

# Long Covid Practitioner Programme

WEBINAR THREE

Presented by Antony Haynes, Nutritional Therapist BA(Hons), Dip ION, mCNHC, mBANT

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#### 1. Monday 23rd September 12 noon

Introduction to Long Covid, review of symptoms, example case history. Review of Nutritional Therapy solutions.

#### 2. Friday 27th September 12 noon

Functional Medicine model of Long Covid from Dr Leo Galland, including blood clotting, viral persistence, and mitochondrial disruption. Nutritional Therapy solutions.

#### 3. Monday 30th September 12 noon

Exploration into Mast Cell Activation Syndrome (MCAS) and its involvement in Long Covid symptomology. Nutritional Therapy solutions.

#### 4. Friday 4th October 12 noon

Viral persistence and viral reactivation as causes of Long Covid and the negative impact on heme by spike protein. Nutritional Therapy solutions.

#### 5. Monday 7th October 12 noon

Neurotransmitter imbalances as an explanation for multiple Long Covid symptoms. Nutritional Therapy solutions.

#### 6. Monday 14th October 12 noon

Spike protein pathogenesis. Nutritional Therapy solutions. Review and summary and presentation of Model of Long Covid including lab tests and potential therapeutic interventions.

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### 3. Monday 30th September 12 noon

# Exploration into Mast Cell Activation Syndrome (MCAS) and its involvement in Long Covid symptomology.

Nutritional Therapy solutions.





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- Mast cells are primitive cells of the immune system, and are scattered throughout your tissues and organs.
- They are also known as a mastocyte or a labrocyte.
- They do not circulate in your blood.
- Mast cells derive from the bone marrow but unlike other white blood cells, mast cells are released into the blood as mast cell progenitors and do not fully mature until they are recruited into the tissue where they undergo their terminal differentiation.
- Stem cell factor (SCF) is a cytokine essential for mast cell development, proliferation and survival.



- Mast cells can be distinguished from other cell types in tissue sections by Toludine blue staining that stains mast cells blue.
- Mast cells produce and secrete about 200 different chemicals (major ones are detailed in the next slide), called mast cell mediators, and they do so in response to a variety of internal or external triggers, which include food, drugs, temperature, environmental chemicals, physical exertion, and various types of physical trauma.
- Mast cells normally protect against infection, especially fungal or parasitic infection, and they play a major role in acute allergic reactions.
- In a well-functioning immune system, mast cell activation subsides once the trigger is either neutralised or removed.

# Mast Cell Mediators



- Histamine
- Leukotrienes (including LTC4 and LTE4)
- Prostaglandin D2 (PGD2)
- Trypsin
- Chymase
- Transforming Growth Factor-beta 1 (TGF-β1)

- Tumour Necrosis Factor-alpha (TNF-α)
- Interleukins (IL)
- Serotonin
- Substance P
- Calcitonin Gene-Related Peptide (CGRP)
- Beta-Hexosaminidase
- Nerve Growth Factor (NGF)
- These mediators are involved in various physiological processes, including allergic responses, inflammation, and immune modulation.
- Some of these mediators, such as histamine and leukotrienes, are well-established players in allergic diseases, while others, like TGF-β1 and NGF, have more nuanced roles in regulating cellular behaviour.
- It's worth noting that mast cell biology is a complex and diverse.



### Mast Cell Activation



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Mast Cells | British Society for Immunology



### Effects of Mast Cell Activation



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#### Mast Cells | British Society for Immunology

- The best known of these mediators is histamine, which produces many symptoms of allergy.
- Mast cell mediators can cause constriction (narrowing) or dilation (widening) of blood vessels; they can also make blood vessels and membranes leaky, so that fluid escapes from them.
- Mast cell mediators may cause pain, swelling, redness, shortness of breath, diarrhoea, high or low blood pressure.
- They contribute to migraine headaches, asthma and irritable bowel syndrome.
- In addition to causing symptoms on their own, mast cell mediators influence the function of more complex and evolved immune cells, like lymphocytes.
- Covid-19 can cause mast cell activation.

- In some people, once mast cells become activated, they do not "turn off" (i.e. they continue to release mediators that cause any of the above symptoms).
- Like a machine gun with its trigger stuck, they create havoc and random damage, a condition called mast cell activation syndrome (MCAS).
- Mast cell activation may contribute to microthrombosis and endothelitis.
- When patients treated for Long Covid have one of the problems listed above, or do not respond as expected or have unusual adverse reactions to treatments that should be helping them, mast cell activation (MCA) is usually the cause.
- For those people in whom MCAS is pivotal, it can dominate the syndrome or the web as Dr Galland described it, contributing to microthrombosis, endothelitis and T-cell impairment, so recognising its presence and treating it directly is essential.



Mast Cell Activation Disease and the Modern Epidemics of Chronic Illness and Medical Complexity

LAWRENCE B. AFRIN, M.D.

# MAST CELLS UNITED

A Holistic Approach to Mast Cell Activation Syndrome

AMBER WALKER

# THE TRIFECTA PASSPORT

Tools for Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos Syndrome



### AMBER WALKER

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### Some Research Papers by Dr Lawrence Afrin



- Afrin LB et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". Diagnosis (Berl). 2020 Apr 22;8(2):137-152. <u>View Abstract</u>
- Weinstock LB, Pace LA, Rezaie A, Afrin LB, Molderings GJ. Mast Cell Activation Syndrome: A Primer for the Gastroenterologist. Dig Dis Sci. 2021 Apr;66(4):965-982. <u>View Abstract</u>
- Afrin LB, Butterfield JH, Raithel M, Molderings GJ. Often seen, rarely recognized: mast cell activation disease--a guide to diagnosis and therapeutic options. Ann Med. 2016;48(3):190-201. <u>View Abstract</u>
- Dorff SR, Afrin LB. Mast cell activation syndrome in pregnancy, delivery, postpartum and lactation: a narrative review. J Obstet Gynaecol. 2020 Oct;40(7):889-901. <u>View Abstract</u>
- Aich A, Afrin LB, Gupta K. Mast Cell-Mediated Mechanisms of Nociception. Int J Mol Sci. 2015 Dec 4;16(12):29069-92. View Abstract
- Molderings GJ, Haenisch B, Brettner S, Homann J, Menzen M, Dumoulin FL, Panse J, Butterfield J, Afrin LB. Pharmacological treatment
  options for mast cell activation disease. Naunyn Schmiedebergs Arch Pharmacol. 2016 Jul;389(7):671-94. <u>View Abstract</u>
- Seidel H, Hertfelder HJ, Oldenburg J, Kruppenbacher JP, Afrin LB, Molderings GJ. Effects of Primary Mast Cell Disease on Hemostasis and Erythropoiesis. Int J Mol Sci. 2021 Aug 20;22(16):8960. <u>View Abstract</u>
- Afrin LB, Khoruts A. Mast Cell Activation Disease and Microbiotic Interactions. Clin Ther. 2015 May 1;37(5):941-53. View Abstract
- Afrin LB, Self S, Menk J, Lazarchick J. Characterization of Mast Cell Activation Syndrome. Am J Med Sci. 2017 Mar;353(3):207-215. <u>View Abstract</u>
- Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. Transl Res. 2016 Aug;174:33-59. <u>View</u> <u>Abstract</u>

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### Some Research Papers by Dr Lawrence Afrin

- Conclusions
- MCA symptoms were increased in Long Covid and mimicked the symptoms and severity reported by patients who have MCAS.
- Increased activation of aberrant mast cells induced by SARS-CoV-2 infection by various mechanisms may underlie part of the pathophysiology of Long Covid, possibly suggesting routes to effective therapy.

 Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in Long-COVID. Int J Infect Dis. 2021 Nov;112:217-226. <u>View</u> <u>Abstract</u>





## Spike Protein triggers MCAS



- Schieffer et al., 2022 notes that "exposure to the S-protein either by vaccination or SARS-CoV-2 infection may trigger identical immuno-inflammatory cascades resulting in long-Covid symptoms," which further supports the idea that the spike protein may prompt MCAS.
- A therapeutic strategy targeting both, post-VAC and post-SARS-CoV-2 long-Covid symptoms is warranted since exposure to the S-protein either by vaccination or SARS-CoV-2 infection may trigger identical immuno-inflammatory cascades resulting in long-Covid symptoms.

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Schieffer E, Schieffer B. The rationale for the treatment of long-Covid symptoms - A cardiologist's view. Front Cardiovasc Med. 2022 Sep 15;9:992686. doi: 10.3389/fcvm.2022.992686. Erratum in: Front Cardiovasc Med. 2023 Jul 21;10:1244340. Full Paper

# Spike Protein triggers MCAS

- Two sides of the same evil. SARS-CoV-2 binds via its spike protein to the angiotensin-converting enzyme (ACE)2-receptor located on multiple cell types, i.e., vascular endothelial cells, immune cells, and pulmonary epithelial cells.
- mRNA vaccines encode for the SARS-CoV-2 spike protein which is synthesised and released by the transfected cells and binds to cells carrying the ACE2-receptor.



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Schieffer E, Schieffer B. The rationale for the treatment of long-Covid symptoms - A cardiologist's view. Front Cardiovasc Med. 2022 Sep 15;9:992686. doi: 10.3389/fcvm.2022.992686. Erratum in: Front Cardiovasc Med. 2023 Jul 21;10:1244340. <u>Full Paper</u>

### Spike Protein triggers MCAS



Key points:

- MCAS shares similar symptoms with Long Covid
- MCAS may be triggered by the spike protein of SARS-CoV-2
- Hyper-inflammation caused by COVID-19 may be mediated by mast cell activation
- Exposure to the S-protein may trigger identical immuno-inflammatory cascades resulting in long-Covid symptoms

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Schieffer E, Schieffer B. The rationale for the treatment of long-Covid symptoms - A cardiologist's view. Front Cardiovasc Med. 2022 Sep 15;9:992686. doi: 10.3389/fcvm.2022.992686. Erratum in: Front Cardiovasc Med. 2023 Jul 21;10:1244340. Full Paper





- MCAS is a condition in which the patient experiences repeated episodes of the symptoms of anaphylaxis – allergic symptoms such as hives, swelling, low blood pressure, difficulty breathing and severe diarrhoea.
- High levels of mast cell mediators are released during those episodes. The episodes respond to treatment with inhibitors or blockers of mast cell mediators. The episodes are called "idiopathic" which means that the mechanism is unknown that is, not caused by allergic antibody or secondary to other known conditions that activate normal mast cells.
- Evaluation for MCAS starts with determining whether the symptoms occur in separate attacks and are typical symptoms of an anaphylactic reaction without a clear cause.



- Mast cell mediators increase during the episode. Those mediators should be measured during acute episodes and at baseline looking for elevations during symptoms.
- Finally, the improvement with treatment using inhibitors of mast cell mediators completes the diagnosis.
- N.B. "We" do not need any formal diagnosis of MCAS before engaging clients with anti-inflammatory nutritional therapy.



### Mast Cell Activation Syndrome (MCAS) -Genetics

- Mast cell activation is influenced by a number of genes, so one leading theory is that MCAS occurs in people who have inherited genes that produce hyperactive mast cells, which respond excessively to multiple minor or innocuous triggers.
- Lyons et al., 2021 mentions that "human tryptase genetics" play a role in mast cellassociated disorders, including MCAS. Tryptase is a biomarker used to diagnose mast cell-associated disorders, and variations in the gene encoding tryptase may impact clinical phenotypes.
- Lyons JJ, Yi T. Mast cell tryptases in allergic inflammation and immediate hypersensitivity. Curr Opin Immunol. 2021 Oct;72:94-106. <u>View Abstract</u>

### Genes involved in MCAS & Histamine Intolerance

- Genetic variations related to tryptase and possibly other mast cell-related genes may contribute to susceptibility.
- Histamine Intolerance: Genetic variations affecting methylation pathways may potentially contribute to susceptibility.
- Nervous, Immune: HNMT, MAOB and NAT2
- Methylation: MTHFR
- Gastro Intestinal: ALDH2, DAO and GPX1
- Comparison: Insufficient information is available to directly compare the genes involved in MCAS and histamine intolerance. Further research is needed to clarify the relationship between the two conditions.





- The symptoms most consistent with MCAS are:
- Skin related symptoms: itching (pruritus), hives (urticaria), swelling (angioedema) and skin turning red (flushing).
- Fatigue
- Heart related symptoms: rapid pulse (tachycardia), low blood pressure (hypotension) and passing out (syncope).
- Lung related symptoms: wheezing, shortness of breath and harsh noise when breathing (stridor) that occurs with throat swelling.
- Gastrointestinal tract symptoms: diarrhoea, nausea with vomiting and crampy abdominal pain.
- Feelings of being cold or occasionally hot.



- A very wide range of environmental triggers may activate symptoms of MCAS, including drugs, insect stings, allergens, pressure, extremes of temperature (hot or cold), sunlight.
- In fact, any new environmental exposure may provoke symptoms of MCAS.
- Because mast cells are found throughout the body and because they release so many mediators with such a variety of effects, potential symptoms of MCAS are numerous and vary greatly from person-to-person.



Image from https://tmsforacure.org - The Mast Cell Disease Society



- Aside from allergic and hypersensitivity disorders, conditions associated with MCAS include fibromyalgia, chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), migraine, vulvar vestibulitis syndrome, interstitial cystitis (IC), endometriosis, autistic spectrum disorders (ASD), osteoporosis, hypothyroidism, micronutrient malabsorption, POTS (postural orthostatic tachycardia syndrome), and joint hypermobility syndromes.
- Researchers believe that chronic release of mast cell mediators may contribute to the formation of each of these conditions or to their symptoms.



# Mast Cell Disease Coexisting Conditions



Image from mastcelldisease.com

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# Similarity of Long-Covid & MCAS Symptoms

### Long-Covid

- Heart Related: palpitations, low blood pressure, chest pains
- **Respiratory:** shortness of breath
- Digestive: IBS Symptoms
- **Cognitive / Neurological:** fatigue, headaches, insomnia, anxiety and depression.
- Not being able to think straight or focus ('brain fog')
- Rhinitis
- Poor Exercise Tolerance
- Joint or muscle pain

### MCAS

- Heart Related: Rapid pulse (tachycardia), low blood pressure (hypotension) & passing out (syncope).
- Respiratory: wheezing, shortness of breath and harsh noise when breathing (stridor) that occurs with throat swelling.
- **Digestive:** diarrhoea, nausea with vomiting and crampy abdominal pain.
- **Skin:** itching (pruritus), hives (urticaria), flushing, skin going red.
- Swelling (angioedema)



- Acute covid exacerbates MCAS in patients who have this condition, which may be hitherto unrecognised and untreated.
- Acute covid-19 causes MCAS in the minority of patients with Long-Covid.
- Mast cells (MCs) are activated by SARS-CoV-2.
- Although only recently recognised, MC activation syndrome (MCAS), usually due to acquired MC clonality, is a chronic multisystem disorder with inflammatory and allergic themes, and an estimated prevalence of 17%.
- Hyperinflammatory cytokine storms in many severely symptomatic Covid-19 patients may be rooted in an atypical response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than a normal response by normal MCs.
- If proven, this theory has significant therapeutic and prognostic implications.

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Afrin LB et al. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov; 100: 327–332. Published online 2020 Sep 10. <u>Full Paper</u>

Organ and system involvement in mast cell activation syndrome. Conditions highlighted in bold are also seen in Covid-19 acute infection and/or post-infectious syndrome.

Organ/system	Symptom/finding				
Constitutional	Fatigue, fevers, chills, weight loss, weight gain				
Ears, nose and	Conjunctivitis, rhinitis, sinusitis, dysosmia/anosmia, tinnitus, hearing loss,				
throat	dysgeusia/ageusia, sore throat				
Neurologic	Headaches, migraines, brain fog, anxiety, depression, insomnia, seizures				
Cardiovascular	Chest pain, palpitations, hypotension				
Pulmonary	Cough, dyspnoea, wheezing				
Urogenital	Frequency, urgency, dysuria, pelvic pain				
Oesophageal	Heartburn, dysphagia, globus, chest pain				
Stomach	Dyspepsia, nausea, vomiting				
Small	Bloating, food intolerance, abdominal pain, diarrhoea, constipation				
intestine/colon					
Hepatic	Elevated transaminases, hepatomegaly				
Salivary Glands	Swelling				
Lymphatics	Lymphadenopathy				
Dermatologic	Flushing, pruritis, urticaria, haemangiomas, nodules, rashes, alopecia				
Musculoskeletal	Myalgias, arthralgias, oedema				

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	Mast Cell (MC) Population(s): State(s)		Mast Cell (MC) Population(s): State(s)		Mast Cell (MC) Population(s): State(s)	
Healthy Patient	Normal MCs:	Appropriately quiescent	Normal MCs:	Appropriately quiescent	Normal MCs:	Appropriately quiescent
Unrecognized/ Undiagnosed/ Untreated MCAS Patient	Normal MCs:	Appropriately quiescent Inappropriately	Normal MCs:	Appropriately activated (mild to moderate	Normal MCs:	Appropriately quiescent
	Dysfunctional (likely somatically mutated) MCs:	activated (symptoms anywhere from subclinical to severe)	Dysfunctional MCs:	symptoms) Inappropriately hyperactivated (severe symptoms)	Dysfunctional MCs:	Inappropriately activated (mild to severe symptoms)
Diagnosed/Treated MCAS Patient	Normal MCs: Dysfunctional	Appropriately quiescent Controlled	Normal MCs:	Appropriately activated (mild to moderate symptoms)	Normal MCs:	Appropriately quiescent
	(likely somatically mutated) MCs:	(mild symptoms)	Dysfunctional MCs:	Controlled (mild to moderate symptoms)	Dysfunctional MCs:	Controlled (mild to moderate symptoms)
	Baseline		Acute Infection		Post-Infection	

### Time

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Afrin LB et al. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov; 100: 327–332. Published online 2020 Sep 10. Full Paper



# **Description of Illustration**

- Normal mast cells (MCs) react normally to SARS-CoV-2, participating in driving mild to moderate symptoms through the network of inflammatory cells, and returning to a quiescent state once the virus has been eradicated.
- Some of the MCs will be abnormal/dysfunctional and prone to constitutive and reactive hyperactivation if mast cell activation syndrome (MCAS) is present.
- If MCAS is undiagnosed and thus untreated, the abnormal MCs may react inappropriately and excessively to SARS-CoV-2, driving a hyperinflammatory state via excessive release of their mediators and excessive recruitment (also via their released mediators) of other inflammatory cells.
- If MCAS is diagnosed and treated, the abnormal MCs will be relatively controlled, diminishing their aberrant hyperreactivity to SARS-CoV-2.
- As major stressors (such as infections and hyperinflammation) can induce major escalations in baseline MC dysfunction in MCAS (likely via induction of additional mutations in the stem cells and multipotent progenitors at the root of the patient's population of dysfunctional MCs), the abnormal MCs in MCAS will have potential to drive post-Covid inflammatory syndrome (with clinical specifics dependent on the mutational profiles in the individual patient's MCs), but the severity of that syndrome may be mitigated by recognition/diagnosis of the patient's MCAS and pharmacologic control of the patient's dysfunctional MCs.

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Afrin LB et al. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov; 100: 327–332. Published online 2020 Sep 10. <u>Full Paper</u>



- Covid-19 infection causes mild to moderate symptoms in the majority of patients. However, these early data also suggest that even if symptoms are just 'mild to moderate' during the acute infection, fibrotic lung damage develops in some, potentially leading to long-term complications for a subset of patients (Spagnolo et al., 2020, Leask, 2020, Lechowicz et al., 2020, George et al., 2020).
- It is well known that over-activated MCs play a crucial role in the development of fibrotic conditions.
- Given that up to 17% of the population is generally pre-disposed to developing syndromes and diseases related to MC activation (Molderings et al., 2013), it is conceivable that people with this predisposition might have increased risk of developing the chronic respiratory, neurologic or other illnesses increasingly being seen following acute Covid-19 illness.



### **References - Mast Cell Activation Syndrome**

- George P.M., Wells A.U., Jenkins R.G. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020 doi: 10.1016/S2213-2600(20)30225-3. <u>Full Paper</u>
- Leask A. COVID-19: is fibrosis the killer? J Cell Commun Signal. 2020;14(2):255. Full Paper
- Lechowicz K., Drożdżal S., Machaj F. COVID-19: the potential treatment of pulmonary fibrosis associated with SARS-CoV-2 infection. J Clin Med. 2020;9(6):1917. <u>Full Paper</u>
- Molderings G.J., Haenisch B., Bogdanow M., Fimmers R., Nöthen M.M. Familial occurrence of systemic mast cell activation disease. PLoS One. 2013;8(9) doi: 10.1371/journal.pone.0076241. <u>Full Paper</u>
- Spagnolo P., Balestro E., Aliberti S. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020 doi: 10.1016/S2213-2600(20)30222-8. <u>Full Paper</u>

# MCAS & EMFs



- Olle Johannson of Sweden is leading the way with research into the effects of EMFs on mast cell physiology. Johannson describes a phenomenon called electro-hypersensitivity ("EHS") where certain patients experience reactions to the full-body penetration of electric and magnetic fields in their environment. Specifically, patient labeling of "environmental illness" or "multiple chemical sensitivity" are the strongest predictors of electro-hypersensitivity to EMFs.
- The unnatural environmental trigger of EMFs can cause system-wide symptoms and alterations in the immune system function. Specifically, Johannson noted that "EMFs disturb immune function through stimulation of various allergic and inflammatory responses, as well as effects on tissue repair processes."
- Johannson describes "hypersensitivity reaction" events and theorises that they are caused by three different types of antigens: (a) infectious agents, (b) environmental disturbances, and (c) self-antigens. EMFs are most certainly considered environmental disturbances.

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Johansson O. Disturbance of the immune system by electromagnetic fields—A potentially under-lying cause for cellular damage and tissue repair reduction which could lead to disease and impairment, Pathophysiology (2009) <u>Full Paper</u>



### **MEDIATORS & TESTS**

- Mast cells are known to produce many molecules that cause inflammation, but only a few mediators or their stable breakdown products (metabolites) have been found reliably elevated in episodes of MCAS and measurable in commercial laboratory tests.
- Increases in serum mast cell tryptase (a major mast cell granule protein) and in urine levels of N-methylhistamine, 11B -Prostaglandin F2α (11B-PGF2α) and/or Leukotriene E4 (LTE4) are the only useful tests in diagnosis of MCAS.
- Total serum mast cell tryptase should be drawn between 30 minutes and two hours after the start of an episode, with baseline level obtained many days later.
- The urine tests are performed on a 24 hour collection of urine that is started immediately.
- These are not standard laboratory tests.


# Tests for Mast Cell Activation Syndrome (MCAS) include:

- Increases in serum mast cell tryptase
- Urine levels of N-methylhistamine, 11B-Prostaglandin F2α (11B-PGF2α), and/or Leukotriene E4 (LTE4)
- Gene test "<u>Histamine Intolerance Report</u>" by LifeCodeGx
- Review of medical history and physical exam
- Blood and urine tests to rule out other causes
- Bone marrow tests to confirm diagnosis
- Investigating response to treatment
- Ruling out other diagnoses
- Mast Cell Activation Syndrome: Tools for Diagnosis and Differential Diagnosis



# **Histamine Receptors**

- Histamine may attach to and activate several different receptors, which have different effects, often complementary to one another, sometimes contradictory to one another.
- The first type of histamine receptor discovered is called the H1 receptor.
- H1 activation dilates blood vessels, producing redness and heat, and makes them leaky, so that blood plasma seeps out from the blood vessels into the surrounding tissues, causing swelling.
- H-1 activation causes many of the symptoms associated with classic allergic reactions, like sneezing and hives.



# **Histamine Receptors & Blockers**

- Standard antihistamine drugs are H-1 receptor blockers.
- H-2 receptors also make blood vessels dilate but they are best known for increasing secretion of stomach acid.
- Drugs that are H-2 blockers are mostly used to reduce stomach acid but may have anti-allergic effects that are additive with those of H-1 antihistamines.
- Famotidine (Pepcid) is an H2 blocker that has been shown to be beneficial in the treatment of acute Covid and Long Covid.
- Both H1 and H2 blockers have shown benefits in Long Covid, not only through relieving symptoms but by enhancing T-lymphocyte function.
- They are first-line treatments for MCAS and for a separate condition called Histamine Intolerance.



# Mast Cell Activation Syndrome (MCAS)

### TREATMENT

- If indicated by the severity of symptoms, start with epinephrine / adrenaline.
- First generation **histamine type 1 receptor blockers**, diphenhydramine and hydroxyzine can be effective for itching, abdominal discomfort and flushing, but their use may be limited by side effects (sleepiness).
- Second generation antihistamines, including loratadine, cetirizine and fexofenadine, are preferable due to fewer side effects.
- Treatment with **histamine type 2 receptor blockers**, such as ranitidine or famotidine, can be helpful for abdominal pain and nausea.
- Aspirin blocks production of prostaglandin D2 and can reduce flushing.
- Montelukast and zafirlukast block the effects of leukotriene C4 (LTC4) and zileuton blocks LTC4 production, so these reduce wheezing and abdominal cramping.
- Corticosteroids are helpful for oedema, hives and wheezing but should only be used as a last resort.
- Omalizumab (which blocks binding of IgE to its receptors) has been reported to reduce mast cell reactivity and sensitivity to activation which can reduce anaphylactic episodes.

# How to Treat MCAS



- Dr Tina Peers (UK MD) successfully treating patients with MCAS for five years.
- She believes that mast cells maybe heavily implicated in the symptoms of Long-Covid.
- Predominantly, we react to infections via mast cells.
- Dysfunctional mast cells over-react to all kinds of stimuli including infections.
- It aligns well with the Long-Covid picture.
- Symptoms observed by Dr Tina Peers in those with MCAS and Long-Covid are compellingly similar.
- Just as one individual with MCAS may manifest differently to another, so it is with Long-Covid. On average there are 7 distinct symptoms for each patient.
- Long-Covid take longer to respond to MCAS patients.
- Viral Persistence may be a factor; this keeps mast cells activated.
- Assess for and treat any infections (e.g. EBV, Lyme Disease) and mould allergy and toxicity.

## Tests for Viruses and Mould issues



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Callus on: 03331 210 305 AONM ARMINLABS ORDER FORM TEST NO. TEST NAME MATERIAL PRICE TEST NO. TEST NAME				Email: info@aonm.org				VIRUSES	
BACTERIA	MATERIAL	PRICE		TNO. TEST NAME 50 Parvovirus B19 IgG/IgM antibodies	MATERIAL PRICE Serum £50				TIKOSES
1 Borrelia Elispot	CPDA	£174		94 TBE IgG/IgM antibodies	Serum £62			26	EBV/ Elicopt (2 antigons: lytic + latent)
a Borrelia iSpot	CPDA	£268		TICKPLEX ANTIBODY SCREENING				20	EBV Elispot (2 antigens: lytic + latent)
	Hep & EDTA	£127		74 Tickplex Basic IgG/IgM antibodies (Borrelia)	Serum £120			27	EDV/LO/LNA CEDNA CEL
3 Borrelia IgG/IgM ELISA     4a Borrelia IgG/IgM Seraspot	Serum Serum	£60 £138		Tickplex Plus IgG/IgM antibodies (Borrelia, Bartonella, Babesia, Ehrlichia, Coxsackie, EBV, Parvovirus B19,	Serum £585	Armin Labs via		27	EBV IgG/IgM + anti-EBNA antibodies
4b Borrelia IgG/IgM Immunoblot	Serum	£138		Mycoplasma fermentans/pneumoniae, Rickettsia)					
56 Borrelia miyamotoi Elispot     5 Borrelia miyamotoi iSpot	CPDA	£83		YEASTS & MOULDS				28b	HSV 1 + 2 Elispot
5 Borrelia miyamotoi ispot 57 C6 ELISA (Borrelia)	CPDA Serum	£135 £44		ToxiPlex Basic (Mycotoxins: Aflatoxin B1, 03 Deoxynivalenol, Fumonisin (B1&B2), Ochratoxin A	Serum £232	AONM		20.0	
6 Ehrlichia & Anaplasma Elispot	CPDA	£83		Zearalenone)		//0////		28w	HSV 1 + 2 iSpot
6w Ehrlichia & Anaplasma iSpot	CPDA	£135		0a Candida albicans Elispot 0w Candida albicans iSpot	CPDA £83			2000	1157 1 + 2 15pot
7a Anaplasma phagocyt. IgM/IgG antibodies     7b Ehrlichia chaffeensis IgM/IgG antibodies	Serum Serum	£87 £87		0w Candida albicans iSpot 70 Candida IgG/IgA/IgM antibodies	CPDA £135 Serum £105			28	USV 1 + 2 JaC /JaA /JaM aptibodies
9a Bartonella henselae Elispot	CPDA	£83		2a Aspergillus Peptide Mix 1&2 Elispot	CPDA £167			20	HSV 1 + 2 IgG/IgA/IgM antibodies
9w Bartonella henselae iSpot	CPDA	£135		2w Aspergillus Peptide Mix 1&2 iSpot	CPDA £225				
<ul> <li>9 Bartonella (henselae + quintana) IgG antibodies</li> <li>10 Bartonella (henselae + quintana) IgM antibodies</li> </ul>	Serum Serum	£87 £87		AONM TEST PANELS 77 Panel A2 Standard Virus Panel	CPDA & £479			29	CMV Elispot (2 antigens: lytic + latent)
12a Babesia microti Elispot	CPDA	£83		78 Panel B2 Extended Virus Panel	Serum £737		_		
12w Babesia microti iSpot	CPDA	£135		79 Panel C2 Comp. Bacteria Panel	CPDA, £910 Serum, EDTA £844			30	CMV IgG/IgM + anti-EBNA antibodies
12 Babesia IgG/IgM antibodies     15 Chlamydia pneumoniae Elispot	Serum CPDA	£87 £83		80 Panel D2 Stealth Pathogen Panel 201 Post COVID Viral Reactivation Panel: Light	8 Hep £844 CPDA & £344				citt 16d/16th and 20th and boards
15w Chlamydia pneumoniae iSpot	CPDA	£135		02 Post COVID Viral Reactivation Panel: Advanced	Serum £606			31a	Varicella Zoster Virus (VZV) Elispot
16 Chlamydia pneumoniae IgG/IgA antibodies	Serum	£60		COMPLEMENTARY AND ADDITIONAL TEST	-			Jia	vancena zoster virus (vzv) Liispot
17 Chlamydia trachomatis Elispot     17w Chlamydia trachomatis iSpot	CPDA CPDA	£83 £135		2b Immune Profile (CD19/CD3-/CD57+/CD56+/CD45 Cells)	+ Hep & £169 EDTA £169			71	Variable ZastenVinus (VZV) iCast
18 Chlamydia trachomatis IgG/IgA antibodies	Serum	£60		05 RANTES	Serum £62			31w	Varicella Zoster Virus (VZV) iSpot
19a Mycoplasma pneumoniae Elispot	CPDA	£83		58 CCP antibodies	Serum £38				
19w Mycoplasma pneumoniae iSpot     19 Mycoplasma pneumoniae IgG/IgA antibodies	CPDA Serum	£135 £60		Antinuclear Antibody (ANA) titer     ds-DNA antibodies	Serum £25 Serum £26			31	VZV IgG/IgM/IgA antibodies
21 Yersinia enterocolitica Elispot	CPDA	£83	-	42 c- and p-ANCA	Serum £50				
21w Yersinia enterocolitica iSpot     22 Yersinia enterocolitica IgG/IgA antibodies	CPDA Serum	£135 £60		43 C-Reactive Protein (CRP) 44 Diarrhoea/Coeliac Disease	Serum £18 Serum £90			- 33	Coxsackievirus A7 + B1 IgG/IgA antibodies
22 resina enerciconica igu/igr annuccies     23a Rickettsia Elispot	CPDA	£83		Organ Profile: FBC, CK, Sodium, Potassium, Alk					consactierin do / in · Briga/ig/ antiboarcs
23w Rickettsia iSpot	CPDA	£135		45 Phos., AST, ALT, GGT, LDH, CHE, Amylase, Lipase, Bilinibin. Uric Acid. Creatinine. eGER. TSH	Serum & £74 EDTA			86	Echovirus IgG/IgA antibodies
23 Rickettsia IgG antibodies (rickettsii + typhi)     24 Rickettsia IgM antibodies (rickettsii + typhi)	Serum Serum	£87 £87						00	ECHOVILUS ISU/ISA antiboules
101 Campylobacter jejuni IgG/IgA Immunoblot	Serum	£131		Total Protein, Protein Electrophoresis (Albumin, Alpha1-, Alpha2-, Beta, Gamma globulin, Total	Serum £20			0.5	Enternal interlation (International Inter
102 Helicobacter pylori ELISA IgG/IgA antibodies	Serum	£63		protein)				95	Enterovirus IgG/IgA antibodies
VIRUSES 26 EBV Elispot (2 antigens: lytic + latent)	CPDA	£132		<ul> <li>Lipid profile (cholesterol, triglycerides, HDL, LDL)</li> <li>Thyroid hormones (TSH, FT3, FT4)</li> </ul>	Serum £15 Serum £64				
26 EBV EISPOL (2 anugers, iyuc + iaterit)     27 EBV IgG/IgM + anti-EBNA antibodies	Serum	£152 £138		Thyroid normones (TSN, 113, 114) Thyroid antibodies (TPO abs, TG Abs, TSH				34a	HHV-6 Elispot
28b HSV 1 + 2 Elispot	CPDA	£132		receptor Abs)	Serum £125				
28w HSV 1 + 2 iSpot     28 HSV 1 + 2 iSpot     28 HSV 1 + 2 igG/igA/igM antibodies	CPDA Serum	£225 £83		61 Reverse T3 87 Zonulin antibodies	Serum £49 Serum £64			34w	HHV-6 iSpot
28 HSV 1+ 2 (gG/)gA/(gA/ antibodies     29 CMV Elispot (2 antigens: lytic + latent)	CPDA	£132		88 TNF Alpha antibodies	Serum £38			5.00	init o opot
30 CMV IgG/IgM + anti-EBNA antibodies	Serum	£62		89 Interleukin 6 (IL-6) antibodies	Serum £64			34	HHV-6 IgG/IgM antibodies
31a Varicella Zoster Virus (VZV) Elispot     31w Varicella Zoster Virus (VZV) iSpot	CPDA CPDA	£83 £135		90 Interleukin 2 (IL-2) Receptor antibodies 92 Anti-DNase B	Serum £64 Serum £18			54	THIN-0 Igu/Igivi antiboules
31 VZV IgG/IgM/IgA antibodies	Serum	£83		93 Anti-Streptolysin O	Serum £21			75-	LUDV 7 Ellement
33 Coxsackievirus A7 + B1 IgG/IgA antibodies	Serum	£124		96 Immunoglobulin levels IgA/IgM/IgG	Serum £39			35a	HHV-7 Elispot
B6 Echovirus IgG/IgA antibodies     95 Enterovirus IgG/IgA antibodies	Serum Serum	£86 £49							
□ 34a HHV-6 Elispot	CPDA	£83	- D					35w	HHV-7 iSpot
34w HHV-6 iSpot	CPDA	£135		VITAMINS					
34 HHV-6 IgG/IgM antibodies     35a HHV-7 Elispot	Serum CPDA	£78 £83		51 Vitamin D3 (25 OH) 52 Vitamin B6 Pvroxidine	Serum £42 EDTA £49			35b	HHV-7 IgG antibodies
□ 35w HHV-7 iSpot	CPDA	£135		53 Vitamin B12	Serum £22			550	
35b HHV-7 IgG antibodies	Serum	£44		54 Vitamin B9 Folate	Serum £22			36	HHV-8 IgG antibodies
36 HHV-8 IgG antibodies  valid until new edition Academy of Nutritional Medicine	Serum	E44		91 Biotin (Vitamin B7/Vitamin H) on Centre, Cowley Road, Cambridge, CB4 OWS	Serum £42			- 50	nnv-o igu anuboules
				Email: Info@aonm.org	Page 2 of 2				

## Tests for Viruses and Mould issues

	1 1a 2 3 4a 4b 56	TEST NAME BACTERIA Borrelia Elispot Borrelia iSpot CD3-/CD57+/CD35+/CD45+ Cells	CPDA	PRICE		TEST NO.	TEST NAME Parvovirus B19 IgG/IgM antibodies	MATERIAL	PRICE
	1a 2 3 4a 4b 56	Borrelia Elispot Borrelia iSpot CD3-/CD57+/CD56+/CD45+ Cells	CPDA			50	Damasing R10 Int /Int antibodies	Conum	
	1a 2 3 4a 4b 56	Borrelia iSpot CD3-/CD57+/CD56+/CD45+ Cells	CPDA			- 50	Parvovirus b19 igo/igivi anuboules	Serum	£50
	2 3 4a 4b 56	CD3-/CD57+/CD56+/CD45+ Cells		£174		94	TBE IgG/IgM antibodies	Serum	£62
	3 4a 4b 56		CPDA	£268			TICKPLEX ANTIBODY SCREENING		
	4a 4b 56		Hep & EDTA	£127		74	Tickplex Basic IgG/IgM antibodies (Borrelia)	Serum	£120
	4b 56	Borrelia IgG/IgM ELISA	Serum	£60			Tickplex Plus IgG/IgM antibodies (Borrelia, Bartonella,		
	56	Borrelia IgG/IgM Seraspot	Serum	£138		75	Babesia, Ehrlichia, Coxsackie, EBV, Parvovirus B19,	Serum	£585
		Borrelia IgG/IgM Immunoblot	Serum	£138			Mycoplasma fermentans/pneumoniae, Rickettsia)		
		Borrelia miyamotoi Elispot	CPDA	£83			YEASTS & MOULDS		
	5	Borrelia miyamotoi iSpot	CPDA	£135			ToxiPlex Basic (Mycotoxins: Aflatoxin B1,		
	57	C6 ELISA (Borrelia)	Serum	£44		103	Deoxynivalenol, Fumonisin (B1&B2), Ochratoxin A,	Serum	£232
	6	Ehrlichia & Anaplasma Elispot	CPDA	£83			Zearalenone)		
	6W	Ehrlichia & Anaplasma iSpot	CPDA	£135		70a	Candida albicans Elispot	CPDA	£83
	7a	Anaplasma phagocyt. IgM/IgG antibodies	Serum	£87		70w	Candida albicans iSpot	CPDA	£135
	7b	Ehrlichia chaffeensis IgM/IgG antibodies	Serum	£87		70	Candida IgG/IgA/IgM antibodies	Serum	£105
	9a	Bartonella henselae Elispot	CPDA	£83		72a	Aspergillus Peptide Mix 1&2 Elispot	CPDA	£167
	9w	Bartonella henselae iSpot	CPDA	£135		72w	Aspergillus Peptide Mix 1&2 iSpot	CPDA	£225
	9	Bartonella (henselae + quintana) IgG antibodies	Serum	£87			AONM TEST PANELS		
	10	Bartonella (henselae + quintana) IgM antibodies	Serum	£87		77	Panel A2 Standard Virus Panel	CPDA &	£479
	12a	Babesia microti Elispot	CPDA	£83		78	Panel B2 Extended Virus Panel	Serum	£757
	12w	Babesia microti iSpot	CPDA	£135		79	Panel C2 Comp. Bacteria Panel	CPDA,	£910
	12	Babesia IgG/IgM antibodies	Serum	£87		80	Panel D2 Stealth Pathogen Panel	Serum, EDTA - & Hep	£844
	15	Chlamydia pneumoniae Elispot	CPDA	£83		201	Post COVID Viral Reactivation Panel: Light	CPDA &	£344
	15w	Chlamydia pneumoniae iSpot	CPDA	£135		202	Post COVID Viral Reactivation Panel: Advanced	Serum	£606
	16	Chlamydia pneumoniae IgG/IgA antibodies	Serum	£60			COMPLEMENTARY AND ADDITIONAL TESTS		
	17	Chlamydia trachomatis Elispot	CPDA	£83			Immune Profile (CD19/CD3-/CD57+/CD56+/CD45+	Hep &	
	17W	Chlamydia trachomatis iSpot	CPDA	£135		2b	Cells)	EDTA	£169
	18	Chlamydia trachomatis IgG/IgA antibodies	Serum	£60		105	RANTES	Serum	£62
	19a	Mycoplasma pneumoniae Elispot	CPDA	£83		38	CCP antibodies	Serum	£38
	19w	Mycoplasma pneumoniae iSpot	CPDA	£135		39	Antinuclear Antibody (ANA) titer	Serum	£25
ŏ	19	Mycoplasma preumoniae IgG/IgA antibodies	Serum	£60		40	ds-DNA antibodies	Serum	£26
	21	Yersinia enterocolitica Elispot	CPDA	£83		40	c- and p-ANCA	Serum	£50
	21w	Yersinia enterocolitica iSpot	CPDA	£135		43	C-Reactive Protein (CRP)	Serum	£18
	22	Yersinia enterocolitica IgG/IgA antibodies	Serum	£60		44	Diarrhoea/Coeliac Disease	Serum	£90
	23a	Rickettsia Elispot	CPDA	£83				Jerum	2.50
	2.3a 23W	Rickettsia iSpot	CPDA	£135		45	Organ Profile: FBC, CK, Sodium, Potassium, Alk Phos., AST, ALT, GGT, LDH, CHE, Amylase, Lipase,	Serum &	£74
	23	Rickettsia IgG antibodies (rickettsii + typhi)	Serum	687	-		Bilirubin, Uric Acid, Creatinine, eGFR, TSH	EDTA	274
	24	Rickettsia IgM antibodies (rickettsii + typhi)	Serum	687					-
	101	Campylobacter jejuni IgG/IgA Immunoblot	Serum	£131		46	Total Protein, Protein Electrophoresis (Albumin, Alpha1-, Alpha2-, Beta, Gamma globulin, Total	Serum	£20
	102	Helicobacter pylori ELISA IgG/IgA antibodies	Serum	£63		40	protein)	Seruili	EZU
-	102	VIRUSES	Serum	100		47	Lipid profile (cholesterol, triglycerides, HDL, LDL)	Serum	£15
-	26	EBV Elispot (2 antigens: lytic + latent)	CPDA	£132		47	Thyroid hormones (TSH, fT3, fT4)	Serum	£64
	20	EBV IgG/IgM + anti-EBNA antibodies	Serum	£132		40		Seruili	204
		010				49	Thyroid antibodies (TPO abs, TG Abs, TSH	Serum	£125
	28b 28w	HSV 1 + 2 Elispot HSV 1 + 2 iSpot	CPDA CPDA	£132 £225		61	receptor Abs) Reverse T3	Serum	649
					-				2.15
	28	HSV 1 + 2 IgG/IgA/IgM antibodies	Serum	£83 £132		87 88	Zonulin antibodies	Serum	£64 £38
		CMV Elispot (2 antigens: lytic + latent)	CPDA				TNF Alpha antibodies	Serum	
	30 31a	CMV IgG/IgM + anti-EBNA antibodies	Serum CPDA	£62 £83		89 90	Interleukin 6 (IL-6) antibodies	Serum	£64 £64
		Varicella Zoster Virus (VZV) Elispot		1.01.0			Interleukin 2 (IL-2) Receptor antibodies	Serum	2.01
	31w	Varicella Zoster Virus (VZV) iSpot	CPDA	£135	<u> </u>	92	Anti-DNase B	Serum	£18
	31	VZV IgG/IgM/IgA antibodies	Serum	£83		93	Anti-Streptolysin O	Serum	£21
	33	Coxsackievirus A7 + B1 IgG/IgA antibodies	Serum	£124		96	Immunoglobulin levels IgA/IgM/IgG	Serum	£39
	86	Echovirus IgG/IgA antibodies	Serum	£86					L
	95	Enterovirus IgG/IgA antibodies	Serum	£49					
	34a	HHV-6 Elispot	CPDA	£83					L
	34w	HHV-6 iSpot	CPDA	£135			VITAMINS		
	34	HHV-6 IgG/IgM antibodies	Serum	£78		51	Vitamin D3 (25 OH)	Serum	£42
	35a	HHV-7 Elispot	CPDA	£83		52	Vitamin B6 Pyroxidine	EDTA	£49
	35W	HHV-7 iSpot	CPDA	£135		53	Vitamin B12	Serum	£22
	35b	HHV-7 IgG antibodies	Serum	£44		54	Vitamin B9 Folate	Serum	£22
	36	HHV-8 IgG antibodies	Serum	£44		91	Biotin (Vitamin B7/Vitamin H)	Serum	£42
valid un	til new ed	ition Academy of Nutritional Medicin	ne (AONM), S		Innov		entre, Cowley Road, Cambridge, CB4 OWS		

	YEASTS & MOULDS
103	ToxiPlex Basic (Mycotoxins: Aflatoxin B1, Deoxynivalenol, Fumonisin (B1&B2), Ochratoxin A, Zearalenone)
70a	Candida albicans Elispot
70w	Candida albicans iSpot
70	Candida IgG/IgA/IgM antibodies
72a	Aspergillus Peptide Mix 1&2 Elispot
72w	Aspergillus Peptide Mix 1&2 iSpot

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## Tests for Viruses and Mould issues



• Via Regenerus Labs



• Sample Reports: Mycotoxin Panel (RealTime Lab) and Mycotoxin (Mosaic Diagnostics)

# DAO & HNMT



- DAO (diamine oxidase) & HNMT (H-n-methyltransferase) are the two enzymes that break down histamine.
- MTHFR & MAOB also play roles in the process of degrading histamine.

Nutrients required to support these enzymes:

- DAO Vitamin B2, B6
- HNMT Folate, B12, B6, B2 (methylation), zinc, magnesium
- MTHFR Folate, B12, B6, B2 (methylation)
- MAOB Vitamin B2, magnesium, zinc

# Cromolyn



- Cromoglicic acid (INN) also referred to as cromolyn (USAN), cromoglycate (former BAN), or cromoglicate - is traditionally described as a mast cell stabiliser, and is commonly marketed as the sodium salt sodium cromoglicate or cromolyn sodium.
- This drug prevents the release of inflammatory chemicals such as histamine from mast cells.

### Luteolin as Mast Cell Stabiliser and Anti-Histamine



- Tsilioni et al., 2024 states that luteolin is significantly more potent than cromolyn in inhibiting the release of histamine, tryptase, metalloproteinase-9, and vascular endothelial growth factor from cultured human mast cells.
- Hao et al., 2022 reports that luteolin inhibits Fc epsilon RI- and Mas-related G protein-coupled receptor X2 (MRGPRX2)-mediated mast cell activation, including degranulation and release of cytokines in vitro.
- Kritas et., 2013 confirm that luteolin belongs to a flavone group of compounds called flavonoids, which has anti-oxidant properties, inhibits some cancer cell proliferation and exerts a regulatory effect on mast cell-mediated inflammatory diseases and allergy.
- Tsilioni I, Theoharides T. Luteolin Is More Potent than Cromolyn in Their Ability to Inhibit Mediator Release from Cultured Human Mast Cells. Int Arch Allergy Immunol. 2024;185(8):803-809. <u>View Abstract</u>
- Hao Y, Che D, Yu Y, Liu L, Mi S, Zhang Y, Hao J, Li W, Ji M, Geng S, Shi J. Luteolin inhibits FccRI- and MRGPRX2-mediated mast cell activation by regulating calcium signaling pathways. Phytother Res. 2022 May;36(5):2197-2206. <u>View Abstract</u>
- Kritas SK, Saggini A, Varvara G, Murmura G, Caraffa A, Antinolfi P, Toniato E, Pantalone A, Neri G, Frydas S, Rosati M, Tei M, Speziali A, Saggini R, Pandolfi F, Cerulli G, Theoharides TC, Conti P. Luteolin inhibits mast cell-mediated allergic inflammation. J Biol Regul Homeost Agents. 2013 Oct-Dec;27(4):955-9. <u>View Abstract</u>

### Quercetin as Mast Cell Stabiliser and Anti-Histamine



- Quercetin is more effective than cromolyn in inhibiting IL-8 and TNF release from LAD2 mast cells stimulated by substance P.
- Moreover, Quercetin reduces IL-6 release from hCBMCs in a dose-dependent manner. Quercetin inhibits cytosolic calcium level increase and NF-kappa B activation.
- Interestingly, Quercetin is effective prophylactically, while cromolyn must be added together with the trigger or it rapidly loses its effect.
- In two pilot, open-label, clinical trials, Quercetin significantly decreased contact dermatitis and photosensitivity, skin conditions that do not respond to conventional treatment. In summary, Quercetin is a promising candidate as an effective mast cell inhibitor for allergic and inflammatory diseases, especially in formulations that permit more sufficient oral absorption.
- Weng Z, Zhang B, Asadi S, Sismanopoulos N, Butcher A, Fu X, Katsarou-Katsari A, Antoniou C, Theoharides TC. Quercetin is more
  effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in
  humans. PLoS One. 2012;7(3):e33805. <u>Full Paper</u>

### LAD2 Mast Cells



• Laboratory of allergic diseases 2 (LAD2) human mast cells were developed over 15 years ago and have been distributed worldwide for studying mast cell proliferation, receptor expression, mediator release/inhibition, and signaling.

# Curcumin inhibits Mast Cell Activation



- Curcumin inhibits PAR2- and PAR4-mediated human mast cell activation, not by inhibition
  of trypsin activity but by block of extracellular signal-regulated kinase (ERK)
  phosphorylation pathway.
- Curcumin can inhibit the expression of inflammatory mediators by suppressing NF-κB activation in human mast cell line 1, HMC-1. Curcumin inhibits the ERK, JNK, p38 MAPK, and NF-κB pathways.
- Regulation of cytokine secretion from mast cells by curcumin is also an important therapeutic strategy for inflammatory diseases.
- Baek OS, Kang OH, Choi YA, Choi SC, Kim TH, Nah YH, Kwon DY, Kim YK, Kim YH, Bae KH, Lim JP, Lee YM. Curcumin inhibits
  protease-activated receptor-2 and -4-mediated mast cell activation. Clin Chim Acta. 2003 Dec;338(1-2):135-41. <u>View Abstract</u>
- Kinney SR, Carlson L, Ser-Dolansky J, Thompson C, Shah S, Gambrah A, Xing W, Schneider SS, Mathias CB. Curcumin Ingestion Inhibits Mastocytosis and Suppresses Intestinal Anaphylaxis in a Murine Model of Food Allergy. PLoS One. 2015 Jul 6;10(7):e0132467. <u>Full Paper</u>
- Makuch S, Więcek K, Woźniak M. The Immunomodulatory and Anti-Inflammatory Effect of Curcumin on Immune Cell Populations, Cytokines, and In Vivo Models of Rheumatoid Arthritis. Pharmaceuticals (Basel). 2021 Apr 1;14(4):309. <u>Full</u> <u>Paper</u>

# How to Treat MCAS



- Low histamine diet
- Drinks can block histamine breakdown
- Some foods elicit histamine release
- Address any infection
- Address spike protein

### Anti-histamine drugs

- Type 1 anti-histamine trial and error process – "go low and slow" – 2-3 X per day
- Type 2 anti-histamine (prescribed) 40mg per day (e.g. Famotidine)
- Mast Cell Stabiliser (leukotriene inhibitor) (prescribed)(e.g. Montelukast)

### Vitamins & Minerals & Plant Extracts

- Vitamin D 3,000 iu
- Vitamin C 1000mg x 3 (natural anti-histamine)
- Niacin 100mg-250mg +
- Zinc 15-30 mg
- Selenium 100mcg per day
- Magnesium 100mg 2-3 X per day
- Help with methylation: MTHF, active B12, active B6
- Quercetin 300mg x 3 per day
- Luteolin 100mg x 3 per day
- Curcumin 500mg = x 2-3 per day

# Foods that may inhibit histamine breakdown



- Tea, especially green tea, which contains catechins that can inhibit DAO activity.
- Coffee, which contains caffeine and other compounds that can inhibit DAO and HNMT activity.
- Dark chocolate, which contains flavanols that can inhibit DAO activity.
- Berries, such as blueberries and raspberries, which contain anthocyanins that can inhibit DAO activity.
- Cruciferous vegetables, such as broccoli and cauliflower, which contain sulforaphane that can inhibit HNMT activity.
- Isoflavones, found in soybeans and soy products (directly inhibit DAO or HNMT).
- Flavanones, found in citrus fruits and juices (directly inhibit DAO or HNMT).
- Phenolic acids, found in apples and apple juice (directly inhibit DAO or HNMT).

### How relevant is this information?

# Supplements vs MCAS



### **Nutritional Supplements to consider**

- Aller Aid L92 (AR) 1 before each meal
- Quercetin 300 (AR) 1 before each meal
- CurcumRx<sup>M</sup> (BR) 1 with two or three meals
- Magnesium Powder (AR) 1 scoop in water 2-3X a day
- Mg-Zyme (BR)(100mg) 1 with one or two meals
- Homocysteine Plus (AR) 1 with two or three meals
- Bio-ADEK-Mulsion (BR) 5 drops with dinner
- Microliposomal C (AR) 1 teaspoon twice daily
- No Flush Niacin (AR) 1 with lunch
- Zn-Zyme Forte (BR) (25mg) 1 with dinner
- Se-Zyme Forte (BR)(100mcg) 1 with breakfast & dinner



## Specific Information about Luteolin

## Specific Information about Luteolin



- Luteolin is a flavonoid that is present in many fruits, vegetables, and medicinal herbs. It is the principal yellow dye compound that is obtained from the plant Reseda luteola.
- Luteolin was first isolated in pure form, and named, in 1829 by the French chemist Michel Eugène Chevreul.
- Flavonoids protect plants from microbes and other environmental threats and provide us with a range of health benefits and Luteolin has many of them.

## Luteolin as anti-inflammatory agent



- Research shows that luteolin may reduce or prevent chronic inflammation.
- In cell studies, luteolin inhibits TNF-alpha and IL-6 released via suppressing NF-κB. TNFalpha and IL-6 are linked to many chronic diseases caused by elevated inflammatory cytokines.
- In other research, luteolin reduces IL-6 (interleukin 6), an inflammatory cytokine produced in response to bacterial infections.
- In microglial cells, luteolin and another flavonoid, apigenin, suppress IL-31 and IL-33. IL-31 is an inflammatory cytokine produced by activated T lymphocytes, and it plays a role in chronic inflammatory diseases.
- All in all, the research shows luteolin as a specific anti-inflammatory to target elevated TNF, IL-6, IL-31, and IL-33.
- Through protecting against inflammatory cytokine over-production, luteolin protects against oxidative stress in cells.

### www.nutri-link.co.uk

Huang L, Kim MY, Cho JY. Immunopharmacological Activities of Luteolin in Chronic Diseases. Int J Mol Sci. 2023 Jan 21;24(3):2136. <u>Full Paper</u>

## Luteolin as anti-inflammatory agent



- Luteolin appears to be an excellent candidate for alleviating pain in chronic inflammatory conditions (e.g., rheumatoid arthritis, osteoarthritis, inflammatory bowel disease), inhibiting major inflammatory mediators involved in manifestation of pain as a symptom of the disease.
- Based on its strong anti-inflammatory and antioxidant properties shown in preclinical studies, luteolin can inhibit the major components of pain pathogenesis in neuropathy, namely oxidative stress and neuroinflammation, that lead to nerve damage and chronic pain.
- Moreover, as we described previously, there is evidence that it can also show analgesic effect via interaction with GABAA receptors.
- Luteolin appears (from preclinical and clinical data) to have a very good safety profile, making it even more appealing for clinical implementation.

### www.nutri-link.co.uk

Ntalouka F, Tsirivakou A. Luteolin: A promising natural agent in management of pain in chronic conditions. Front Pain Res (Lausanne). 2023 Mar 1;4:1114428. <u>Full Paper</u>

### **Biological Activities of Luteolin**





### www.nutri-link.co.uk

Huang L, Kim MY, Cho JY. Immunopharmacological Activities of Luteolin in Chronic Diseases. Int J Mol Sci. 2023 Jan 21;24(3):2136. <u>Full Paper</u>

## Luteolin as mast cell stabiliser and anti-histamine - References



- Kempuraj D, Tagen M, Iliopoulou BP, Clemons A, Vasiadi M, Boucher W, House M, Wolfberg A, Theoharides TC. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell-dependent stimulation of Jurkat T cells. Br J Pharmacol. 2008 Dec;155(7):1076-84. <u>Full Paper</u>
- Jeon IH, Kim HS, Kang HJ, Lee HS, Jeong SI, Kim SJ, Jang SI. Anti-inflammatory and antipruritic effects of luteolin from Perilla (P. frutescens L.) leaves. Molecules. 2014 May 27;19(6):6941-51. <u>Full Paper</u>
- Cárdenas-Rodríguez N, Bandala C, Vanoye-Carlo A, Ignacio-Mejía I, Gómez-Manzo S, Hernández-Cruz EY, Pedraza-Chaverri J, Carmona-Aparicio L, Hernández-Ochoa B. Use of Antioxidants for the Neuro-Therapeutic Management of COVID-19. Antioxidants (Basel). 2021 Jun 17;10(6):971. <u>Full Paper</u>

# Mechanisms of neuronal damage related to redox imbalance in COVID-19 & Long Covid





19. Antioxidants (Basel). 2021 Jun 17;10(6):971. Full Paper

## Luteolin's anti-inflammatory and antioxidant effects



 Luteolin inhibits major inflammatory signaling pathways (e.g., NF-κB, JAK-STAT, NLRP3), leading consequently to reduced expression of pro-inflammatory mediators (e.g., TNF-α, IL-6, COX-2, iNOS, MMPs, IL1β, IL18).

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 Moreover, luteolin seems able to activate the major antioxidant factor Nrf2, and increase the expression of antioxidant enzymes (e.g., SOD, CAT, GPx, GSH, HO-1).

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Ntalouka F, Tsirivakou A. Luteolin: A promising natural agent in management of pain in chronic conditions. Front Pain Res (Lausanne). 2023 Mar 1;4:1114428. Full Paper

# Oxidative damage and neuroinflammation in neuropathy can be inhibited by luteolin



- An illustration of the pathogenetic mechanisms implicated in neuropathic pain.
- ROS and NOS can induce nitro-oxidative damage in the vulnerable neuronal cells and activation of TRP channels which are involved in neuropathic pain transduction.
- Neuroinflammation induced from neuronal cell damage - involves the activation of resident immune cells and glial activation.
- Oxidative damage and neuroinflammation, which are considered to be reciprocal processes, can be inhibited by luteolin.

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Ntalouka F, Tsirivakou A. Luteolin: A promising natural agent in management of pain in chronic conditions. Front Pain Res (Lausanne). 2023 Mar 1;4:1114428. <u>Full Paper</u>



# Luteolin inhibits SAR-CoV-2 replication



• Luteolin, as well as curcumin, quercetin, melatonin, capsaicin, EGCG, ellagic acid, and others, inhibits SARS-Cov-2 replication.

 Cárdenas-Rodríguez N, Bandala C, Vanoye-Carlo A, Ignacio-Mejía I, Gómez-Manzo S, Hernández-Cruz EY, Pedraza-Chaverri J, Carmona-Aparicio L, Hernández-Ochoa B. Use of Antioxidants for the Neuro-Therapeutic Management of COVID-19. Antioxidants (Basel). 2021 Jun 17;10(6):971. <u>Full Paper</u>

## Aller Aid<sup>™</sup> L92 (AR)



Per 1 capsule

- BOSWELLIN<sup>®</sup> (Boswellia serrata resin)(Standardised to 70% Boswellic Acid) 265mg
- Vitamin C (as Ascorbic Acid) 250mg
- Luteolin 100mg
- Lactobacillus acidophilus L-92<sup>®</sup> 11mg



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# Specific Information about Cannabidiol (CBD), the Endocannabinoid System (ECS) & MCAS

## Cannabidiol (CBD)



 One option for helping those with MCAS that is gaining traction is Cannabidiol (CBD), a natural compound found in hemp. While research into CBD for MCAS is still in its early stages, there's a growing body of evidence suggesting its potential to influence the very systems involved in MCAS and its flare-ups.

### • The Endocannabinoid System (ECS)

• Your body has a built-in regulatory system specifically designed to maintain balance and promote well-being. This is the role of the endocannabinoid system (ECS), a complex network of receptors and signaling molecules naturally produced within the body. (1)

## Vital roles of the Endocannabinoid System (ECS)



- The ECS plays a crucial role in regulating various physiological processes, including: (2, 3, 4, 5)
- Inflammation: The ECS helps modulate inflammatory responses, preventing excessive immune system activation.
- **Pain:** ECS receptors are found throughout the nervous system, influencing pain perception and transmission.
- Immune Function: The ECS plays a role in immune cell activity and helps maintain a balanced immune response.
- **Sleep:** The ECS is involved in regulating sleep cycles and promoting relaxation.
- Mood: Emerging research suggests the ECS may influence mood and emotional regulation.

## The Endocannabinoid System (ECS)



- The ECS functions by producing its own natural cannabinoids, called endocannabinoids. These endocannabinoids bind to specific receptors located on various cells throughout the body. When activated, these receptors trigger a cascade of signals that influence various physiological functions.
- Cannabinoids, like CBD, share a structural similarity with our body's natural endocannabinoids. While CBD doesn't directly bind to the same receptors, it's believed to interact with the ECS in other ways.
- Here's where the potential for CBD to influence health comes in. CBD may:
  - Modulate the enzyme activity that breaks down endocannabinoids, allowing them to remain active for longer periods.
  - Interact with other receptors in the body, potentially influencing ECS signaling indirectly.
  - Influence the production of endocannabinoids by the body.

## The Endocannabinoid System (ECS) & MCAS



- While the exact mechanisms by which CBD interacts with the ECS are still being explored, this potential interaction offers a framework for understanding how CBD might influence various physiological processes, including those relevant to MCAS.
- Anti-inflammatory Properties and Immune Modulation:
- MCAS is characterised by excessive inflammation. Studies suggest CBD may possess anti-inflammatory properties. For example, research indicates CBD might influence the activity of cytokines, signaling molecules involved in the inflammatory response. (6) Additionally, CBD might interact with the immune system, potentially promoting a more balanced immune response. (7)

### Direct antioxidant effects of CBD





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Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and Anti-Inflammatory Properties of Cannabidiol. Antioxidants (Basel). 2019 Dec 25;9(1):21. <u>Full Paper</u>

## The Endocannabinoid System (ECS) & MCAS



### • Mast Cell Stabilisation & Potential for Reduced Histamine Release:

 Mast cells are central players in MCAS, and their activation leads to histamine release, triggering various symptoms. Some studies suggest CBD might influence mast cell function. For instance, preliminary research indicates CBD may interact with certain receptors or enzymes involved in mast cell activation and histamine release. (8)

### • Impact on Gut Health:

 There's growing interest in the gut-mast cell connection; digestive issues feature in many MCAS patients. Early research suggests CBD might positively influence gut health by promoting beneficial gut bacteria and reducing inflammation in the gut lining. (9) While the link between CBD and gut health in MCAS specifically needs further investigation, it's an interesting area to explore.

### The Endocannabinoid System (ECS) & MCAS



 The research on CBD and its potential benefits for MCAS is still in its early stages, but the initial findings are encouraging. The potential impact on gut health, where some MCAS symptoms originate, adds another layer of potential benefit. As research continues to evolve, CBD may become a valuable tool in the comprehensive management of MCAS.



### www.nutri-link.co.uk

Pacher P, Kunos G. Modulating the endocannabinoid system in human health and disease--successes and failures. FEBS J. 2013 May;280(9):1918-43. <u>Full Paper</u>

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## Cannabidiol (CBD) & MCAS - References



- Pacher P, Kunos G. Modulating the endocannabinoid system in human health and disease--successes and failures. FEBS J. 2013 May;280(9):1918-43. <u>Full Paper</u>
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- Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. Pharmacol Res. 2009 Aug;60(2):85-92. <u>Full Paper</u>
- 4. Kesner AJ, Lovinger DM. Cannabinoids, Endocannabinoids and Sleep. Front Mol Neurosci. 2020 Jul 22;13:125. Full Paper
- 5. Lu HC, Mackie K. Review of the Endocannabinoid System. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 Jun;6(6):607-615. <u>Full Paper</u>
- 6. Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and Anti-Inflammatory Properties of Cannabidiol. Antioxidants (Basel). 2019 Dec 25;9(1):21. <u>Full Paper</u>
- 7. Almogi-Hazan O, Or R. *Cannabis*, the Endocannabinoid System and Immunity-the Journey from the Bedside to the Bench and Back. Int J Mol Sci. 2020 Jun 23;21(12):4448. <u>Full Paper</u>
- 8. Nayak AP, Loblundo C, Bielory L. Immunomodulatory Actions of Cannabinoids: Clinical Correlates and Therapeutic Opportunities for Allergic Inflammation. J Allergy Clin Immunol Pract. 2023 Feb;11(2):449-457. <u>Full Paper</u>
- 9. De Filippis D, Esposito G, Cirillo C, Cipriano M, De Winter BY, Scuderi C, Sarnelli G, Cuomo R, Steardo L, De Man JG, Iuvone T. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS One. 2011;6(12):e28159. <u>Full Paper</u>

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# CBD Oil

- <u>100% Organic C\*B\*D Oil | NutriGold</u>
- 100% raw Canabidol<sup>™</sup> oil containing 500mg C\*B\*D (5%), as well as terpenes, phytocannabinoids and essential oils from Cannabis Sativa L. plant buds grown legally in the UK.
- Nutrigold Canabidol<sup>™</sup> C\*B\*D oil is extracted from the buds of Cannabis Sativa L. (hemp) plants grown organically and legally in the UK and with a fully traceable manufacturing process. All Canabidol<sup>™</sup> products are considered by the MHRA and Home Office to be legal, legitimate and have met all the required standards.
- Our Canabidol<sup>™</sup> C\*B\*D oil contains 500mg cannabidiol (C\*B\*D), an important bioactive component of cannabis plants renowned for revolutionary health promoting properties. The raw oil is carefully extracted to isolate and remove all the unwanted compounds, including tetrahydrocannabinoid (THC; the psychoactive component of cannabis), whilst maximising levels of C\*B\*D, synergistic phytocannabinoids, terpenoids, essential oils and other beneficial compounds found in this specially bred cannabis strain.
- Each batch of oil is rigorously and independently tested to ensure maximum quality, purity and C\*B\*D potency and to ensure that the THC content is <0.05%, which four times lower than the UK legal limit of 0.2% for THC in C\*B\*D (hemp) oil products.





# Supplements vs MCAS (V2)



### **Nutritional Supplements to consider**

- Aller Aid L92 (AR) 1 before each meal
- Quercetin 300 (AR) 1 before each meal
- Magnesium Powder (AR) 1 scoop in water 2-3X a day
- Mg-Zyme (BR)(100mg) 1 with one or two meals
- Homocysteine Plus (AR) 1 with two or three meals
- Bio-ADEK-Mulsion (BR) 5 drops with dinner
- Microliposomal C (AR) 1 teaspoon twice daily
- No Flush Niacin (AR) 1 with lunch
- Zn-Zyme Forte (BR) (25mg) 1 with dinner
- Se-Zyme Forte (BR)(100mcg) 1 with breakfast & dinner
- CBD Oil (NutriGold) build up to as high as 14 drops twice daily to determine benefit

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### Most Relevant Supplements ?





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## THE END

## TIME FOR QUESTIONS & COMMENTS

### 4. Friday 4th October 12 noon

Viral persistence and viral reactivation as causes of Long Covid and the negative impact on heme by spike protein. Nutritional Therapy solutions.