea, allergy

- Diarrhea and cramping, brain fog, mast-cell insomnia
- Also covers allergic-type symptoms: flushing, itch, rhinitis
- Compounded: 0.5 mg qHS → 1 mg qHS → 1 mg BID → 2 mg BID
- Sedating — avoid when fatigue is profound

CROMOLYN · WORKS WHERE YOU PUT IT

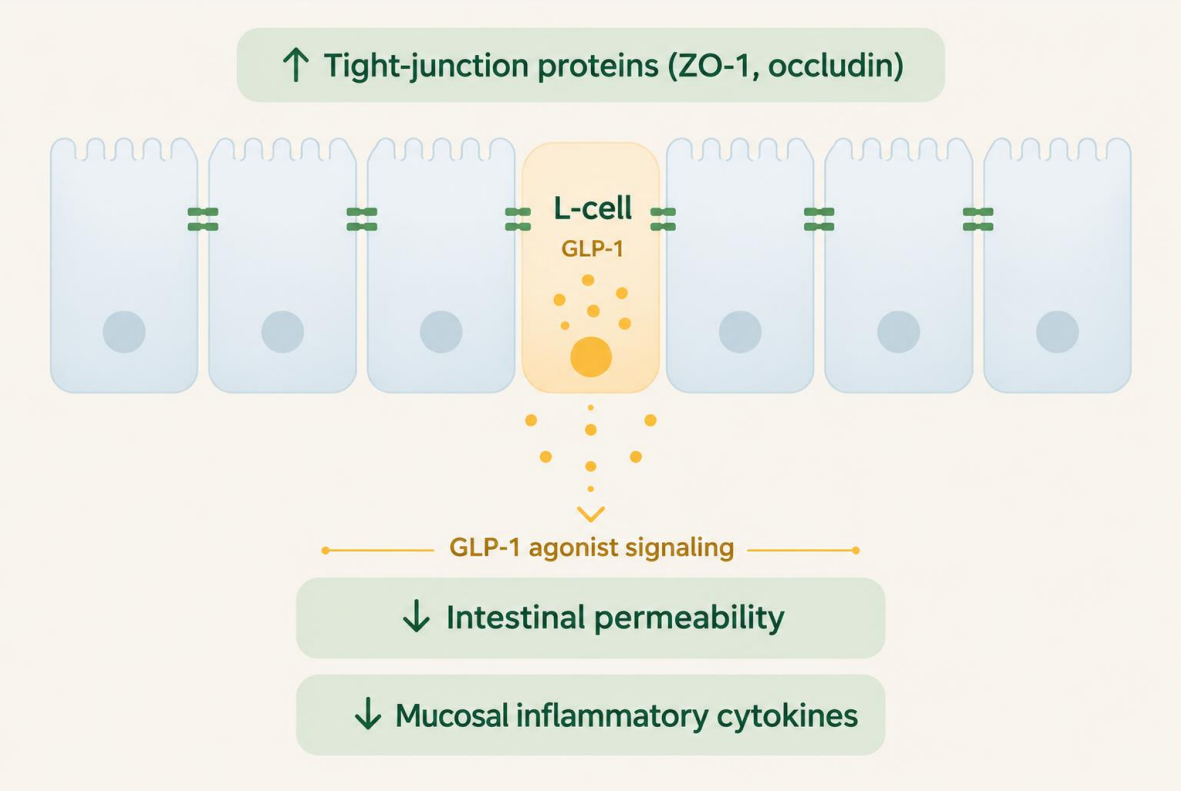
Food intolerance, loose stools

- Not absorbed — acts on the proximal gut mucosa
- Post-meal symptoms and food reactions; covers reintroduction
- ½ vial daily → 100 mg TID → up to 200 mg TID
- Can flare the first 2–5 days; 4–6 weeks for full effect

Klooker TK, et al. Gut 2010;59:1213–21 · Lobo B, et al. UEG J 2017;5:887–97

GOING UPSTREAM

Low-dose GIP/GLP-1 for the gut-driven patient



Who it helps

Food intolerances, immediate distension, reactive hypoglycemia, brain fog

Dose

Tirzepatide 0.25 mg weekly; Semaglutide 0.025 mg weely; check in every 3 weeks and titrate

Cautions

Screen for eating disorders; set weight-loss stop rules up front

Off-label. Barrier data: Wang W, et al. Aging 2023 · Holst JJ. Physiol Rev 2007

A PRACTICAL TOOL FOR BLOATING

FODZYME at the meal

Fructan hydrolase	Fructans — wheat, onion, garlic
α-galactosidase	GOS — beans, lentils, chickpeas
Lactase	Lactose — dairy

For bloating and distension from the two most common FODMAP offenders — so patients can keep foods instead of cutting them.

Sprinkled on food at the meal. Doesn’t cover fructose or polyols, and doesn’t work after symptoms start.

Enzyme composition per Kiwi Biosciences product information; supportive data are early

WHEN IT'S VERY PAIN-PREDOMINANT

Then reach for neuromodulators

DRUG	DOSE	WHY THIS ONE
Cyproheptadine	2 mg BID → up to 8 mg TID	H1 + 5-HT_2 block; pain, nausea, sedating
Amitriptyline	10 mg qHS → 25–50 mg	Best evidence (ATLANTIS), potent H1; caution in POTS
Nortriptyline	10 mg qHS → 25–50 mg	Similar analgesia, less sedation and tachycardia
Duloxetine	20–30 mg → 60 mg daily	When anxiety is prominent or POTS is poorly controlled
Mirtazapine	15 mg qHS → 7.5 mg qHS	Nausea, early satiety, appetite, sleep

Pair with GI psychology — and make sure compression isn't the cause. Refractory: memantine, oxcarbazepine.

Ford AC, et al. Lancet 2023 · Drossman DA, et al. Gastroenterology 2018 · Rodriguez L, et al. J Pediatr 2013

BEFORE CALLING IT VISCERAL HYPERSENSITIVITY

Make sure compression isn’t present

MEDIAN ARCUATE LIGAMENT SYNDROME

MALS

- Post-meal epigastric pain, sometimes with exercise
- Food fear and weight loss
- Epigastric bruit that changes with breathing
- Duplex ultrasound with inspiration/expiration, or CTA

SUPERIOR MESENTERIC ARTERY SYNDROME

SMAS

- Post-meal pain, early satiety, nausea, bilious vomiting
- Weight loss shrinks the fat pad — a vicious cycle
- Relief lying on the left side or knee-to-chest
- CT/MR angiography: narrow aortomesenteric angle and distance

Pain you can set your watch to after meals — think compression before calling it visceral hypersensitivity.

Kim EN, et al. JAMA Surg 2016 · Milunsky A, et al. Am J Med Genet A 2025

Stress is a biochemical mast-cell trigger

The experiment

Guilarte and colleagues perfused the jejunum of IBS-D patients and healthy controls, then gave IV CRF — the brain's stress hormone.

The whole-body stress response was the same in both groups — ACTH, cortisol, heart rate.

BUT IN IBS-D THE GUT RESPONDED MORE

↑ **Tryptase**	More mast-cell activation
↑ **Albumin leak**	A leakier barrier
↑ **Water secretion**	Looser stools
↑ **Pain**	Only in IBS-D

Guilarte M, et al. Am J Gastroenterol 2020;115:2047–59 · Vanuytsel T, et al. Gut 2014;63:1293–99

STRESS MANAGEMENT THROUGH AN MCAS LENS

Why GI psychology works on mast cells



Stress or anticipation of symptoms

CRH and adrenaline reach mast-cell receptors

Degranulation, a leakier barrier, sensitized nerves

More pain and more flares — and more anxiety

CBT and gut-directed hypnosis	Strong evidence in IBS; lower the central gain on gut signals
Sleep and vagal work	Slow breathing, sleep repair — less sympathetic input to mast cells
When the body is “wired”	Guanfacine 0.5–1 mg qHS to quiet sympathetic tone

THE RULE FOR EVERY DRUG

Go low and slow

Start at ¼ to ½ the usual dose

These patients react to doses that suit everyone else

One change at a time

2–4 week windows, so you know what helped and what hurt

Compound when fillers are the problem

Do whatever we can to limit chance of a reaction

A reaction isn’t failure

Switch the formulation first, then the drug, then the class

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Thank you

Questions and discussion

Ever Better Medicine

