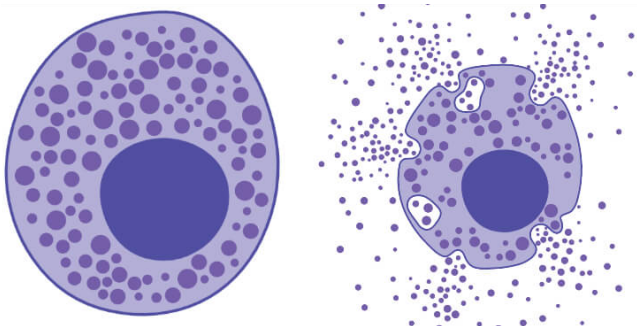
MCAS

Mast Cell Activation Syndrome

In Patients With ME/CFS, FM, and Long COVID

Ric Arseneau, MD FRCPC MA(Ed) MBA FACP CGP
BC Centre for Long COVID, ME/CFS, & Fibromyalgia (BC-CLMF)
Clinical Professor
Division of General Internal Medicine
St. Paul's Hospital
University of British Columbia



bc-clmf.org

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html

Aboriginal Health Be Well Vancouver CoastalHealth

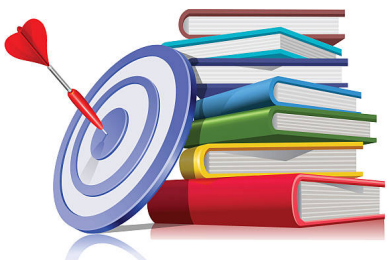
Faculty/Presenter Disclosure

- **Ric Arseneau**

- **NO** relationships with financial sponsors to disclose, including:
  - Any direct financial relationships including receipt of honoraria
  - Memberships on advisory boards or speakers' bureau
  - Patents for drugs or devices
  - Other: financial relationships/investments

Objectives

- Describe the common symptoms of MCAS
- List the common triggers MCAS
- List the common comorbidities of MCAS
- Describe a practical approach to diagnosing MCAS
- Compare the various treatment options for MCAS



BC Centre for Long COVID, ME/CFS, & Fibromyalgia (BC-CLMF)

- > 7,000 patients – ongoing care
- Virtual group-based model of care
- Patients participate as soon as referred (not after seen in consultation)
- Program
  - Individual consultation
  - Follow-up visits: Group Medical Visit (GMV) – 10 to 12 patients for one hour
    - Triage for individual follow-up visits
  - Medication visits: Group Medication Visit (GMedV) – 50 patients for one hour
  - Groups
    - 40 different groups led by MD, OT, PT, Dietician, Counsellor/Psychologist, Naturopath, etc.
    - 4 weeks to 6 months long
  - Special lectures
    - Weekly: recurring and one-off (YouTube Channel: ME TV)

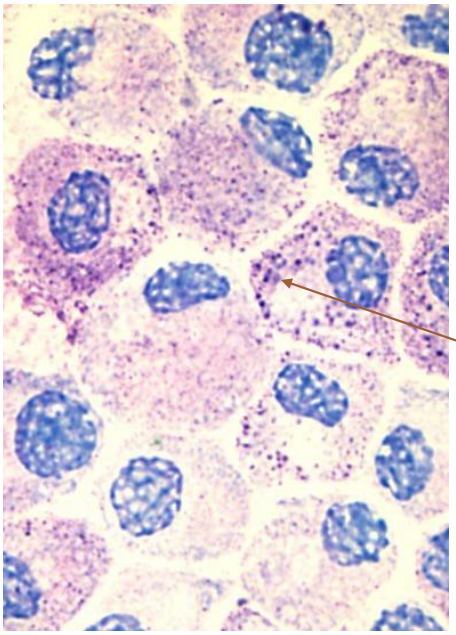
And so the story begins…

- 1863
- Friedrich von Recklinghausen
- German doctor
- Identify *granulated cells* in unstained connective tissues from different species.

And so the story begins…

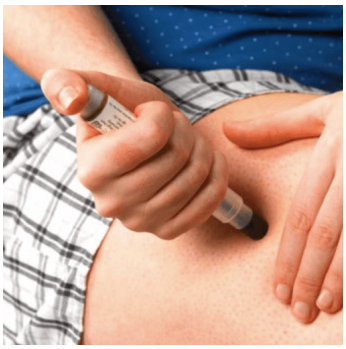
- 1878
- Paul Ehrlich
- German doctor
- Identification and description of *Mast Cells*

And so the story begins…

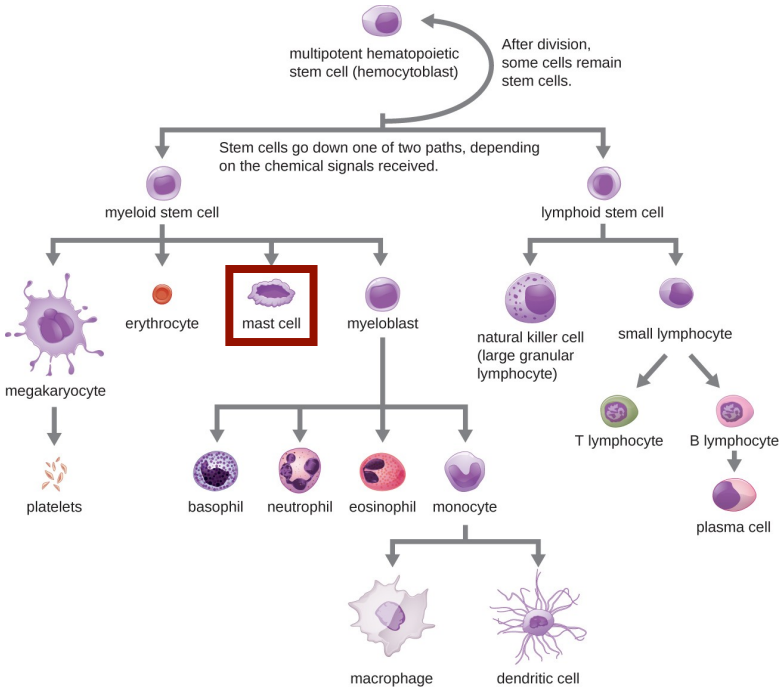


- 1953
- Mast cells contain *Histamine*

Claim to fame…



All in the Family…



Migration and Diaspora…

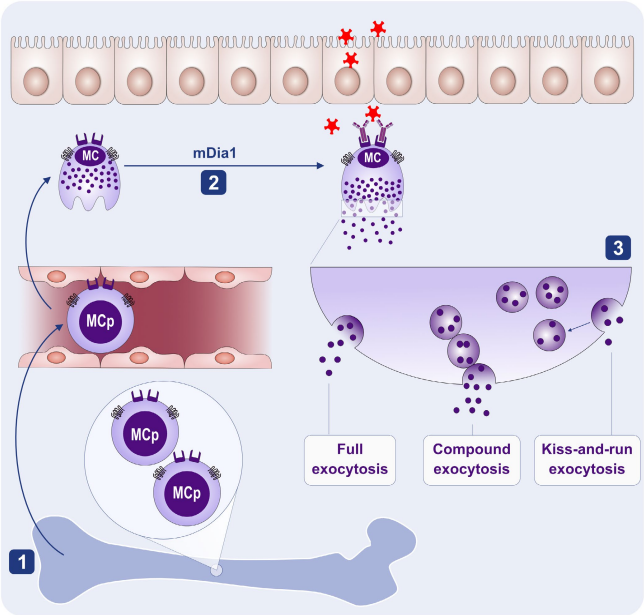
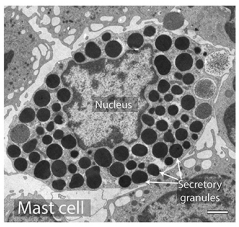


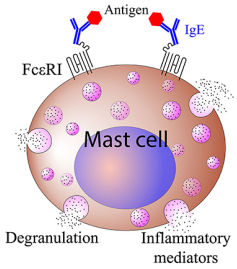
FIGURE 5 Fate decisions in the life of the mast cell. Mast cell progenitors (MCp) in the bone marrow (1) are entering the bloodstream and are recruited into the tissue (2). During this process, the cells have to avoid premature degranulation (2). In the tissue (3) MCs can degranulate in three possible modes, either by full exocytosis, compound exocytosis, or by kiss-and-run exocytosis

Allergy. 2022;77:83–99.

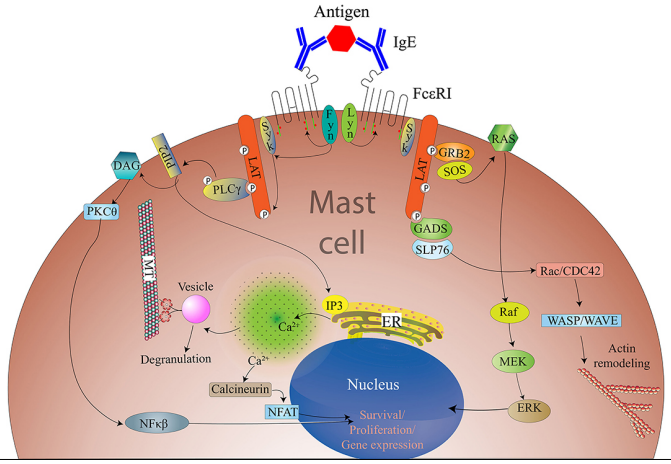
- MCp = baby mast cells
- Maturation depends on tissue "neighbourhood"
- Different
  - Roles / jobs
  - Different receptors
  - React to different stimuli
  - Produce different mediators (e.g., histamine, tryptase, etc.)
- Homeostasis
- Surveillance
- Defence / Protection

Allergies - IgE Mediated



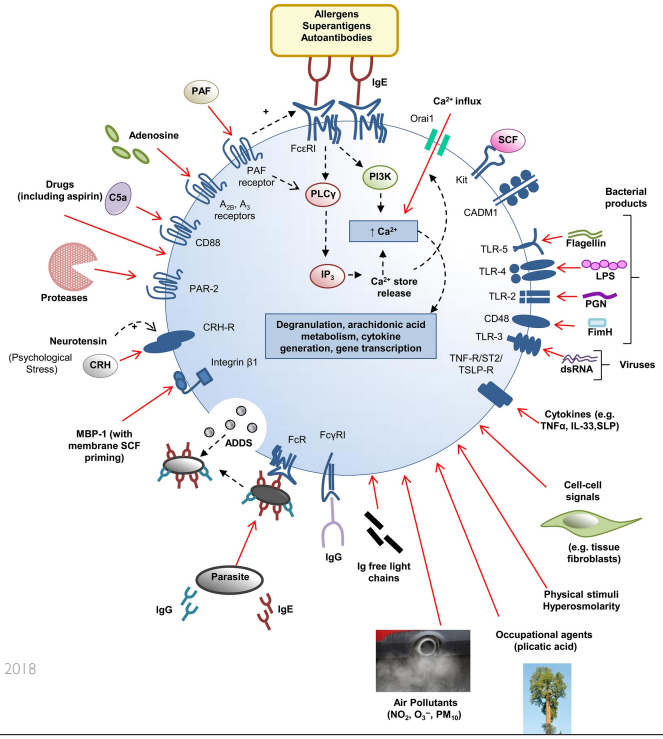


Inflammatory Mediators
TNFα, leukotrienes, IL-12, IL-6, CCL20, IFN γ, histamine, IL-5, IL-13, IL-16, IL-8/CXCL8, IL-1β, MCP-1, CCL5, MC tryptase, IL-4, TGFβ, IL-2, IL-10, serotonin, etc.



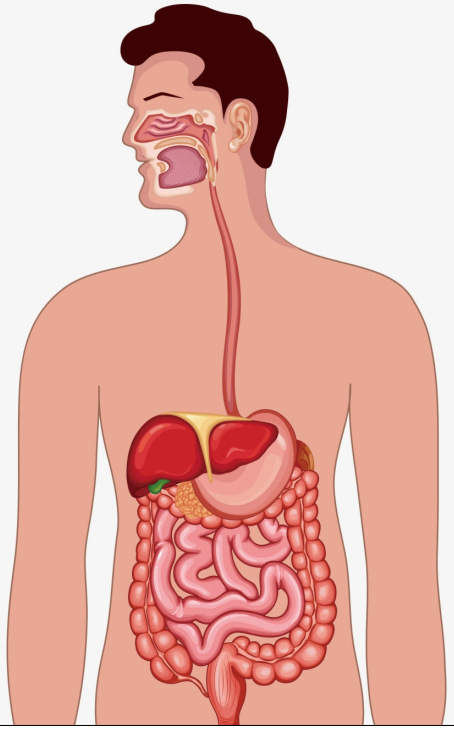
Front. Immunol., 17 June 2020

Mast Cell Receptors



Immunol. Reviews 12 February 2018

The GI Tract – Inside is out…



- Mast cells defend border between the body and the *outside* environment
- GI tract has the largest population of mast cells
- Intestinal mucosa (gut lining) is the largest interface that separates the inner and outer environments
- Intestinal barrier

Mast Cell Function in the GI Tract

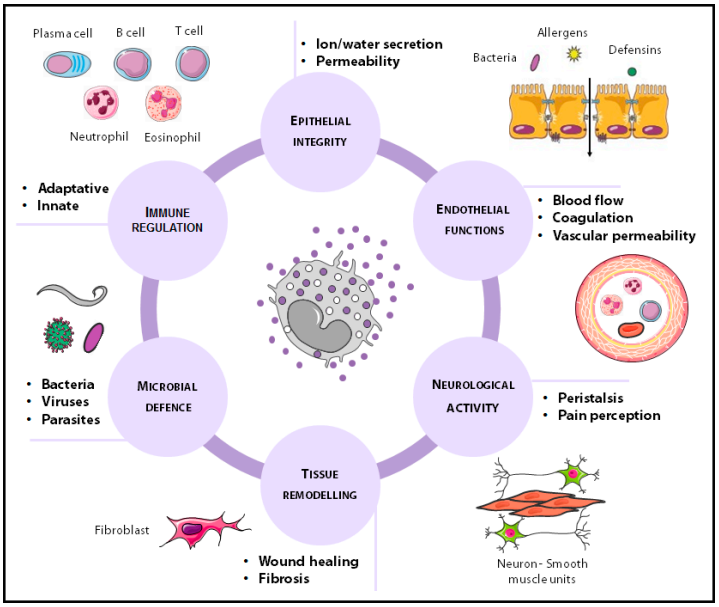


Figure 2. Physiological functions of mast cells in the gastrointestinal tract. Mucosal mast cells play an important role in multiple functions necessary for gut homeostasis, including epithelial, endothelial and neurological functions, tissue transformation, host defence, and immunity.

Cells 2019, 8, 135; doi:10.3390/cells8020135

Role of MCs in the regulation of intestinal barrier function: secretion and permeability

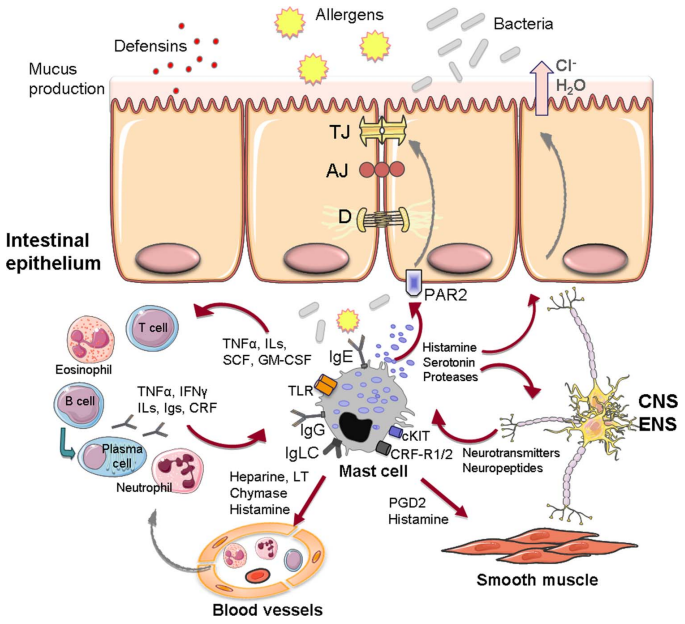
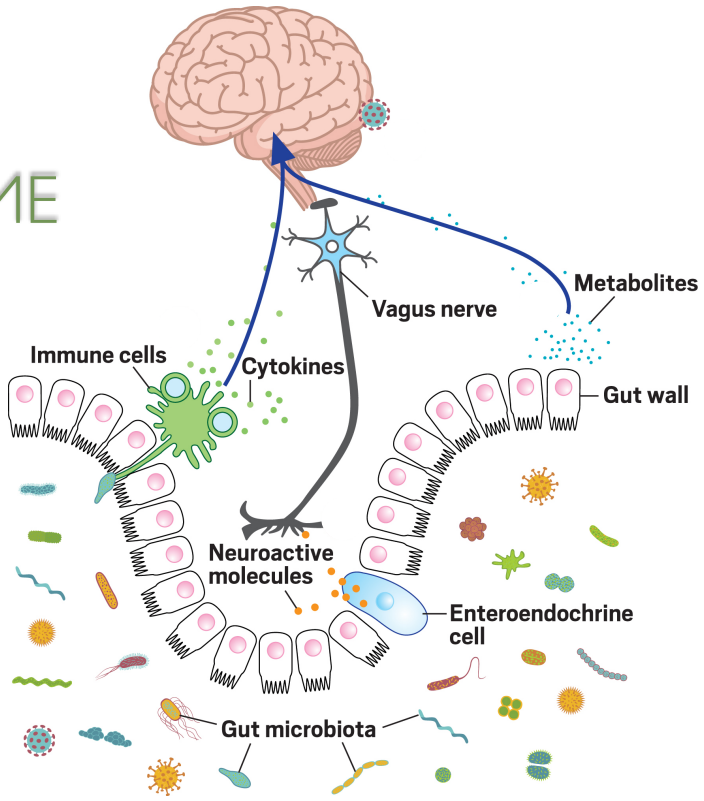


Figure 4 Intestinal barrier function elements and mast cell interactions in the intestinal mucosa. Illustration of the potential mast cell interactions in the regulation of barrier function, including epithelial permeability (through TJ modulation and secretory response), recruitment and activation of other immunocytes, endothelial functions (vascular permeability and blood flow), peristalsis and pain signalling through bidirectional communication with the nervous system.

Wouters MM, *et al*. *Gut* 2016;**65**:155–168. doi:10.1136/gutjnl-2015-309151

Microbiome Gut Brain Axis

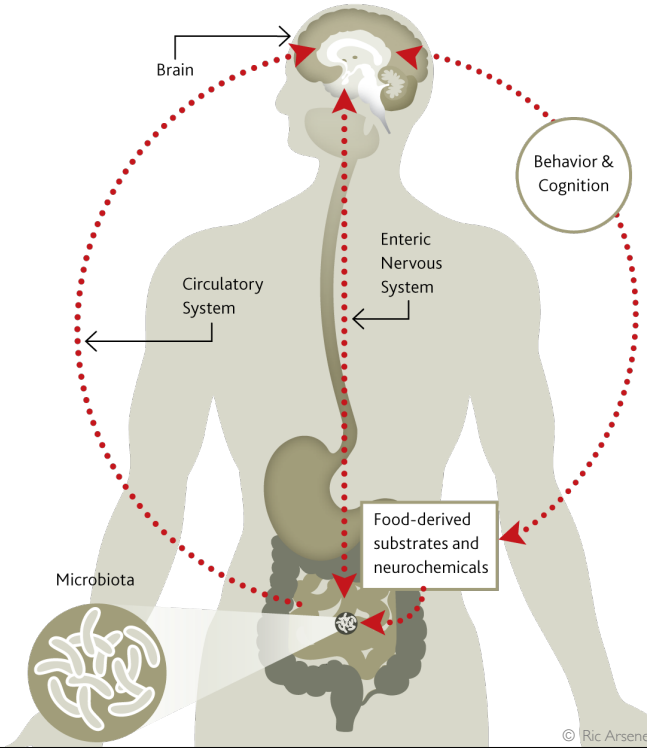


17

Microbiome-Gut-Brain Axis

Enteric Nervous System

The Second Brain

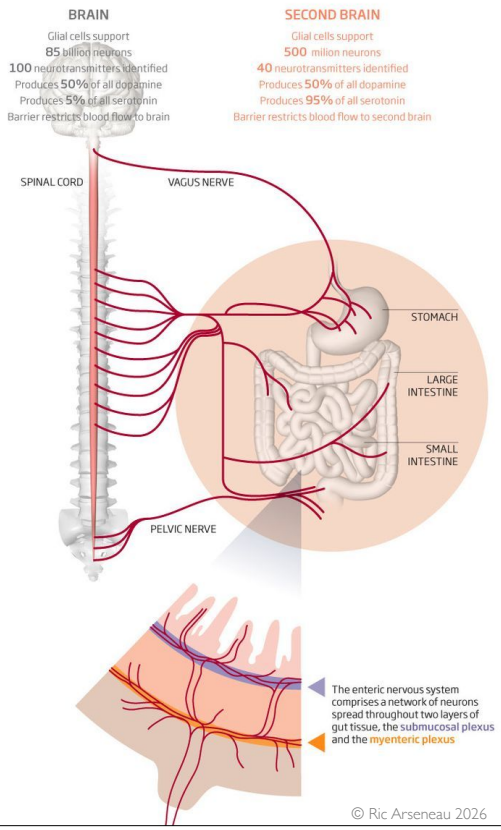


18

Fun Facts

BRAIN
Glial cells support
85 billion neurons
100 neurotransmitters identified
Produces **50**% of all dopamine
Produces **5**% of all serotonin
Barrier restricts blood flow to brain

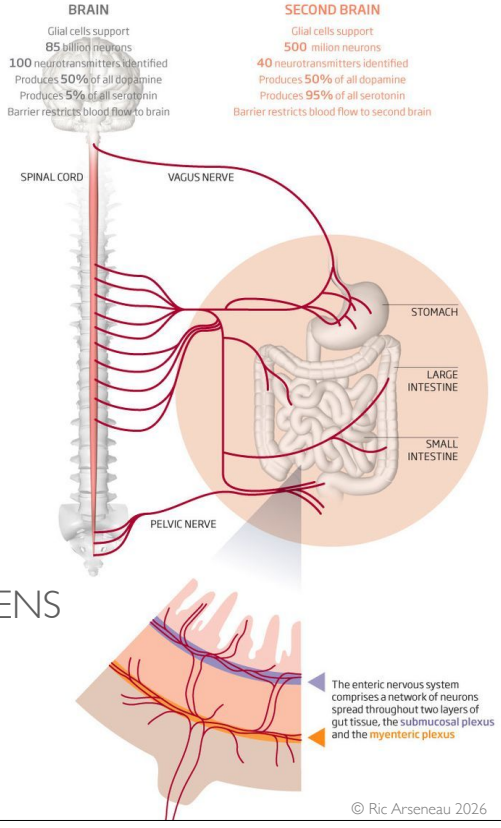
SECOND BRAIN
Glial cells support
500 million neurons
40 neurotransmitters identified
Produces **50**% of all dopamine
Produces **95**% or all serotonin



GABA & ENS

Both GABA and its receptors are widely distributed through the ENS

Lactobacillus and *Bifidobacterium* are effective at increasing GABA in the ENS



The role of mast cells in functional GI disorders

Wouters MM, *et al*. *Gut* 2016;**65**:155–168. doi:10.1136/gutjnl-2015-309151

- FGIs are characterized by chronic complaints arising from disorganized brain–gut interactions leading to dysmotility and hypersensitivity
- Rome IV Criteria (2016)
  - Gradual phasing out of the descriptor "functional"
  - "Disorders of Gut-Brain Interaction"
- E.g.,
  - Functional dyspepsia (non-ulcer dyspepsia)
  - IBS
  - Globus (hystericus)
  - Centrally mediated abdominal pain
  - Functional chest pain (non-cardiac chest pain)

The role of mast cells in functional GI disorders

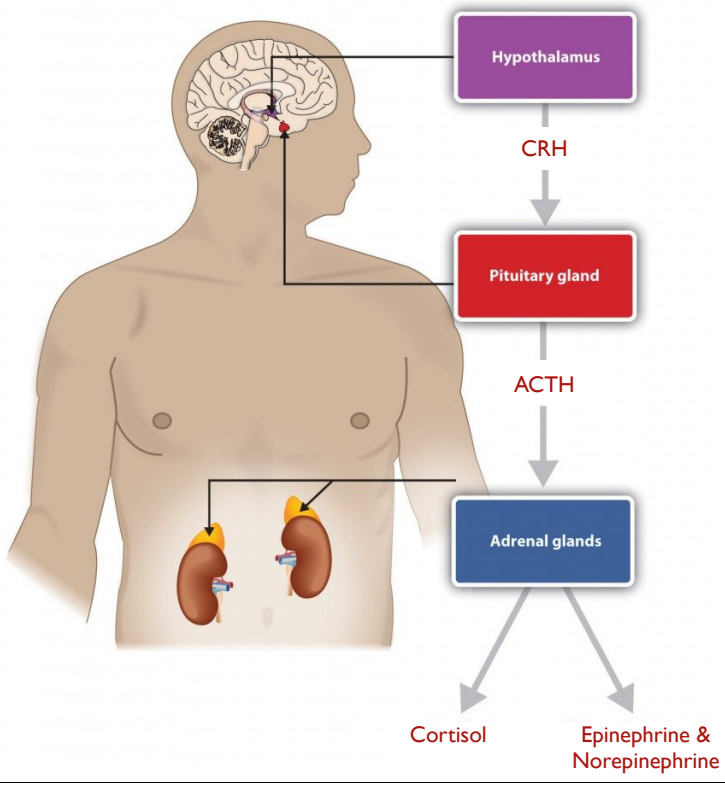
Wouters MM, *et al*. *Gut* 2016;**65**:155–168. doi:10.1136/gutjnl-2015-309151

- Low-grade mucosal inflammation and immune activation
- Presence of mast cells, eosinophils and lymphocytes
- Impaired epithelial barrier function
- Neuronal sensitivity
- Disrupted microbiome
- Food antigens as trigger for mast cell activation

- Role of MCs in stress
- Role of MCs in visceral hypersensitivity and motility changes: motor and neuronal activation and sensitization
- Role of MCs in the regulation of intestinal barrier function: secretion and permeability

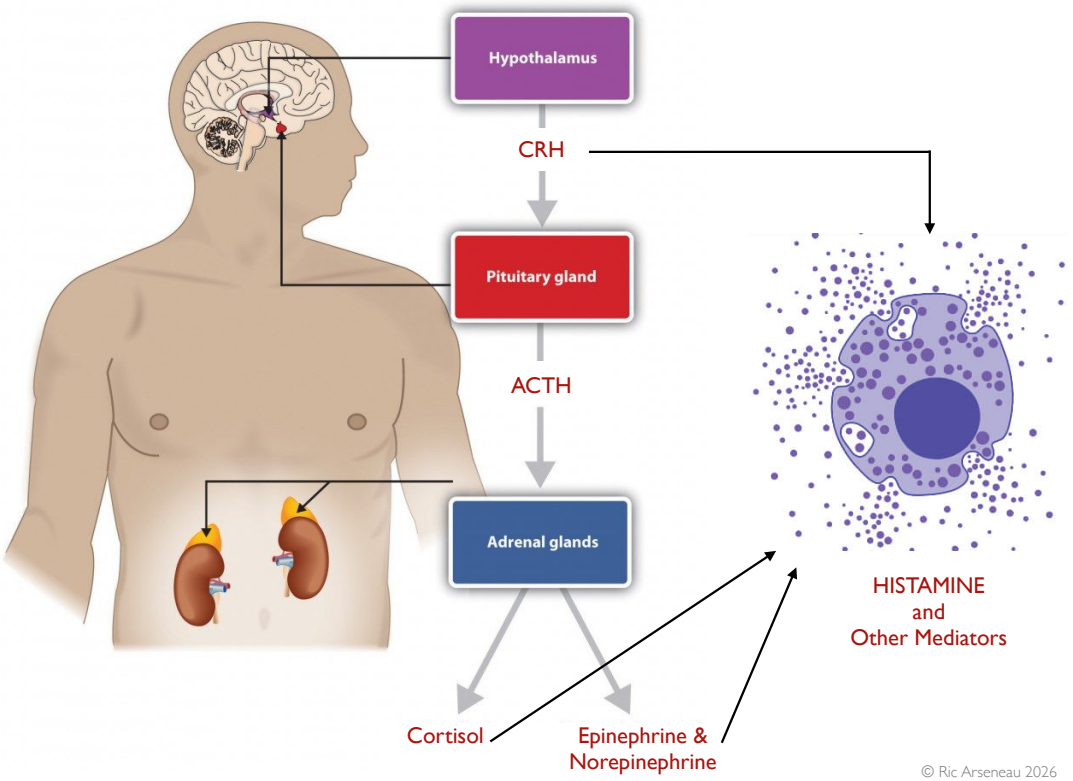
23

HPA Axis



24

HPA Axis



Role of MCs in visceral hypersensitivity and motility changes: motor and neuronal activation and sensitization

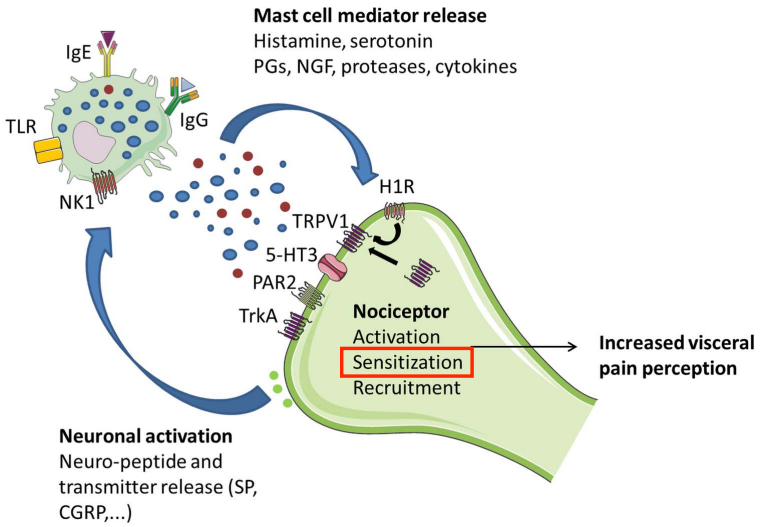


Figure 3 Schematic illustration of mast cell–nerve interactions in human gut. MCs and nerves communicate bidirectionally, thereby modulating peristalsis and pain signalling. The release of bioactive, pro-inflammatory, mediators by mast cells results in a variety of neuronal effects including activation, sensitisation and recruitment of nociceptors to the cell membrane, neurogenic inflammation and neural sprouting, ultimately leading to visceral hypersensitivity. On the other hand, neuronal activation triggers the release of neuropeptides and neurotransmitters, thereby further activating mast cells.

Wouters MM, *et al*. *Gut* 2016;**65**:155–168. doi:10.1136/gutjnl-2015-309151

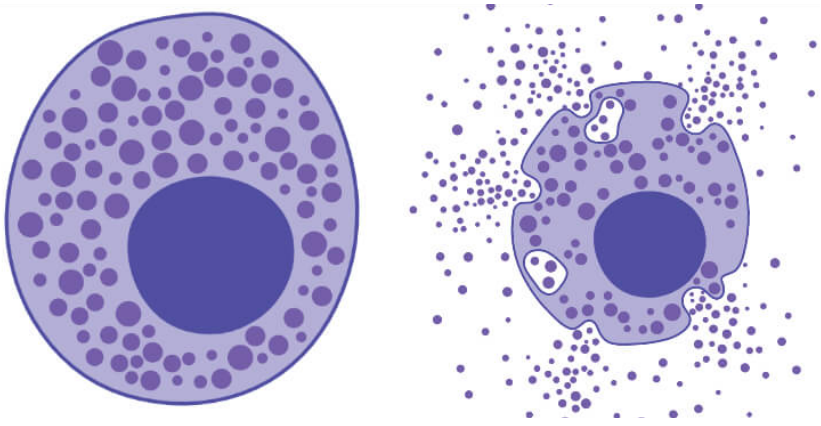
The American Journal of GASTROENTEROLOGY SUPPLEMENT I 2019

Small Intestinal Bacterial Overgrowth Is Common in Mast Cell Activation Syndrome

- 139 MCAS subjects (116 F, 23 M, 46.6 +/- 6.9 years) and 30 controls
- MCAS subjects
  - IBS-mixed: 39.6%
  - IBS-constipation: 22.3%
  - IBS-diarrhea:18.7%
- SIBO was present in 30.9% MCAS subjects vs. 10% in controls

27

Mast Cell Activation

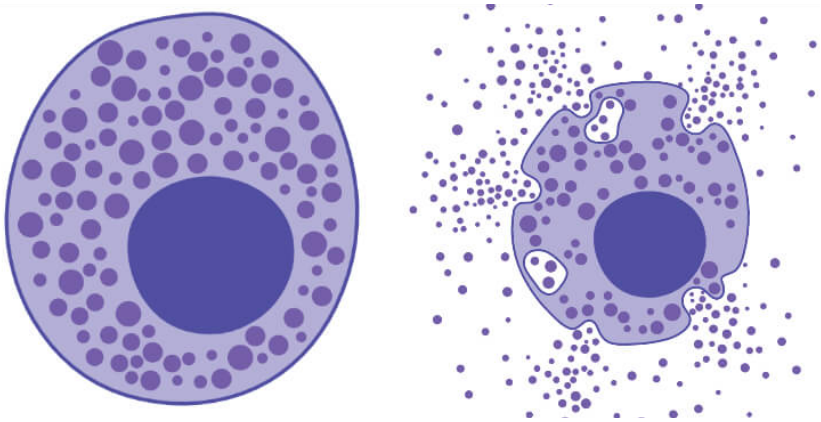


- "Activated" mast cells
- "Twitchy"
  - Lower stimulation threshold
- Non-specific histamine release

- Overlap with ME/CFS and FM symptoms
  - Fatigue, pain, brain fog, others

28

Mast Cell Activation



- "Activated" mast cells
- "Twitchy"
  - Lower stimulation threshold
- Non-specific histamine release

- Bone pain
- Skin (e.g., hives)
- Gut symptoms / food intolerance
- Medication intolerance
- Allergy-type symptoms
- Lung symptoms

Mast Cell Activation Syndromes

"Mast Cell Mediator Disorders"

Table 2. Classification of Mast Cell Activation Syndromes [2,8]

Molecular category	Recognized category	Diagnostic features of MCs	Underlying conditions
Clonal MCs	Primary	D816V *KIT* mutation[a] and/or aberrant expression of CD25+ in MCs in BM (WHO minor SM criteria)	c-MCAS (or MMAS)
		WHO criteria for SM are fulfilled	SM
		Infiltration of skin by MCs, in the absence of WHO criteria for SM[b]	CM
Nonclonal MCs	Secondary	No *KIT* mutations detected[c] Expression of CD25– in MCs in BM	IgE-mediated allergy, another hypersensitivity reaction, or another immunologic (autoimmune, inflammatory) disease that causes MCA
	Idiopathic	No *KIT* mutations detected[c] Expression of CD25– in MCs in BM	Neither primary nor secondary conditions are found

Abbreviations: BM, bone marrow; CM, cutaneous mastocytosis; c-MCAS, clonal mast cell activation syndrome; MC, mast cells; MCA, mast cell activation; MCAS, mast cell activation syndrome; MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis; WHO, World Health Organization.
[a]Other gain-of-function *KIT* mutations are described [3,81].
[b]Skin MC infiltrate is accepted to be clonal MC proliferation.
[c]Potential existence of unknown molecular defects cannot be ruled out.
Adapted with permission from Elsevier [8].

J Investig Allergol Clin Immunol 2021; Vol. 31(6): 461-470 doi: 10.18176/jiaci.0675

MAST CELL ACTION

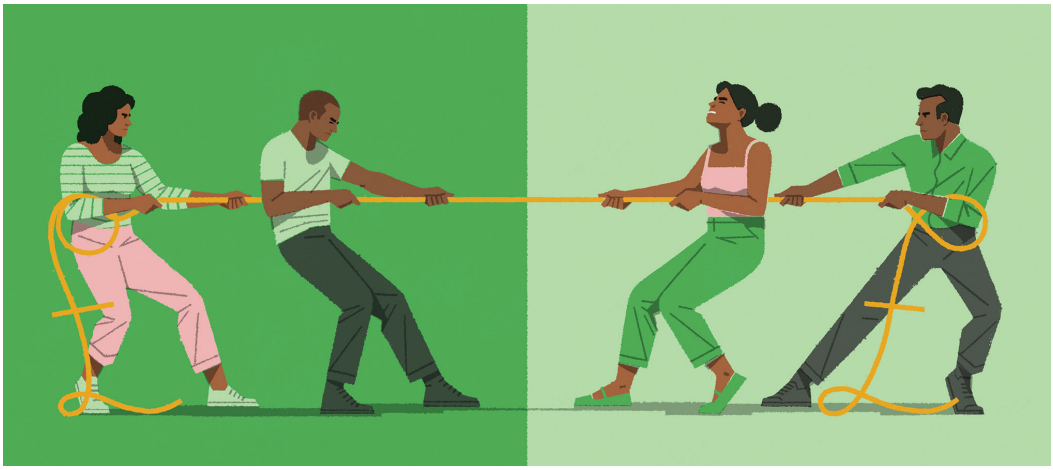
What is Mast Cell Activation Syndrome?

Mast cell activation syndrome (MCAS) is a complex condition that sits within a broad spectrum of disorders associated with oversensitive or inappropriately activated mast cells. MCAS is characterised by the inappropriate or excessive production and/or release of mast cell mediators.[1]

mastcellaction.org

31

MCAS *CONTESTED*



32

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,[a] Jason L. Hornick, MD, PhD,[b] Cem Akin, MD, PhD,[a] Mariana C. Castells, MD, PhD,[a] and Norton J. Greenberger, MD[a] *Boston, Mass*

J Allergy Clin Immunol 2011;128:147-52.

TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

33

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,[a] Jason L. Hornick, MD, PhD,[b] Cem Akin, MD, PhD,[a] Mariana C. Castells, MD, PhD,[a] and Norton J. Greenberger, MD[a] *Boston, Mass*

J Allergy Clin Immunol 2011;128:147-52.

- Most patients treated with anti-MC medications responded *dramatically*
- 66% achieved a complete or major regression in symptoms

34

Published in final edited form as:
Immunol Allergy Clin North Am. 2018 August ; 38(3): 469–481. doi:10.1016/j.iac.2018.04.002.

Non-Clonal Mast Cell Activation: A Growing Body of Evidence

- Over the last decade, recognition of a unique syndrome
  - Signs and symptoms suggesting primary mast cell activation
  - Without fulfilling the established criteria
  - Do not have primary allergic disorders
  - Not clonal
  - Idiopathic Mast Cell Activation Syndrome
- The hallmark of NC-MCAS is inappropriate activation of mast cells to stimuli that otherwise would be tolerated if not in the activated or reactive state

Mast Cell Activation

When the Whole Is Greater than the Sum of Its Parts

Dilawar Khokhar, MD, Cem Akin, MD, PhD*

Med Clin N Am 104 (2020) 177–187

KEYWORDS

• Mast cell activation • MCAS • Mast cell disorder • Mastocytosis
• Idiopathic anaphylaxis • Tryptase • Mast cell mediators

KEY POINTS

- Mast cell activation syndrome (MCAS) is a rare, distinct clinical entity with severe episodic symptoms of mast cell activation associated with elevated mast cell mediators.
- Idiopathic anaphylaxis should be viewed as the prototypical manifestation of MCAS and can be used to establish a framework for evaluation.
- No single sign, symptom, or laboratory test is sufficient for the diagnosis of MCAS.
- Therapy for MCAS is based on avoidance of triggers and antimediator therapy.

Theme Editorial

The Many Faces of Mast Cell Disorders—A House of Mirrors?

David B.K. Golden, MD *Baltimore, Md*

J Allergy Clin Immunol Pract 2019;7:1139-41.

Mast cell disorders have become an increasing focus of our clinical practice due, in part, to the growing popularity of mast cell activation syndrome (MCAS) as an internet diagnosis for whatever ails you.

37

Clinical Commentary Review

Doctor, I Think I Am Suffering from MCAS: Differential Diagnosis and Separating Facts from Fiction

Peter Valent, MD[a], and Cem Akin, MD[b] *Vienna, Austria; and Ann Arbor, Mich*

J Allergy Clin Immunol Pract 2019;7:1109-14

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: April 1, 2019. Credit may be obtained for these courses until March 31, 2020.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Peter Valent, MD, and Cem Akin, MD (authors); David Khan, MD (editor)

Learning objectives:

1. To be able to apply consensus criteria in the diagnosis of mast cell activation syndrome (MCAS).
2. To be able to establish or exclude a diagnosis of MCAS in all patient groups.
3. To be able to classify MCAS using consensus criteria.
4. To be able to manage patients with MCAS.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The authors declare that they have no relevant conflicts of interest. D. Khan is on the Aimmune advisory board; has received honoraria from UpToDate; and is a speaker for Genentech.

38

Clinical Commentary Review

Doctor, I Think I Am Suffering from MCAS: Differential Diagnosis and Separating Facts from Fiction

Peter Valent, MD[a], and Cem Akin, MD[b] *Vienna, Austria; and Ann Arbor, Mich*

J Allergy Clin Immunol Pract 2019;7:1109-14

1. Did my symptoms repeatedly occur in the form of severe attacks requiring immediate medical intervention and/or hospitalization?
2. Did my symptoms lead to an anaphylactic shock requiring hospitalization?
3. Did my doctor(s) measure serum tryptase levels before, during, and after my attacks?
4. Did my doctor(s) tell me that my tryptase levels increased during my attacks?
5. Did my symptoms improve with continuous treatment with antihistamines?
6. Did the frequency of severe attacks decrease since I took steroids or antihistamines?
7. Did my doctor(s) diagnose an IgE-dependent allergy?
8. Did my attacks resolve or decrease in number after I started with omalizumab?

When most of these questions are answered with "no," an MCAS can essentially be ruled out or is very unlikely.

39

DIAGNOSING MCAS

MAST CELL ACTION

KEY DIAGNOSTIC CRITERIA [1,2]

1. The presence of typical clinical MCAS symptoms across multiple body systems.
2. Evidence of raised levels of mast cell mediators (see "Mediator Tests").
3. Substantial systemic response to inhibitors of mast cell activation or inhibitors of mast cell mediator production or action.
4. Exclusion of other potential diagnoses.

Scan for more on diagnosis

MEDIATOR TESTS [3, 4, 5, 6, 7, 8]

Test	Normal Range	Comments
Serum tryptase	2 to 14 ug/L	• Most specific to mast cells • Often raised in clonal MCAS but normal in non-clonal MCAS • Must be measured within 4 hours of a suspected episode and compared with baseline values measured 24 to 48 hours later • An increase of at least 20% over the individual's baseline plus 2ng/ml may indicate anaphylaxis*
Urinary N-methyl histamine	NMH/ creatinine ratio (mcg/mmol) <25	• Fairly specific to mast cells, however also present in basophils • No validated diagnostic threshold • May be influenced by diet or bacterial contamination
Urinary Prostaglandins (PGD2 and its metabolites PGDM and PGF2α)	PG/ creatinine ratio (ng/mmol) PGD2: <825 PGDM: <2300 PGF2α: <105	• Not specific - not recommended as a single marker of mast cell activation • No validated diagnostic threshold • Positive results for all three PGs is more likely in clonal MCAS • A single positive result is more likely in non-clonal MCAS • NSAIDs may reduce PGs, inflammation may raise PGs • Ovulation, menstruation, PCOS and endometriosis may raise PGF2α

40

DE GRUYTER Diagnosis 2021; 8(2): 137–152

Review

Diagnosis of mast cell activation syndrome: a global "consensus-2"

- Disputes regarding diagnostic criteria
- No studies of validity of criteria

Table 2: Broadly accepted characteristics defining the mast cell activation syndrome (MCAS) population.

1. An MCAS patient must have symptoms consistent with *chronic* MCA, which is *aberrant* (i.e. abnormal, whether constitutive/baseline and/or reactive to some identifiable trigger; note most MCAS patients have *both* constitutive and reactive MCA, even if either form is just to a modest degree at a given point), and, in many patients, accompanied by periodic *flares* (a.k.a. "spells," "episodes," and such) of certain subsets of their symptoms
2. An MCAS patient must have signs/symptoms of aberrant MCA in *multiple* (i.e. at least two) organ systems
3. An MCAS patient must (with reasonable confidence) *not* have some other disease accounting better than MCA for the full range and duration of the observed symptoms/signs

The characteristics listed here are a synthesis of the published proposals for diagnostic criteria for MCAS [7–9, 20–22, 24].

41

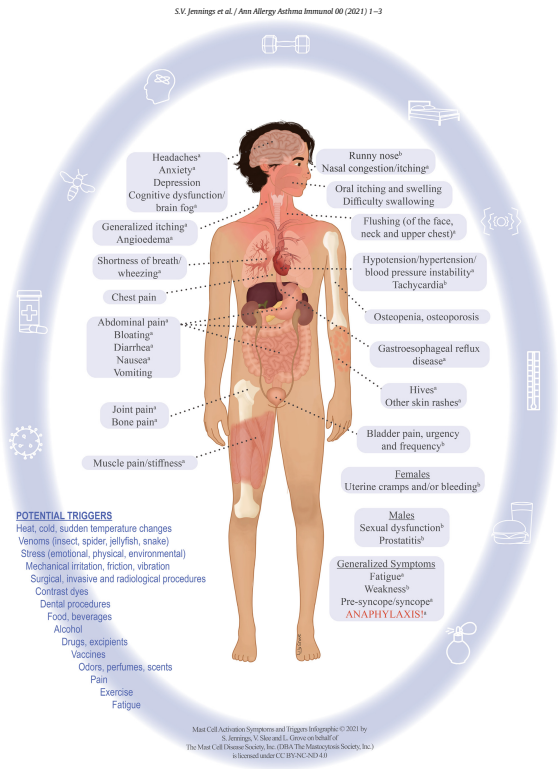
DE GRUYTER Diagnosis 2021; 8(2): 137–152

Review

Diagnosis of mast cell activation syndrome: a global "consensus-2"

"As is the case with most syndromes, the diagnosis of MCAS will continue for many years to come to rest on the demonstration of a specific constellation of findings"

42



Symptoms can be acute, episodic and recurrent, or chronic and frequent, and may present as generalized, systemic symptoms, including anaphylaxis

71% indicated food restrictions

MCAS Symptoms	Mediators
Cardiovascular Hypotension, syncope, light-headedness, tachycardia	CHR, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase
Cutaneous Flushing, pruritus, urticaria, angioedema	CRH, histamine, interleukin-6, 8, 33, PAF, TNF, tryptase
Digestive Abdominal cramps, diarrhoea, esophageal reflux, nausea and vomiting	CHR, histamine, IL-6, neurotensin, PAF, PGD2, serotonin, TNF, tryptase, VIP
Musculoskeletal Aches, bone pain, osteopenia, osteoporosis	IL-6, PGD2, RANKl, TNF, tryptase
Neurologic Anxiety, depression, decreased concentration and memory, insomnia, migraines	CRH, histamine, IL-6, neurotensin, PAF, PGD2, TNF
Respiratory Nasal congestion, nasal pruritus, shortness of breath, throat swelling, wheezing	Histamine, interleukin-6, CysLTs, PAF, PGD2
Systemic Fatigue, generalized malaise, weight loss	CRH, histamine, IL-6, TNF

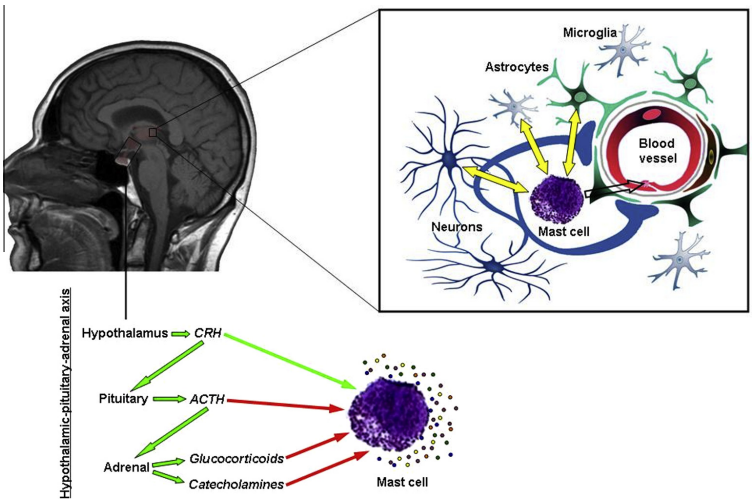
Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Brain, Behavior, and Immunity 50 (2015) 314–321

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases



Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Brain, Behavior, and Immunity 50 (2015) 314–321

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

	Possible symptoms of MCAD
Psychiatry	• Gratuitous upset (e.g., angry, depressed) (Hermine et al., 2008, e32), • motivation disorder (Hermine et al., 2008, e30, e37, e69), • depressive episode (Hermine et al., 2008, e30, e32, e37, e70, e60), • bipolar affective disorder (Afrin et al., 2013; Afrin and Molderings, 2014), • attention deficit hyperactivity disorder (Afrin et al., 2013; Afrin and Molderings, 2014), • anxiety disorder (e30, e14, e72, e60), • posttraumatic stress syndrome (Afrin et al., 2013; Afrin and Molderings, 2014), • visual hallucinations that disappear under blockade of mast cells (own observations), • panic attacks (Afrin et al., 2013), • hyperventilation tetany-like symptoms (Afrin and Molderings, 2014), • psychosis (e73), • disturbance of memory (Afrin et al., 2013; Hermine et al., 2008, e31, e32, e70), • word-finding difficulties (Afrin et al., 2013, e32), • difficulties in concentrating (Hermine et al., 2008, e31, e32 e70, e69).

MCAS Screening Tool

MCAS Screening

1. Do you have episodes or flare-ups of any of the following: flushing, itching, hives, swelling, shortness of breath, throat tightness, dizziness, feeling faint, abdominal cramping, diarrhea, nausea, headache, brain fog, or bone pain?

☐ Yes ☐ No

2. When these episodes happen, do they usually affect 2 or more body systems at the same time, such as skin plus gut symptoms, skin plus breathing symptoms, or gut plus dizziness or faintness?

☐ Yes ☐ No

3. Have you ever had a more severe reaction with trouble breathing, throat swelling, severe flushing, severe dizziness, or almost passing out?

☐ Yes ☐ No

4. Do your symptoms seem to be triggered or worsened by foods, medications, heat, cold, scents, stress, exertion, or infections?

☐ Yes ☐ No

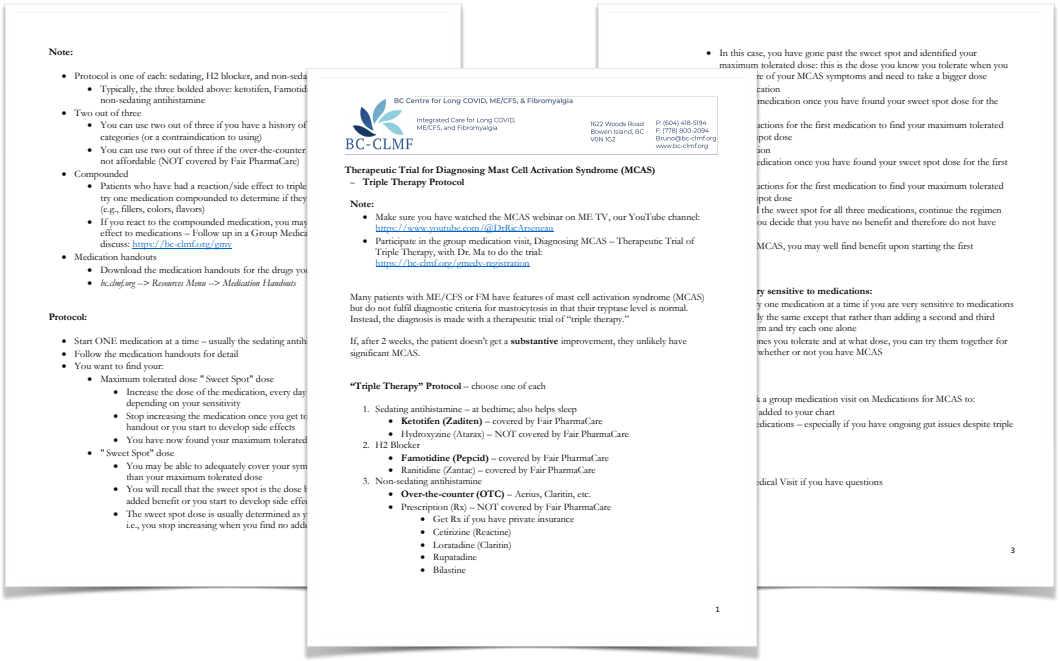
5. Do these symptoms improve, even partly, with antihistamines or other mast cell-directed treatment?

☐ Yes ☐ No

Scoring for MCAS Screen
• Count each "Yes" as 1 point
• Total score: ____ / 5
• Any "Yes" answer is a positive screen and is a reason for further physician assessment.
Interpretation note: This screen is intentionally designed to be highly sensitive rather than specific. It is meant to identify patients who may need further physician assessment, not to diagnose MCAS.

Click to Download

MCAS Resources



BC Centre for Long COVID, ME/CFS, & Fibromyalgia

BC-CLMF — Integrated Care for Long COVID, ME/CFS, and Fibromyalgia

1622 Woods Road, Bowen Island, BC V0N 1G2 — P: (604) 418-5194, F: (778) 800-2094, Bruno@bc-clmf.org, www.bc-clmf.org

Therapeutic Trial for Diagnosing Mast Cell Activation Syndrome (MCAS)
– **Triple Therapy Protocol**

Note:

- Make sure you have watched the MCAS webinar on ME TV, our YouTube channel: https://www.youtube.com/@DrRicArseneau
- Participate in the group medication visit, Diagnosing MCAS – Therapeutic Trial of Triple Therapy, with Dr. Ma to do the trial: https://bc-clmf.org/gmedv-registration

Many patients with ME/CFS or FM have features of mast cell activation syndrome (MCAS) but do not fulfil diagnostic criteria for mastocytosis in that their tryptase level is normal. Instead, the diagnosis is made with a therapeutic trial of "triple therapy."

If, after 2 weeks, the patient doesn't get a **substantive** improvement, they unlikely have significant MCAS.

"Triple Therapy" Protocol – choose one of each

1. Sedating antihistamine – at bedtime; also helps sleep
   - **Ketotifen (Zaditen)** – covered by Fair PharmaCare
   - Hydroxyzine (Atarax) – NOT covered by Fair PharmaCare
2. H2 Blocker
   - **Famotidine (Pepcid)** – covered by Fair PharmaCare
   - Ranitidine (Zantac) – covered by Fair PharmaCare
3. Non-sedating antihistamine
   - **Over-the-counter (OTC)** – Aerius, Claritin, etc.
   - Prescription (Rx) – NOT covered by Fair PharmaCare
     - Get Rx if you have private insurance
     - Cetirizine (Reactine)
     - Loratadine (Claritin)
     - Rupatadine
     - Bilastine

1

Click to Download

MCAS Rarely Occurs In Isolation

diagnostics

MDPI

Article

The Clinical Relevance of Mast Cell Activation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Diagnostics **2025**, *15*, 2828 https://doi.org/10.3390/diagnostics15222828

- 25% of ME/CFS have MCAS and respond to treatment
- ME/CFS + MCAS more orthostatic intolerance (OI) vs ME/CFS

	ME/CFS + MCAS	ME/CFS	
Orthostatic Intolerance (OI)	70.3%	49.7%	p = 0.005
• POTS	50.8%	36.5%	
• Orthostatic Hypotension (OH)	23.1%	13.6%	p = 0.112

Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders

***Hypertension*. 2005; 45:385-390.**

- POTS + MCAS
  - Acute hypertensive crisis – as high as 240/140
- Pseudopheochromocytoma
- Beta blockers commonly used in POTS
  - Use with caution in H-POTS + MCAS – episodes of hypertension

Expert Rev Clin Immunol. 2019 June ; 15(6): 639–656. doi:10.1080/1744666X.2019.1596800.

Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?

Conditions Often Comorbid With Mast Cell Diseases

- Chronic inflammatory response syndrome (CIRS)
- Fibromyalgia syndrome (FMS)
- Ehlers-Danlos Syndrome (EDS)
- Gulf War Illness (GWI)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
- Irritable bowel syndrome (IBS)
- Kounis syndrome
- Multiple chemical sensitivity syndrome (MCSS)
- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- Post-Lyme syndrome
- Postural orthostatic tachycardia syndrome (POTS)
- Post-traumatic stress disorder (PTSD)

Birds of a Feather - CSS

- ME/CFS
- Fibromyalgia (FM)
- Myofascial Pain Syndrome (MPS)
- Migraines
- Tension Type Headaches
- Irritable Bowel Syndrome (IBS)
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Interstitial Cystitis (IC)
- Pelvic Pain Syndrome (PPS)
- PTSD
- Non-Cardiac Chest Pain (Costochondritis)
- Temporomandibular Disorder (TMD)
- Irritable Larynx Syndrome (ILS)
- Central Abdominal Pains Syndrome (AKA Functional)
- Other Pain Syndromes

Birds of a Feather - CSS

- ME/CFS
- Fibromyalgia (FM)
- Myofascial Pain Syndrome (MPS)
- Migraines
- Tension Type Headaches
- Irritable Bowel Syndrome (IBS)
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Interstitial Cystitis (IC)
- Pelvic Pain Syndrome (PPS)
- PTSD
- Non-Cardiac Chest Pain (Costochondritis)
- Temporomandibular Disorder (TMD)
- Irritable Larynx Syndrome (ILS)
- Central Abdominal Pains Syndrome (AKA Functional)
- Other Pain Syndromes

Average: 5 – 6 CSS
Range: 1 – 14

Clinical Reviews in Allergy & Immunology
https://doi.org/10.1007/s12016-019-08755-8

The Relationship Between Hypermobile Ehlers-Danlos Syndrome (hEDS), Postural Orthostatic Tachycardia Syndrome (POTS), and Mast Cell Activation Syndrome (MCAS)

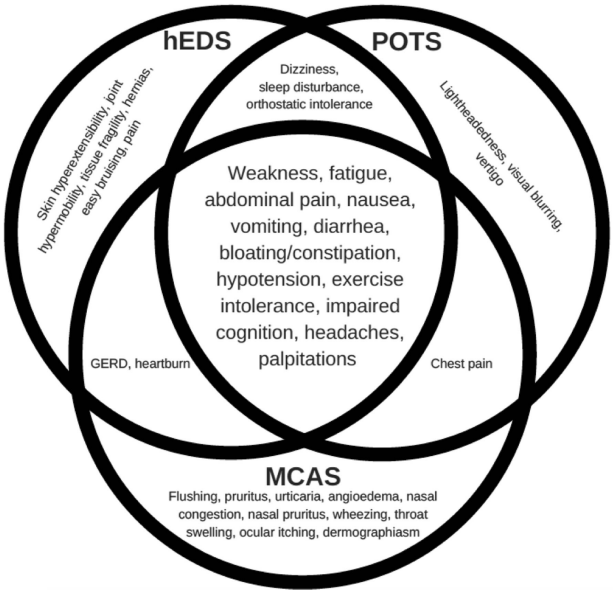
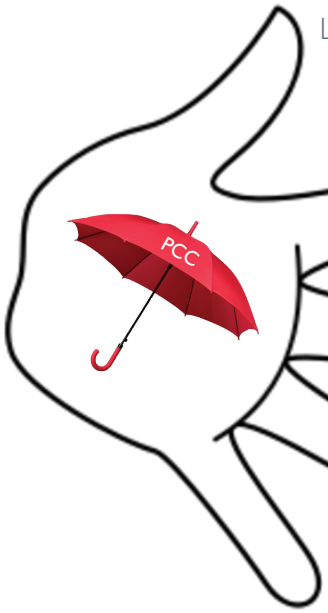


Fig. 3 Patient reported symptoms in hEDS, POTS, and MCAS. (*MCAS* mast cell activation syndrome, *POTS* postural orthostatic tachycardia syndrome, *hEDS* hypermobile Ehlers-Danlos syndrome)

55

Post Covid Conditions (PCC)



Tissue damage / inflammation
Lung scarring, DVT, anosmia, myocarditis

Autoimmune
RA, SLE, IBD, Sjogren's, alopecia, vitiligo

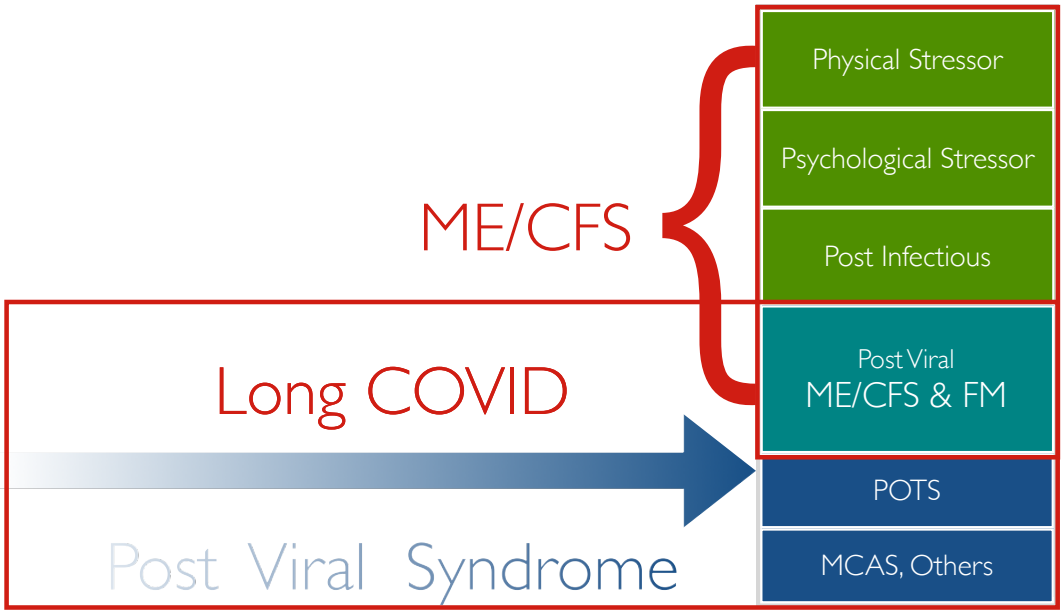
Metabolic
DM, HTN, High cholesterol

Psychiatric / psychological
Depression, anxiety, PTSD

Post-viral syndromes: **Long COVID**
ME/CFS, FM, POTS, MCAS, …

56

LONG COVID SPECTRUM



ELSEVIER

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Mast cell activation symptoms are prevalent in Long-COVID

International Journal of Infectious Diseases 112 (2021) 217–226

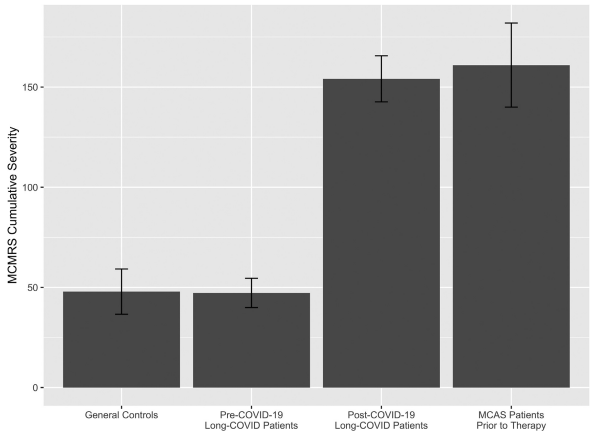


Figure 2. Mean mast cell mediator release syndrome cumulative severity for each group, with whiskers showing 95% confidence intervals.

DOI: 10.1111/all.15188
November 2021

Mast cell activation is associated with post-acute COVID-19 syndrome

- Evidence of mast cell (MC) activation in sera and lung tissue in patients with acute COVID-19 infection
- *While it remains unclear if MC activation is causative in PASC or simply a consequence, larger longitudinal studies to validate our findings and assess the natural history are critical.*

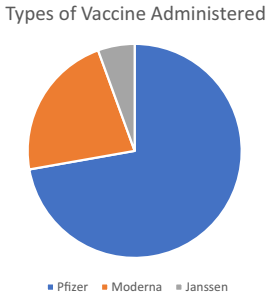
59

Safety of COVID-19 vaccination in patients with mastocytosis and monoclonal mast cell activation syndrome

Rayan Kaakati, MD[a,*], Dilawar Khokhar, MD[b,*], and Cem Akin, MD, PhD[b]

Clinical Implications

- Patients with mastocytosis and monoclonal mast cell activation syndrome tolerate COVID-19 vaccination.



- 259 patients
- Suggest premedication with an antihistamine
- Our findings suggest that most patients with mastocytosis, even those with an allergic or anaphylactic history, can be safely vaccinated.

60

Special Article

COVID-19 Vaccination in Mastocytosis: Recommendations of the European Competence Network on Mastocytosis (ECNM) and American Initiative in Mast Cell Diseases (AIM)

Mastocytosis is a neoplasm characterized by an accumulation of mast cells in various organs and increased risk for severe anaphylaxis in patients with concomitant allergies. Coronavirus disease 2019 (COVID-19) is a pandemic that is associated with a relatively high rate of severe lung disease and mortality. However, even in these patients, severe adverse re-actions are rare. We therefore recommend the broad use of COVID-19 vaccination in patients with mastocytosis on a global basis. The only well-established exception is a known or suspected allergy against a constituent of the vaccine.

AN ALPHABET SOUP OF ACRONYMS

ME/CFS
FM
POTS
MCAS
IBS
hEDS
PTSD
MPS

An Alphabet Soup of Acronyms

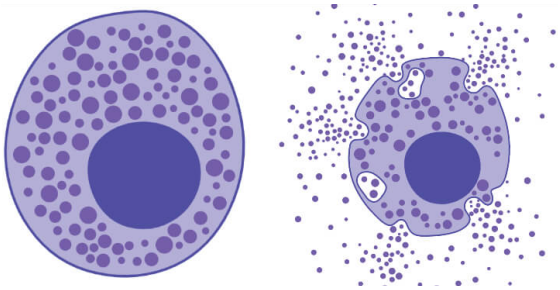
An Alphabet Soup of Acronyms

An Alphabet Soup of Acronyms

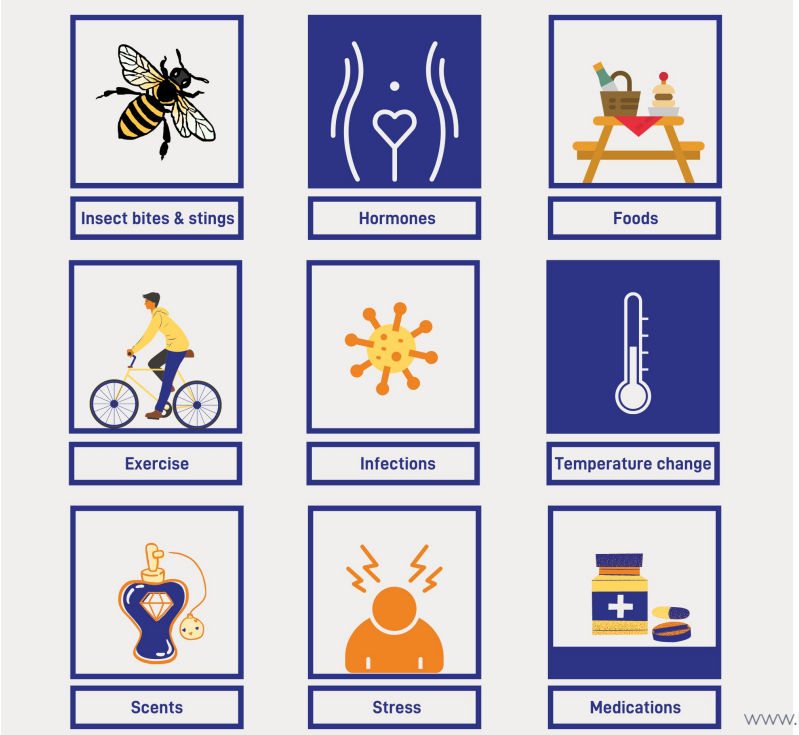
MCAS is a *Worser Maker*

MCAS – Treatment

- Avoid Triggers
- Medication
  - Antihistamines – sedating / non-sedating (block receptors)
  - Mast cell stabilizers (block release)
  - Leukotriene inhibitors
  - Other
- Supplements
  - May not be needed after meds
- Diet
  - May not be needed after meds
  - Too early: risk eating disorders



Mast Cell Triggers



MCAS – Treatment – Avoid Triggers

- Alcohol
- Preservatives
- Spices
- Temperature – heat / cold
- Drugs
- Radiocontrast media,
- Hymenoptera stings
- Physical stimuli (pressure, friction)
- UV light
- Estrogen
- Stress

MCAS – Treatment – Avoid Triggers

- Drugs
  - Antibiotics
  - Non-steroidal Anti-Inflammatory Drugs (NSAIDS)
  - Opioids (narcotics)
  - Neuromuscular Junction Blocking Agent (anesthesia)
  - Niacin
  - β-blockers (use with caution)
  - ACE inhibitors (use with caution)

MCAS – Treatment – Medications

- Optimizing MCAS treatment
  1. Most patients will need 3 medications
     1. Sedating antihistamine
        - Ketotifen (Zaditen) or hydroxyzine (Atarax)
        - Diphenhydramine (Benadryl) – not well tolerated
     2. Non-sedating antihistamine
        - OTC
        - Rupatadine (Rupall) or bilastine (Blexten)
        - None covered by Fair Pharmacare
     3. H2 Blocker
        - Famotidine (Pepcid) or ranitidine (Zantac)

MCAS – TREATMENT – MEDICATIONS

- Optimizing MCAS treatment
  2. Dosing
     - Much higher doses than usual are needed
       - Double or more
       - See medication handouts
     - Finding the optimal dose
       - The "sweet spot"
     - Finding the maximum tolerated dose
       - Symptom flare / vaccination / surgery / etc

MCAS – TREATMENT – MEDICATIONS

- Optimizing MCAS treatment
  3. Significant or ongoing gut symptoms – add / try in order
     - Cromolyn (Nalcrom)
       - Non-absorbable mast cell stabilizer before meals
       - Not an antihistamine – may take 3-4 weeks for benefit
     - PEA (palmitoylethanolamide)
       - Supplement: helps with leaky gut, inflammation, MCAS, +
     - DAO (diamine oxidase)
       - Supplement (formerly *histaminase*)
     - Diet

MCAS – TREATMENT – MEDICATIONS

- Optimizing MCAS treatment
  4. Ongoing symptoms
     - Consider montelukast (Singulair)
       - Leukotriene receptor antagonists
       - Respiratory symptoms
       - Black Box Warning (suicidality)
  5. Severe or uncontrolled symptoms
     - Angioedema or anaphylaxis
     - Should see an allergist immunologist.
       - Biologicals
       - EpiPen

MCAS – TREATMENT – MCAS FRIENDLY

"Two For's" (two for one benefit)

- **Low dose naltrexone (LDN)** 400 mg - 12 mg a day *pain/overall symptoms*
- **Medicinal cannabinoids** *pain/sleep/other*
- **Amitriptyline** 5 - 50 mg at bedtime *pain/sleep/other*
- **Nortriptyline** 10 - 50 mg at bedtime *pain/sleep/other*
- **Guanfacine** 1 - 4 mg at bedtime *brain fog*
- **Nozinan** 2 - 6 mg at bedtime *sleep maintenance*
- **Clonidine** 0.1- 0.2 mg at bedtime *nightmares/sweats*
- **Doxepin** 1.5 - 9 mg at bedtime *sleep maintenance*
- **GLP 1** e.g., Ozempic

Recognition and Management of Medication Excipient Reactivity in Patients With Mast Cell Activation Syndrome

Am J Med Sci 2019;357(6):507–511.

Excipient type	Purpose	Examples
Anti-adherents, lubricants, glidants	Prevent tablets from sticking together	Magnesium stearate, stearic acid, talc, silica, magnesium carbonate
Antimicrobial agents	Reduce the risk of infectious contamination	Benzyl alcohol, phenol, methylparaben
Binders, fillers	Bind ingredients and give volume to tablets when the active ingredient is present in very small amounts	Microcrystalline cellulose, lactose, sucrose, starches, sorbitol, gelatin, polyethylene glycol
Coatings	Protect the tablet or capsule ingredients from deterioration and make tablets easier to swallow	Shellac, gelatin
Dyes	Improve the identification of medications and improve the "aesthetic look" of medications	FD&C red #5, FD&C yellow #10, FD&C blue #2, ferric oxide red, ferric oxide yellow
Flavorings, sweeteners	Used to mask unpleasant tasting active ingredients and improve the likelihood the patient (especially kids) will complete the prescribed course of therapy	Sucralose, xylitol
Preservatives	Increase the shelf-life of the medication; reduce risk of infectious contamination	Methyl paraben, citric acid, retinol palmitate
Solubilizing agents	Solubilize the active ingredient	Alcohols, acetone, glycerol, EDTA, polysorbate 80
Disintegrants	Expand and dissolve when wet, causing the tablet to break apart in the digestive tract, releasing the active ingredient for absorption	Crospovidone, croscarmellose, sodium starch glycolate

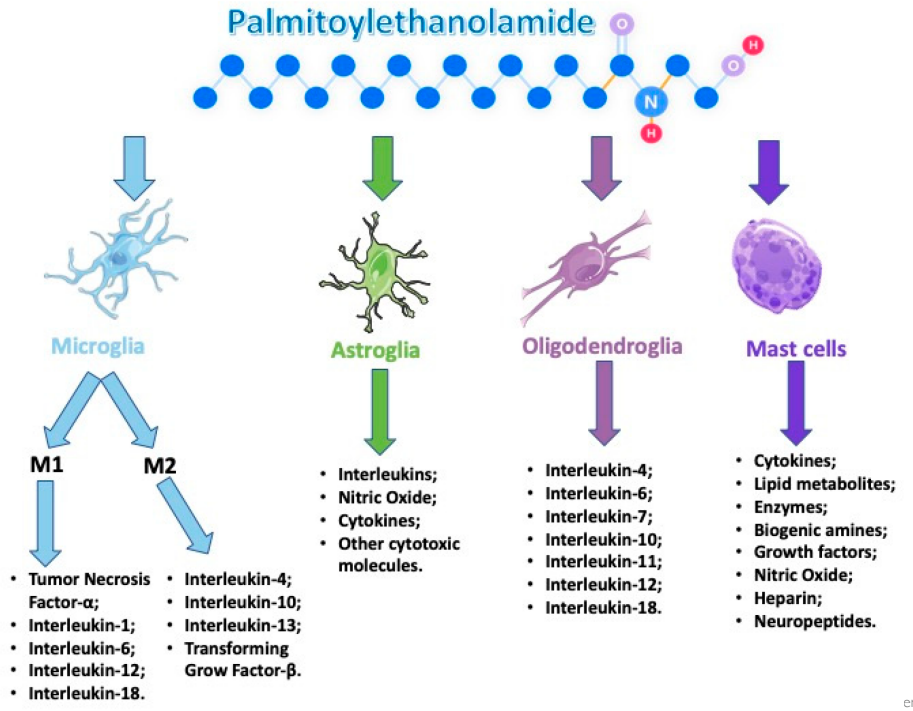
Abbreviations: EDTA, ethylenediaminetetraacetic acid; FD&C, United States Federal Food, Drug, and Cosmetic Act.

MCAS – TREATMENT – SUPPLEMENTS

- **PEA (palmitoylethanolamide)** 400 mg TID or 600 mg BID
- **Vitamin C slow-release** 500 - 1,000 mg a day
- **Vitamin D** 2,000 IU a day
- **N-acetylcysteine (NAC)** 300-600 mg 2x/day
- Flavonoids
  - **Quercetin** 250 - 1,000 mg 2x/day - OTC
  - **Luteolin** 100 - 400 mg 2x/day - OTC
  - **Curcumin** 3x/day —> **Theracurmin** Extra Strength 300 once daily
- **DAO – diamine oxidase** (formerly *histaminase*) 4.2 mg before meals

PEA AND INFLAMMATION

250 + studies: pain, inflammation, **leaky gut**, brain fog, **MCAS**



MCAS – TREATMENT – DIETARY

- **Low histamine diet**
  - Foods that trigger release of histamine
    - Leftovers !
    - Milk
    - Shellfish
    - Eggs
    - Kiwi
    - Strawberry
    - Pineapple
    - Plum
- **FODMAP diet**
- **Elimination diet**
  - Gluten
  - Dairy
  - Soy
- **Low histamine diet – Avoid:**
  - Some Types Of Fish
  - Aged Cheeses
  - Processed Meats
  - Wine And Beer
  - Sauerkraut
  - Fermented Products
  - Spinach
  - Eggplant
  - Tomato
  - Avocado

bc-clmf.org

Home NEW PATIENTS Our Doctors About Contact Resources ME TV on YouTube Referral Form FAQ

- Medication Handouts
- Videos
- Helpful Websites
- POTS Handout (NASA Lean Test)
- Baseline Testing and Evaluation
- Family & Friends
- Primary Care Toolkit

Primary Care Too

ME/CFS, FM, and Long COVID

Patient Symptom Inventory

Assessment Tool

Sit / Stand Test (Rapid exercise tests for exertional desaturation)

NASA Lean Test for POTS and NMH

Baseline Testing and Evaluation

Medication and Treatment Handouts

Webinars – Long COVID, ME/CFS, and FM: A Primary Care Toolkit

Part 1 (Overview)
Part 2 (Using the Toolkit)

79

www.youtube.com/@DrRicArseneau

BC-CLMF
BC CENTRE FOR LONG COVID
ME/CFS & FIBROMYALGIA

ME TV

ME TV

@DrRicArseneau · 4.16K subscribers · 61 videos

Educational videos for patients with ME/CFS, FM, and Long COVID ...more

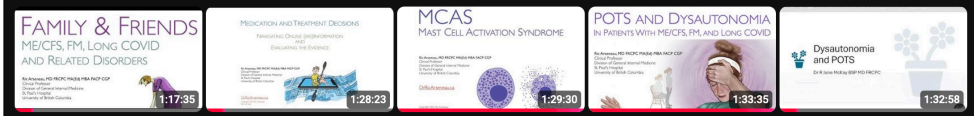
bc-clmf.org and 1 more link

Customize channel Manage videos

Home Videos Playlists Posts

Recommended Videos For New Patients Play all

We encourage all new patients to watch the family and friends video first. This will give you an overview of these conditions. We have selected the videos that we think are most relevant to all...



Family and Friends: ME/CFS, FM, and Long COVID — ME TV — 23K views • 2 years ago

Medication and Treatment Decisions – Navigating... — ME TV — 3.9K views • 2 years ago

Mast Cell Activation Syndrome (MCAS) — ME TV — 6.9K views • 2 years ago

POTS (Postural Orthostatic Tachycardia Syndrome) and... — ME TV — 14K views • 2 years ago

Dysautonomia and POTS (Postural Orthostatic... — ME TV — 1.2K views • 1 year ago

80