MAST CELL ACTIVATION SYNDROME

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MY JOURNEY INTO THE WORLD OF MCAS

Consultant General Physician, Endocrinology & Diabetes

I am not an Immunologist

2008-9 Functional Medicine

Circa 2012-2013 PoTS

Circa 2015 PoTS, EDS

Circa 2017 Left NHS and increasing exposure to MCAS

By now developing strong interest in unexplained conditions

Therefore, impossible to ignore MCAS

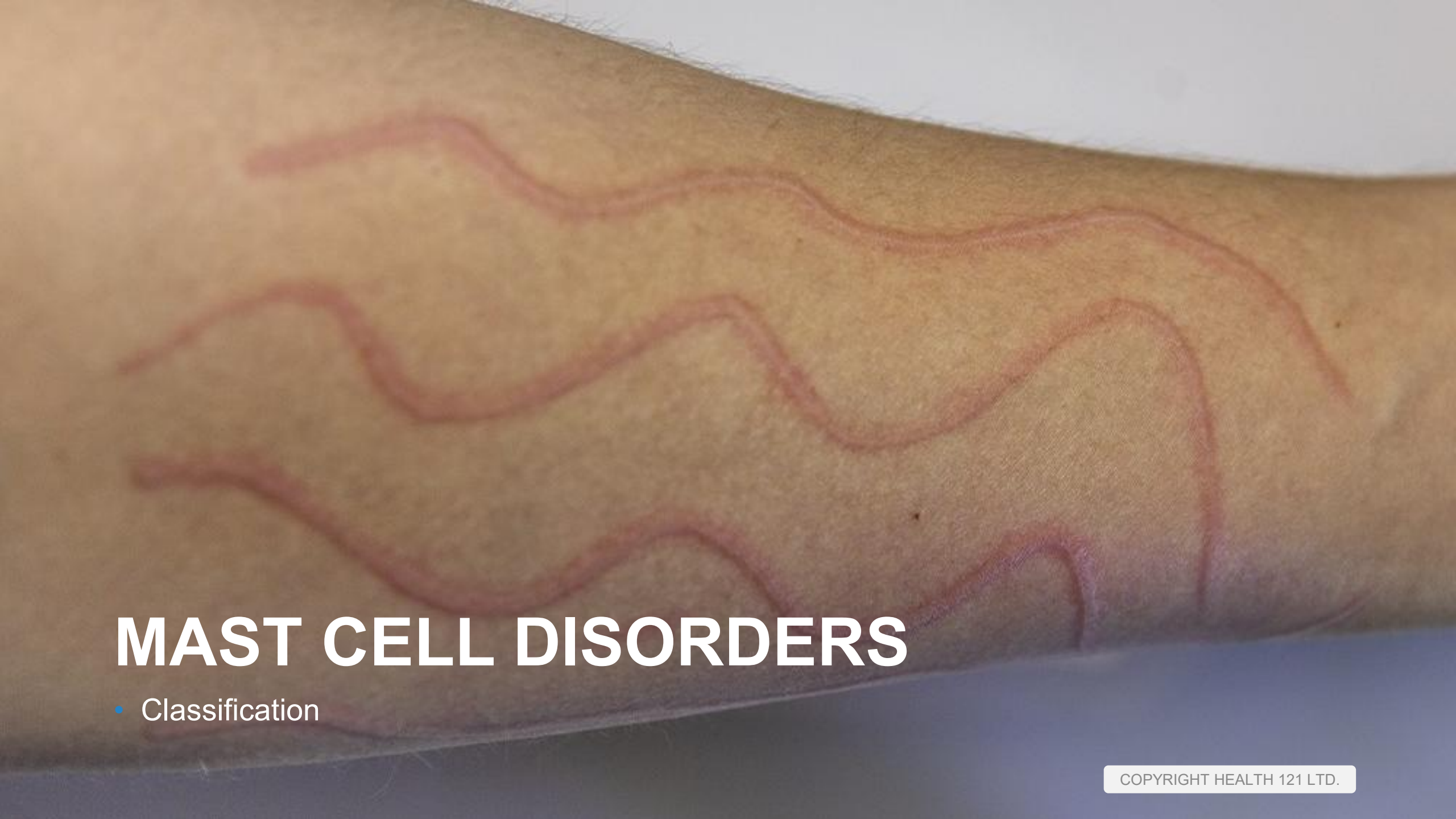
2020 onwards investigating and actively managing MCAS

MAST CELLS

- Blood Cell
- Approximately 0.05% marrow nucleated cells
- Leave the bone marrow soon after made
- Circulate to where they reside
- Tissues that interface the environment.
- Lifespan months – years.

ROLE

- Sense environment
- They (synthesize) and release mediators
- Mobilise parts of the immune system attracting neutrophils, eosinophils etc
- Influence blood vessel permeability.
- Also, phagocytose bacteria, schistosomes, foreign bodies, red cells etc.
- Promote wound healing.

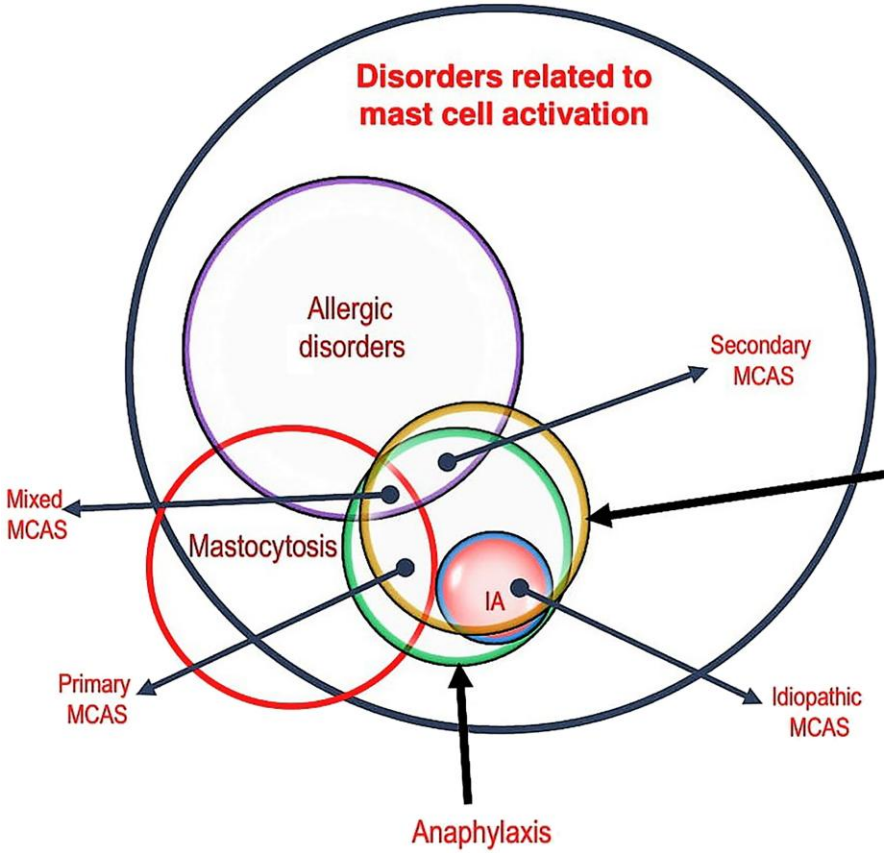


MAST CELL DISORDERS

- Classification

MAST CELL DISORDERS

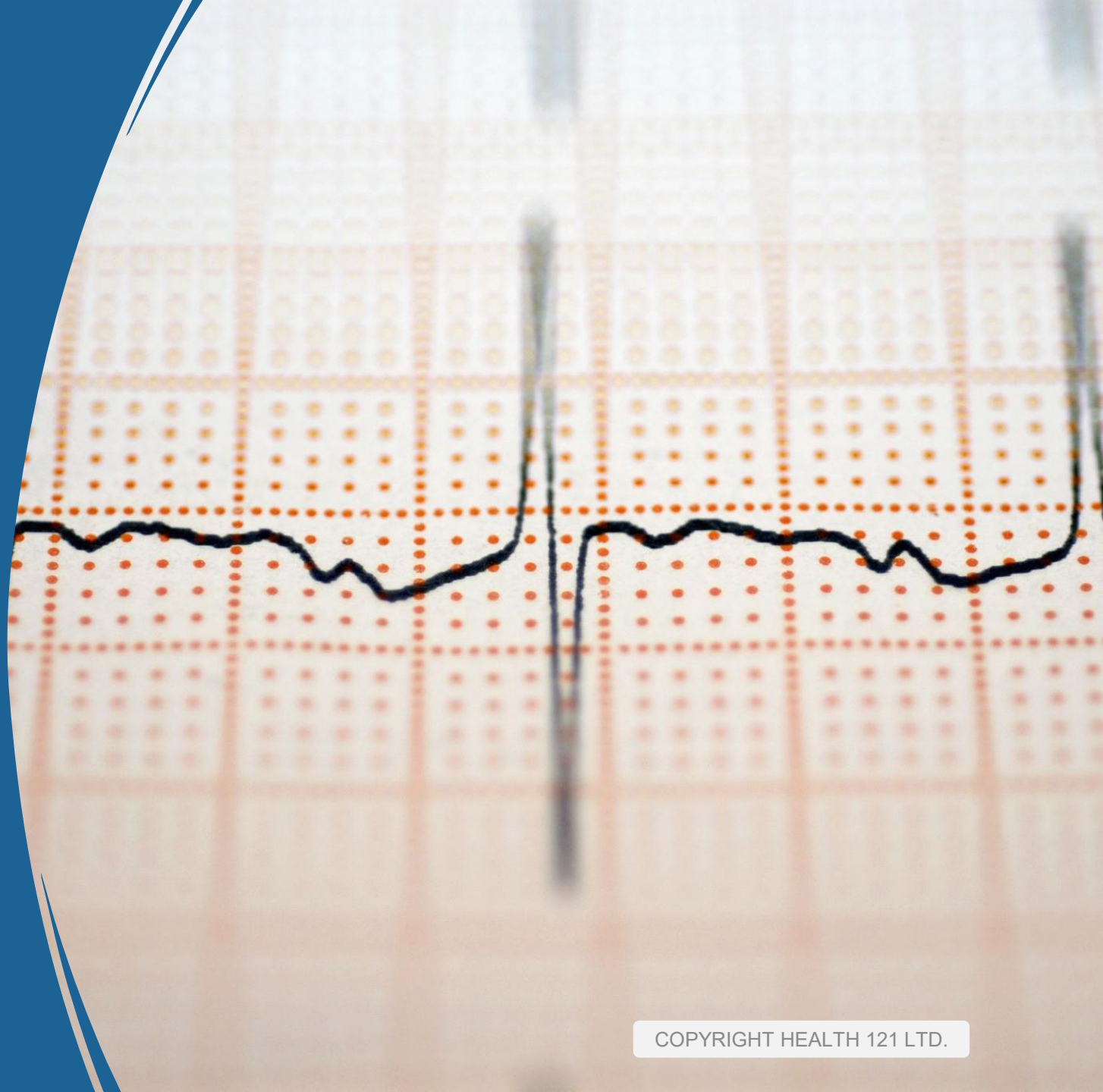
- MCAD= Inappropriate mast cell activation
- Does not necessarily mean increased numbers of mast cells
- Various conditions, some very rare
  - (1) MCAS
  - (2) Allergies
  - (3) Urticaria/angio-oedema
  - (4) Cutaneous mastocytosis (urticaria Pigmentosa)
  - (5) Systemic mastocytosis
  - (5b) Mast cell Leukaemia - ultra rare and highly lethal.
  - (6) Hereditary Alpha-tryptasemia



MCAS SIGNS AND SYMPTOMS/TESTS

- **DIVERSE!!!**
- Eyes: Irritation, episodic, inability to focus, blepharospasm.
- Ears: Irritation, hearing loss, and/or tinnitus
- Oral: Irritation, sores, dysphagia, **globus**, **burning mouth**.
- Nose: congestion, sores, **epistaxis**
- Lymph node swelling
- Dizziness, light-headedness, palpitations, collapse
- **Nausea, cyclical vomiting,** acid reflux, diarrhoea/constipation
- **Recurrent urinary tract infection**
- Flushing, itching, hives, dermatographism, teeth can fall out
- Headaches, vertigo, tremor,
- Sensory symptoms
- Fluctuating FBC indices (WCC, platelet, elevated RDW and MCV)
- Elevated ferritin (inflammation)

DIAGNOSIS



PROBLEMS WITH TESTING

- > 100 different mediators released.
- Half-life in blood and urine variable but can be short.
- Only a few of what is released can be tested.
- Only a small % of that is specific to mast cells.
- So, mediators measured might not be the ones or only ones causing symptoms.
- Some test up to three times.

TESTS

Blood and urine tests

- Serum Tryptase
- Urine and plasma histamine
- Urine Methylhistamine
- Urinary Prostaglandins
  - [PGD2 is produced by several types of cells but the MC produces roughly a thousandfold more PGD2 than any of the other types of cells]
- Urinary Leukotrienes
- CgA
- (Diamine Oxidase activity)
- (Heparin)

Collection

- Need to be done properly.
- Avoid NSAID 5 days.
- CgA – note false positives
- Avoid antihistamines and MC treatments.
- Needs to be chilled quickly.

SHOULD TESTS BE DONE

1. Increases confidence for what is a controversial diagnosis
2. Forms part of the criteria for diagnosis and less invasive than biopsy
3. Helps exclude other mast cell conditions

- Serum Tryptase
  - Reflects mast cell load more than activation per se. So not usually elevated in MCAS
  - If tryptase elevated >20ng/ml then refer exclude/consider SM.
- We offer testing service at HEALTH 121 Ltd (admin@health121.co.uk)

Mast cell counts

- Clinicopathological study 24 patients with Systemic mastocytosis and GI involvement
- Assessment of mucosal mast cell density assessed in SM patients and cf asymptomatic controls and IBS-D patients
- Biopsy sites was colon (19 patients, 95%), ileum (86%), duodenum (80%), and stomach (54%).
- Most common GI symptom diarrhoea then abdominal pain
- MC staining for KIT and CD25
  - MC density in asymptomatic 26 (11 – 55) per single high-power field
  - IBS-D MC density 30 (13 – 59)
  - So, highly variable counts in asymptomatic patients which overlapped with IBS-D!
- But Afrin in Consensus 2 highlights that healthy controls could not be so healthy and need to be vetted by MCAS aware specialist

Doyle LA et al. Am J Surg Pathol 2014;38(6):832–843

MAST CELL ACTIVATION DISORDERS AND THE GASTROINTESTINAL TRACT

- Classical clinical features
- MC Gut physiology and pathophysiology
- MC and gut microbiome
- SIBO

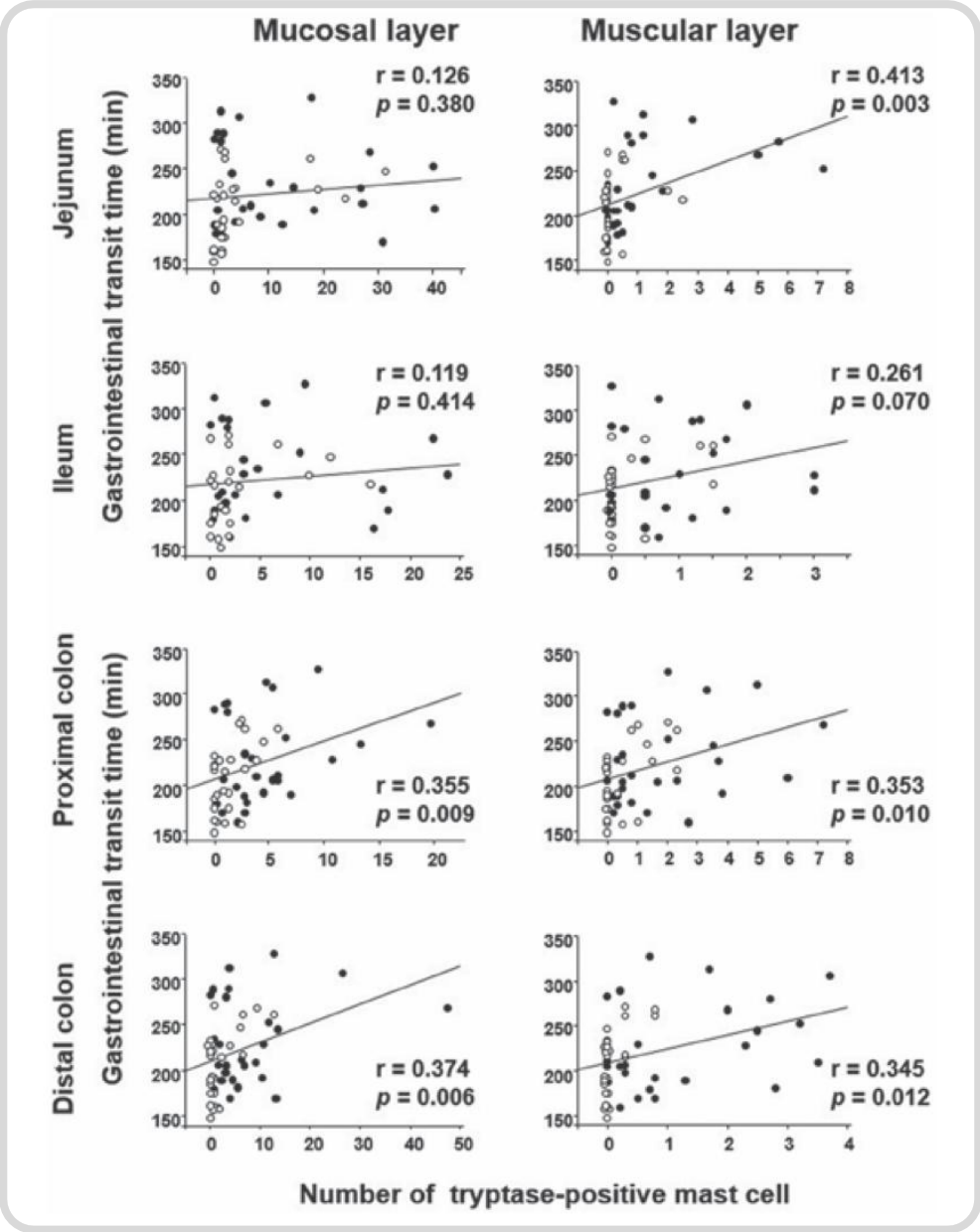
MCAS and Gut from Consensus-2

- “Dyspepsia, gastroesophageal reflux, nausea, vomiting (sometimes cyclical), diarrhea and/or constipation (often alternating), gastroparesis, angioedema, dysphagia (usually proximal), bloating/gas (usually post-prandial, often acute/subacute, sometimes to the appearance of full pregnancy), migratory abdominal pain from luminal or solid organ inflammation or distention, malabsorption; cholecystectomy is common, though often yielding normal pathology; ascites is rare”
- Long list!
- Non-specific symptoms

Diagnosis 2021;8(2):137-152

MC AND THE GI TRACT

- MC present in the gut including mucosa, submucosa, smooth muscle.
- MC conc increase from jejunum to distal ileum and decreases from caecum to rectum



MAST CELL AND DYSMOTILITY

- Dysmotility associated with MC numbers
- Mice study: during recovery from colitis, gut transit time correlated with number tryptase positive MC
- ?due to effect of mediators on myenteric neural cells and dysfunctional motor function

Kodani M et al. Mol Med Rep 17: 8167-8172, 2018.

IBS PATIENTS AS A MODEL

- IBS patients
- Diagnosed according to Rome II Criteria
- Abdominal pain quantified using validated questionnaire
- 34 of 44 (77%) compared to controls showed:
  - Increased area of mucosal MC infiltrates
  - 150% increase in number of degranulating MC
  - Mucosal tryptase and histamine content was increased
  - MC in close proximity to nerve cells correlated with pain scores
- “Colonic MC infiltration and mediator release in proximity to mucosal innervation may contribute to abdominal pain perception in IBS patients.”
- MC treatments have been helpful in IBS

- Barbara G, et al. Gastroenterology. 2004;126(3):693–702
- Neurogastroenterology & Motility. 2022;34:e14339.

MC, THE GUT AND STRESS

- Stress a key trigger for MC activation
- This is the case in the gut
- CRH receptors on MC
- Cold pain stress associated with
  - Increased MC mediators in jejunum in patients with food allergy
  - Stress induced release of tryptase and histamine but not PGD2
  - Greater water flux into lumen
- **Showed that an acute CNS-mediated stressor, rather than intra-luminal, triggered measurable MC mediator release into jejunum.**
- “suggest that mast cells have a role in stress-related gut dysfunction”

Santos J. et al. Gastroenterology. 1998 Apr;114(4):640-8.

MC AND THE GUT

- Prospective study of 16 patients with systemic mastocytosis
- 80% diarrhoea and abdominal pain
- Prospective study 18 patients 2011
- [Historically patients referred to allergy clinic to R/O mastocytosis, symptoms of MC activation; no clonality: “monoclonal mast cell activation syndrome” – predecessor of MCAS]
- GI complaints dominated: abdo pain 94%, diarrhoea in 67%, bloating (44%), reflux (44%) and nausea (33%).
- Average duration of symptoms 4.6 years before diagnosis.

- Gastroenterology. 1988; 95:657-667
- J. Allergy and Clin Immunology, 2011; 128, 147-152.e2

GUT MICROBIOME AND MC

- Gut microbiome communicates with MC and vice versa
- Mediate MC tolerogenic priming under physiological conditions.
- Gut microbiota is continuously sending signals to mucosal mast cells that educate them to have a high threshold for activation
- “This is a safe environment, relax!”

Front. Biosci. (Landmark Ed) 2025, 30(3), 26283.

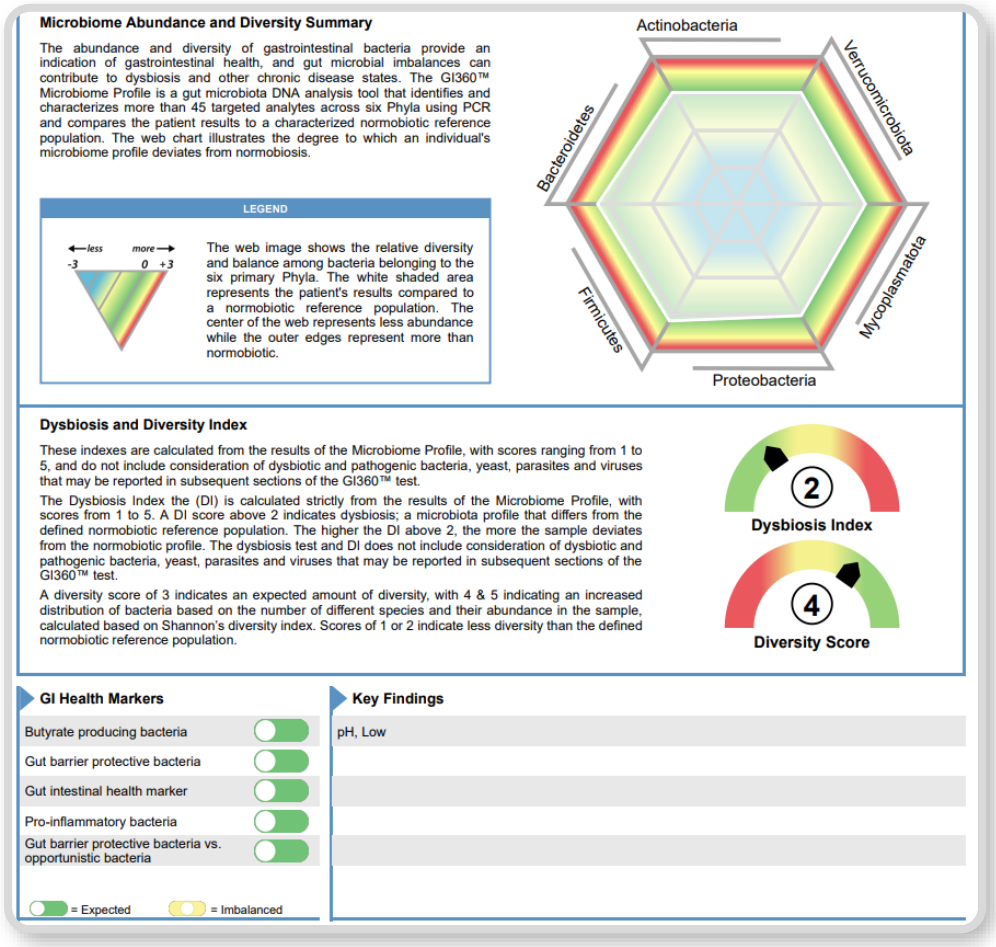
PATTERNS OF GUT DYSBIOSIS IN MCAD

Healthy Individuals

- Dominance of Firmicutes (approximately 60–65%),
- Lower relative Bacteroidetes abundance
- Robust population of SCFA-producing species (e.g. Faecalibacterium prausnitzii, Roseburia, Bifidobacterium, Lactobacillus).
- SCFAs maintain intestinal barrier function and provide tolerogenic signalling to mucosal immune cells including MCs.

SM (and by inference, MCAS):

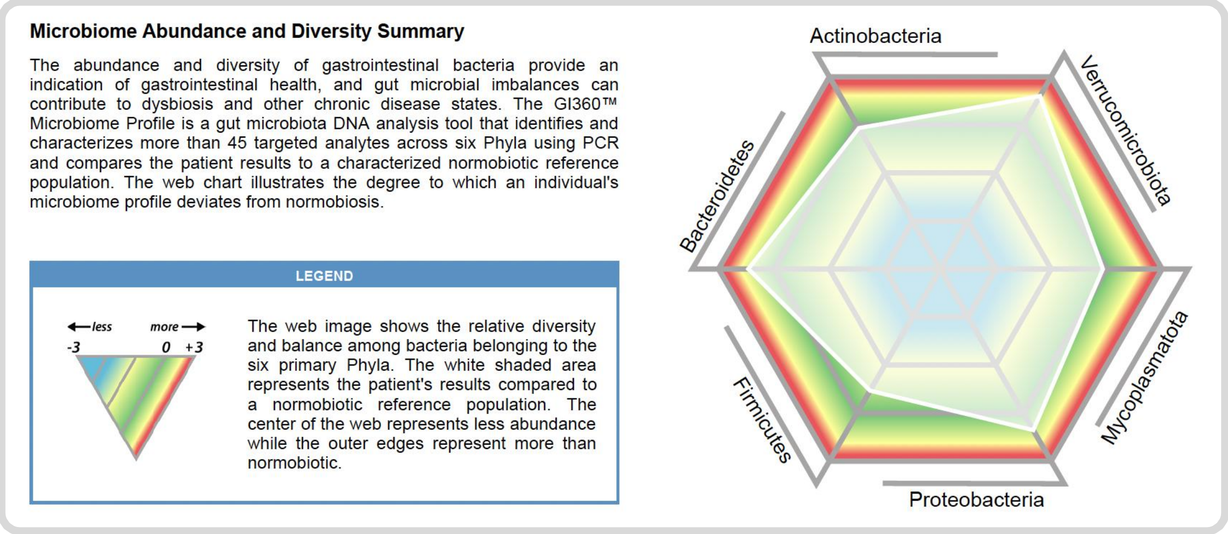
- Reduced relative Firmicutes compositional diversity with shifts toward certain Firmicutes genera (Eisenbergiella, Hungatella, Anaerotruncus)
- Increased Bacteroidetes abundance
- Increased Proteobacteria
- Depletion of SCFA-producing bacteria;
- Increased predicted virulence factor gene abundance
- Reduced predicted bacterial defence mechanisms.

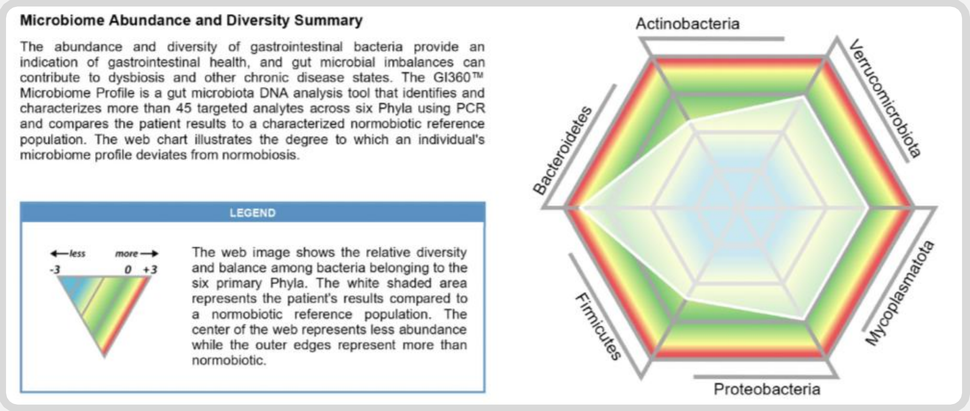


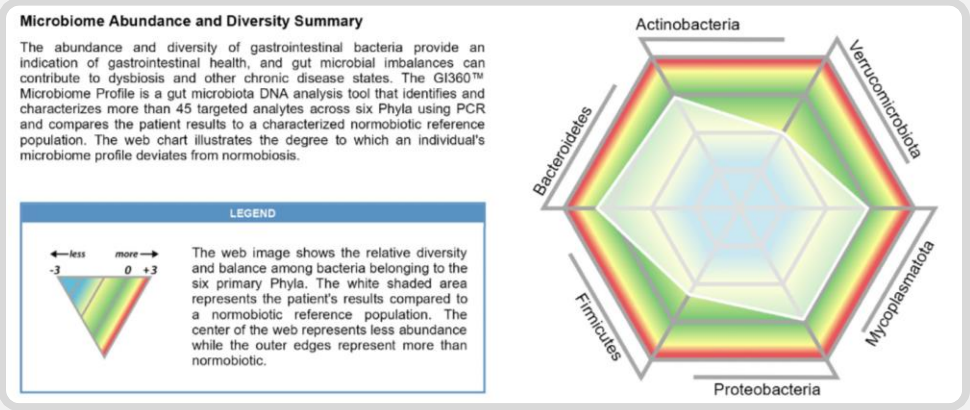
Han W. et al. (2012). Dig. Dis. Sci. 57 311–319. 10.1007/s10620-011-1897-2

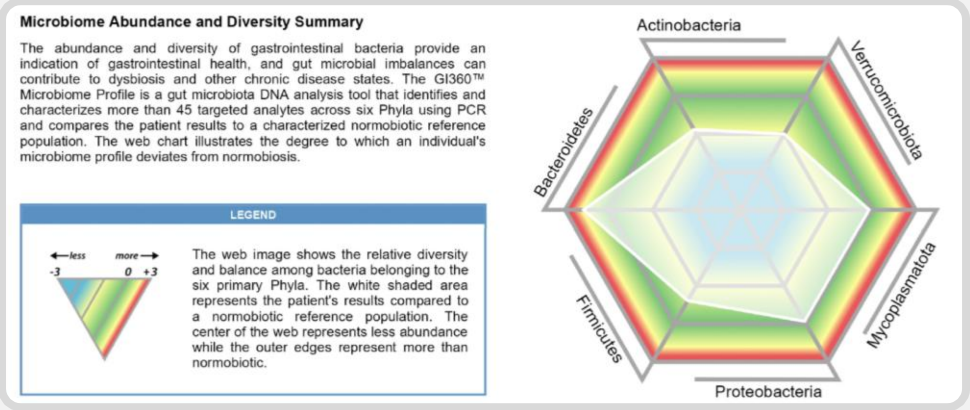
EXAMPLE OF PATIENT WITH MCAS

- White shaded area is patient’s result
- Reduced relative Firmicutes Increased Bacteroidetes abundance
- (Increased Proteobacteria)









Dysfunctional MC and gut microbiome

- Increased production LPS
- For example, from dysbiotic organisms
- LPS administration triggers MC degranulation
- This can be associated with BBB dysfunction and CNS inflammation

Mediators Inflamm. 2020 Feb 24;2020:8098439.

VICIOUS CYCLE: INTESTINAL PERMEABILITY & MC

(1) MC mediators — tryptase, MMP-9, histamine, and TNF-alpha

(2) Degrade tight junction proteins (occludins, claudins) in intestine

(3) Increases intestinal permeability,

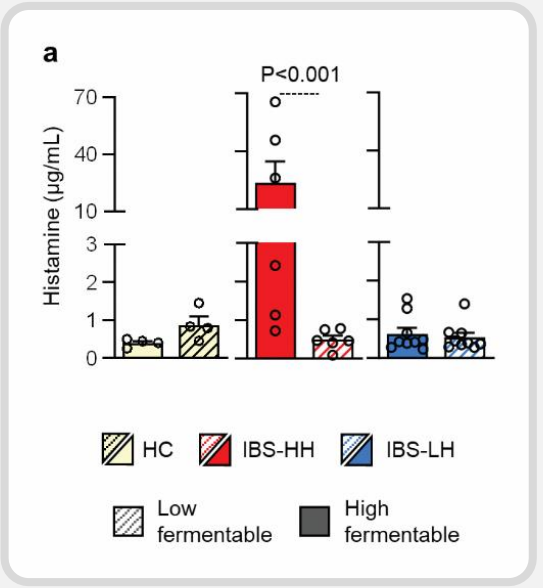
(4) Luminal antigens, bacterial endotoxins (LPS), undigested food proteins translocate into the lamina propria.

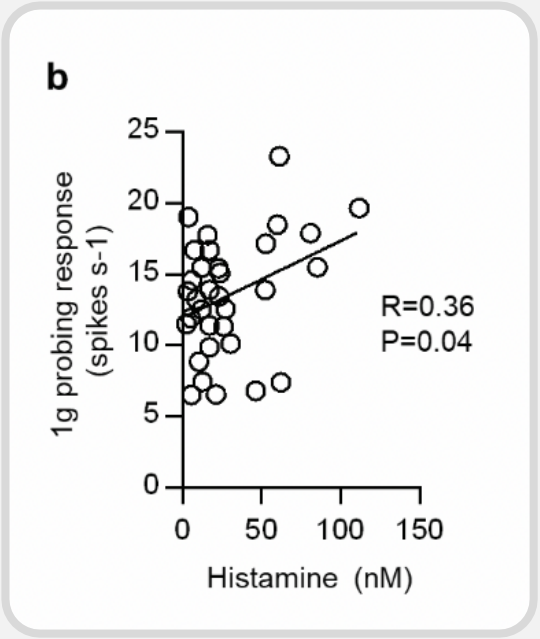
(5) LPS binds Toll-like receptor 4 (TLR4) on MCs, triggering further degranulation, creating a self-perpetuating inflammatory loop.

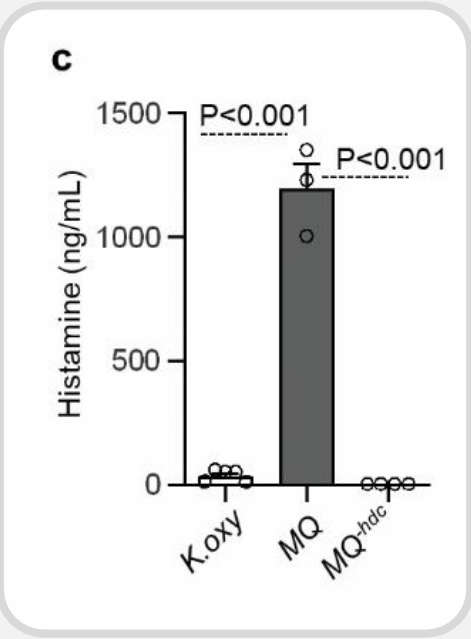
(6) Leukotrienes additionally disrupt endothelial gap junction disruption, compounding barrier dysfunction.

HISTAMINE PRODUCING BACTERIA & DIET

- Germ-free mice colonised with human IBS faecal microbiota
- Klebsiella aerogenes
- Significantly more abundant in IBS patients with high urinary histamine than in healthy controls
- Possesses a histidine decarboxylase gene variant enabling conversion of dietary histidine into histamine.
- This bacterially derived histamine recruited MC accumulation in the colon via histamine 4 receptor (H4R) signalling, inducing visceral hyperalgesia.
- Reducing fermentable carbohydrates in mice lowered visceral hypersensitivity and reduced MC colonic accumulation, implicating diet-microbiota-histamine-MC interaction as a mechanistic pathway



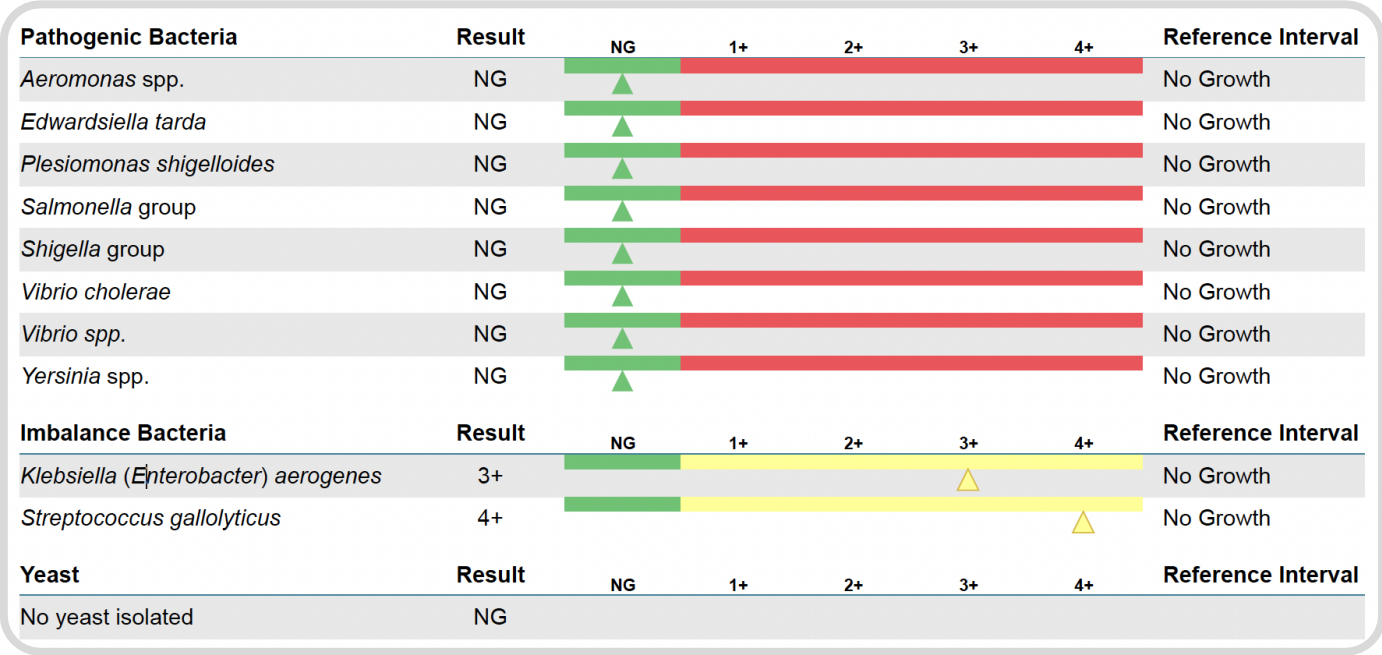




De Palma et al. (2022, Science Translational Medicine)

OVERGROWTH OF KLEBSIELLA AEROGENES

- Not all gut bacteria are equal histamine factories.
- Study looked at different bacteria from the same family (Enterobacteriaceae)
- Found the species differ in how much histamine they produce
- Species from an IBS patient (*Klebsiella aerogenes*) behaves differently from species found in healthy people (*K. oxytoca*, *Enterobacter*)
- Suggests it's specific "bad actor" bacteria driving the high histamine in some IBS patients.



Pathogenic Bacteria	Result	NG	1+	2+	3+	4+	Reference Interval
Aeromonas spp.	NG						No Growth
Edwardsiella tarda	NG						No Growth
Plesiomonas shigelloides	NG						No Growth
Salmonella group	NG						No Growth
Shigella group	NG						No Growth
Vibrio cholerae	NG						No Growth
Vibrio spp.	NG						No Growth
Yersinia spp.	NG						No Growth

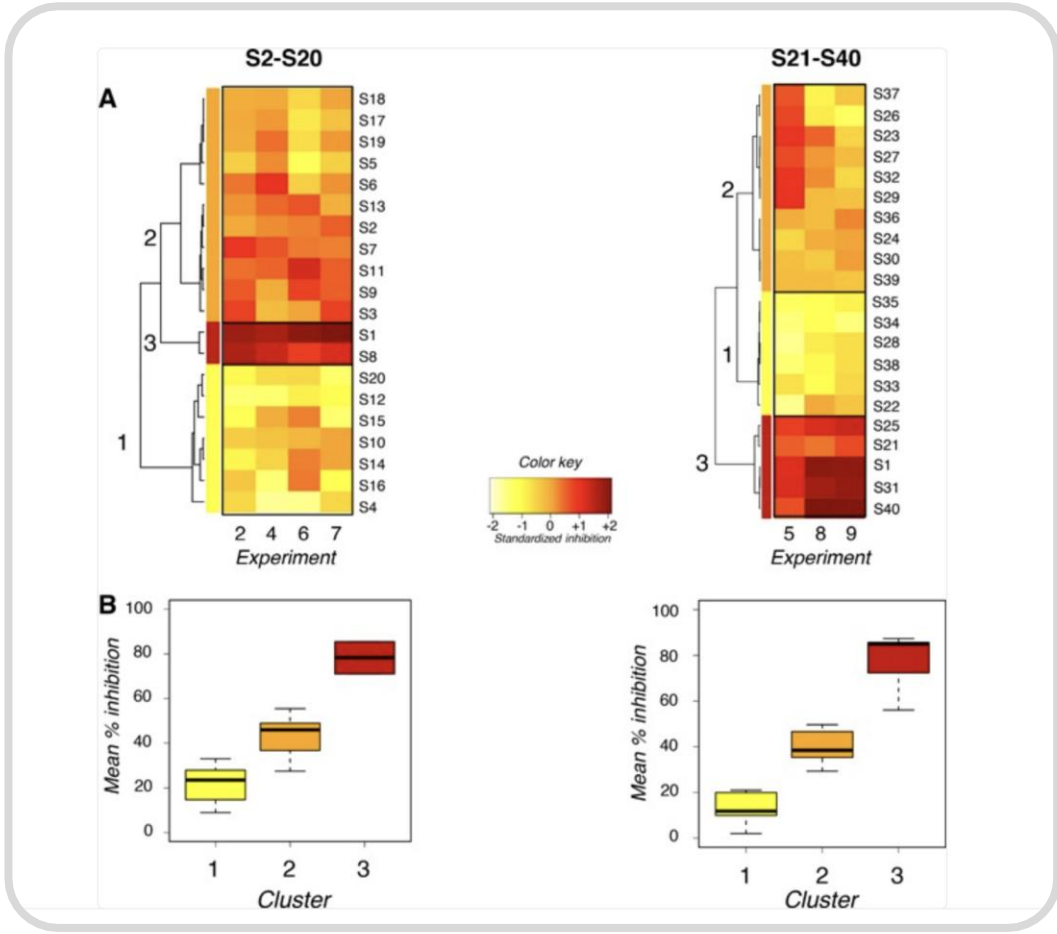
Imbalance Bacteria	Result	NG	1+	2+	3+	4+	Reference Interval
Klebsiella (*Enterobacter*) *aerogenes*	3+						No Growth
Streptococcus gallolyticus	4+						No Growth

Yeast	Result	NG	1+	2+	3+	4+	Reference Interval
No yeast isolated	NG						

De Palma et al. (2022, Science Translational Medicine)

BENEFICIAL BACTERIAL EFFECTS

- *Enterococcus faecalis, Lactobacillus paracasei*, and non-pathogenic *Escherichia coli*:
- Suppress IgE-mediated MC degranulation in mice,
- via peptidoglycan binding to MC surface receptors.
- Lactobacillus rhamnosus GG reduces MC numbers in mucosal tissues in rodent models.
- Oral administration of E. faecalis reduced MC infiltration (mice model)

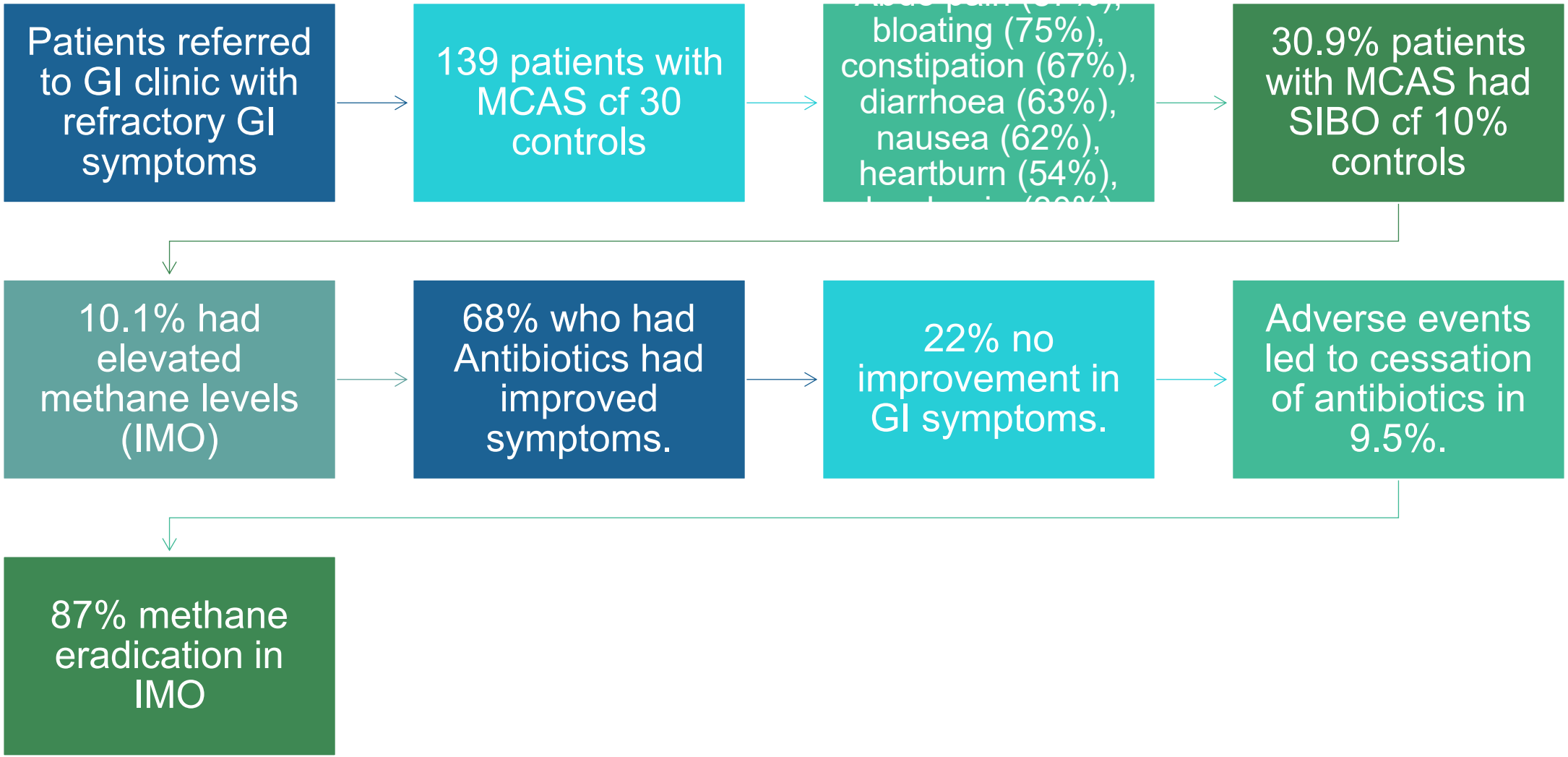


- Cassard L. et al. Immun. Inflamm. Dis. 4 289–299. 10.1002/iid3.113
- Choi E. J. et al. (2016). Nutrients 8:146. 10.3390/nu8030146

SIBO/IMO

- Small intestinal bacterial overgrowth
- 3 key gases
  - Hydrogen, methane and hydrogen sulphide
  - Methane and H2S can be produced by organisms in the colon
  - So, IMO and ISO
- Breath testing
- Relapse rate high
- Treatment failure rate 15%
- Need to focus on underlying causes

SIBO is common in MCAS



Weinstock, Leonard B. et al. Am J Gastro 114():p S671, October 2019.

Treatment

- Treat underlying gut disorder: Very important
- Food intolerances
  - Histamine intolerance common
  - Co-associates with other food intolerances
  - Low histamine diet:
  - Reducing dietary histamine may help manage both MCAS symptoms and promote a healthier microbiome composition
- DAO enzymes
- Avoid triggers – very important
- Reduce stress

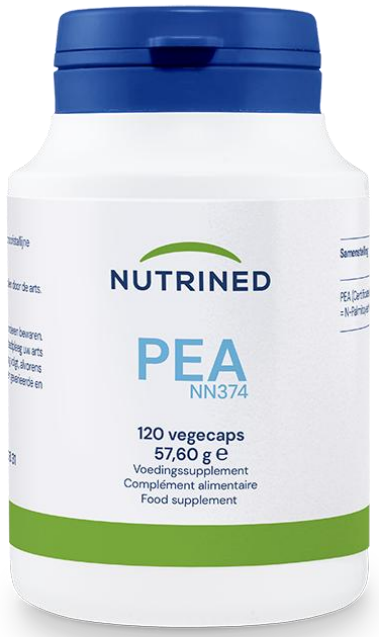
Treatments shown to reduce IBS MC activity

- Antihistamines
  - Reduced abdominal pain, improved QoL
  - Thought antidepressants work in part by H1 antagonism
- Ketotifen
  - Decreased IBS symptoms
- Sodium cromoglycate
  - Inhibited histamine and leukotriene release
  - Significantly reduced abdominal pain
  - Improved stool consistency

- Wouters MM. et al. Gastroenterology. 2016;150:875-887
- Klooker TK, et al. Gut. 2010;59:1213-1221.
- PMCID: PMC2014120 PMID: 17471183
- Lobo B. et al. Gastroenterology. 2011;140(Suppl 1):499-500.

NATURAL TREATMENTS

- Quercetin – stabilises MC
- Luteolin inhibits MC activation
- PEA (Palmitoylethanolamine) – inhibits MC activation
- RG3 nasal spray – stabilises MC, reduces IL-17, immune modulator
- Butyflam (SCFA) stabilises mast cells
- Vitamin C
- Methylation (SAMe) clear histamine
- DAO Supplement



Clin Exp Allergy. 2000b;30:501–508

Excipient Category	Specific Compounds in UK MCAS Medications	MCAS Risk Level	Prevalence in Analyzed Products
FD&C Dyes	Allura Red AC (E129), Iron oxides (E172), Quinoline yellow (E104)	HIGHEST	40-50% of tablets
Alcohols	Propylene glycol, polyvinyl alcohol, benzyl alcohol (in injectables)	HIGHEST	60% of liquids, some tablets
Parabens	Methyl/propyl parahydroxybenzoate	HIGH	All preserved liquids
Lactose	Lactose monohydrate	HIGH	80% of tablets (1.99-107mg range)
Other sugars	Sorbitol, maltitol, sucrose, mannitol	MODERATE-HIGH	All liquid/chewable formulations
Lubricants	Magnesium stearate, talc	MODERATE	70-80% of tablets
Preservatives	Benzalkonium chloride, sodium benzoate	MODERATE	All multi-dose eye drops, some liquids
Fillers	Microcrystalline cellulose	LOW-MODERATE	90% of tablets (source variability matters)
Coating agents	Titanium dioxide, hypromellose	LOW	Most film-coated tablets

Schofield JR, Afrin L. The American Journal of the Medical Sciences. 2019; 357 (6): 507-511,

CONCLUSION

Conclusions

- MC are integral part of the GI tract
- They serve an important function in normal (gut) health
- Dysfunctional MC is associated with
  - Gut dysbiosis
  - SIBO
  - Intestinal permeability
  - Food intolerances
  - SYMPTOMS
- Stool and breath testing provides valuable information
- Do not forget the Gut

THANK YOU

Questions?

Contact admin@health121.co.uk