Mast Cell Disorders COOC . **Diagnosis and Treatment** Keith Berndtson, MD PARK RIDGE **MultiMed**



Warning

Signs and symptoms of mast cell disorders can be extreme and seemingly illogical. They are triggered by medications, supplements, foods, environmental chemicals, emotional reactions, and more.

While many triggers are documented, mast cell activation patterns are highly personal and unique to each individual.

Patients will have multiple sensitivities and many will not qualify as true allergies. The suffering caused by these conditions is compounded by delays in diagnosis. Patients are often labeled with an anxiety disorder.

The increasing incidence of mast cell disorders correlates with increasing exposure to noxious molecules in our environment.

There is a pressing need for increased physician awareness of these disorders and current methods of diagnosis and treatment.







What are Mast Cells?

Mast cells are marrow-derived immune cells that home to varied tissue compartments where they carry out roles in host defenses against infectious pathogens, allergens, toxins, and autoimmune disease.

They are essential to the innate immune response and they participate in both positive and negative regulation of the adaptive immune response.

Beaven M. Our perception of the mast cell from Paul Ehrlich to now. European Journal of Immunology. 2009 Jan;39(1):11-25.

Cardet JC, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Current Allergy and Asthma Reports.* 2013 Feb;13(1):10-18.

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What are Mast Cells?

Mast cells contain Toll-like receptors (TLRs) and receptors for estrogen, progesterone, CRH, and alpha-MSH. They also contain receptors for cytokines and chemokines, nerve growth factor, C3a, C5a, IgE, IgG, and other immune system mediators.

Derived from bone marrow, mast cells circulate in the blood as progenitor cells and acquire their specific roles in processes regulated by local tissue mediators.

Beaven M. Our perception of the mast cell from Paul Ehrlich to now. European Journal of Immunology. 2009 Jan;39(1):11-25.

Cardet JC, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Current Allergy and Asthma Reports.* 2013 Feb;13(1):10-18.

Mast Cell Heterogeneity

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Mast Cell Functions

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Mast Cells vs. Pathogens





Mast Cells vs. Viruses

Upper respiratory viral infections worsen allergic asthma, suggesting increased activation of mast cells during infection.

Mast cells recognize the presence of double-stranded viral RNA and respond by releasing: IL-29, interferon-alpha, interferon-beta, and tumor necrosis factor alpha.

Virally infected mast cells respond by releasing the anti-viral proteins: MxA and IFIT3.

Stimulation of mast cell TLR3 induces mast cell recruitment of anti-viral T cells.

Lappalainen J, et al. Intracellular RNA recognition pathway activates strong anti-viral response in human mast cells. *Clinical and Experimental Immunology*. 2013 Apr;172(1):121-8.

Orinska Z, et al. TLR3-induced activation of mast cells modulates CD8+ T-cell recruitment. Blood. 2005;106:978-987.

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Mast Cells vs. Parasites

Mast cells offer a first line of defense against parasitic pathogens. They are preferentially located in organs targeted by parasites, where they release proteases, recruit neutrophils, and regulate vessel permeability.

Mast cells release antimicrobial peptides. Their early innate immune system signal transmissions play a critical role in priming adaptive immune responses.

Metz M, Maurer M. Mast cells: key effectors in immune response. Trends in Immunology. 2007;28:234-241.



Mast Cells vs. Yeast and Fungal Forms

Parasite antigen stimulation of TLRs) and C-type lectin receptors (CLRs) initiates a wide range of mast cell IgE receptors resulting in the release of pro-inflammatory cytokines, chemokines, and other pre-stored mediators of inflammation.

The release of pre-formed mediators of inflammation is followed by the production of specific IgG1 antibodies against parasite antigens.

Saluja R, Metz M, Maurer M. Role and relevance of mast cells in fungal infections. Frontiers in Immunology. 2012 Jun;13(3):146.

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Mast Cells vs. Bacteria

Mast cells express most TLRs on their membrane surfaces. TLR binding triggers distinctive patterns of mast cell activation including the release of antimicrobial peptides and the production of complement-mediated membrane attack complexes.

Mast cell activation also results in the production of nonpreformed mediators of inflammation including matrix metallproteinase-9 (MMP-9).

Ikeda T, Funaba M. Altered function of murine mast cells in response to lipopolysaccharide and peptidoglycan. *Immunology Letters*. 2003;88:21-26.

McCurdy J. et al. Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. *Journal of Immunology*. 2003;170:1625-1629.



Mast Cells vs. Allergens

Allergen detection leads to mast cell histamine release, tight junction disruption, increased permeability, and recruitment of lymphocytes and eosinophils.

In skin, this leads to wheal and flare reactions. In the gut, this leads to intestinal hyper-permeability, smooth muscle contraction, altered water and ion transport, and intestinal symptoms. In the lungs, this leads to smooth muscle contraction, mucus production, and airway remodeling.



Mast Cells vs. Toxins

Mast cells are known to initiate an immediate IgE-dependent hypersensitivity response to venoms.

Mast cells can also be activated by various endotoxins and exotoxins.

It is not known whether mold or bacterial toxins activate mast cell responses, but mast cells release VEGF and MMP-9, markers affected in biotoxin-mediated inflammation.

Beghdadi W, Blank U, et al. et al. Mast cells as cellular sensors in inflammation and immunity. Frontiers in Immunology. 2011;2:37-91.



Mast Cells vs. Wounds

Mast cells also play non-immunological roles that include angiogenesis, tissue remodeling, and wound healing.

Noli C, Miolo A. The mast cell in wound healing in tumor growth. *Critical Reviews of Immunology*. 2011;31(6):475-529.

Gilfillan AM, Beaven MA. Regulation of mast cell response in health and disease. Critical Reviews of Immunology. 2011;31(6):475-529.



What are Mast Cells?

Master Coordinators of Host Defenses Against Noxious Incitants

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Mast Cells: The Good, the Bad, and the Ugly

The Good

- An essential player in the body's innate immune response.
- They patrol the front lines: skin, connective tissues and mucus membranes.
- They release chemical alarms to summon defenses against pathogens, allergens, toxins, and other noxious incitants.

• These chemicals include histamine, serotonin, heparin, tryptase, chymase, chemokines, eicosanoids, cytokines (TNF-alpha, IL-6, IL-1beta), leukotrienes, antimicrobial peptides, growth factors, substance P, and endothelin.

Mast Cell Mediator Pathways



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Mast Cells: The Good, the Bad, and the Ugly

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The Bad

Over-activation of mast cells can lead to:

- Allergic disease/Asthma/Anaphylaxis
- Eczema/atopic dermatitis
- Migraines/neurological disorders
- Autoimmune disorders
- Gastrointestinal disorders
- Unexplained multi-symptom illnesses

Histamine is only *one* of many inflammatory elements released by mast cells. Excess release of mast cell-derived chemicals results in mast cell-related inflammation.





Mast Cells: The Good, the Bad, and the Ugly

The Ugly

• Abnormal mast cell proliferation results in mastocytosis, which can lead to mast cell tumors and severe forms of cutaneous or systemic disease.

• Systemic mastocytosis commonly results in an unexplained multi-system, multi-symptom illness with damage to multiple organ systems that can go unrecognized in multiple medical settings.





Mast Cells Disorders

The Most Common Forms of Mast Cell Activation Syndrome

• Idiopathic (non-clonal) mast cell activation syndrome (also known as nc-MCAS): occurs more often in women for whom MC triggers are usually unknown. Idiopathic anaphylaxis and mastocytosis should be ruled out. Often indistinguishable from secondary MCAS.

• Secondary mast cell activation syndrome (another form of nc-MCAS): related to underlying inflammation caused by allergy, infection, toxicity, cancer, or autoimmune activity.

Picard M, et al. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndrome. *Clinical Therapeutics*. 2013 May;35(5):548-62.



Mast Cells Disorders

The Less Common Forms of Mast Cell Activation Syndrome

• Monoclonal mast cell activation syndrome (MMAS): systemic reactions to hymenoptera stings or unexplained anaphylaxis with high baseline tryptase. Bone marrow biopsy shows monoclonal MCs but not mastocytosis. Thought to be rare.

• Mastocytosis (SM): presenting as cutaneous or systemic variants.



Picard M, et al. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndrome. *Clinical Therapeutics.* 2013 May;35(5):548-62.



Mast Cells Disorders

Histamine-Overdrive Mast Cell Disorders

• **Histaminosis**: commonly induced by exposure to histamine from foods; rarely, an acute syndrome caused by scromboid poisoning (due to tainted seafood high in histamine).

• Histamine intolerance: sensitivity to histamine from foods and/or from reduced histamine breakdown. Can involve other mast cell mediators as well.

Maintz L, et al. Evidence for reduced histamine degradation capacity in a subgroup of patients with atopic eczema. *Journal of Allergy and Clinical Immunology*. 2006 May;117(5):1106-12.

Maintz L, Novak N. Histamine and histamine intolerance. American Journal of Clinical Nutrition. 2007 May;85(5):1185-96.

Bodmer S, et al. Biogenic amines in foods: histamine and food processing. Inflammation Research. 1999 Jun;48(6):296-300.

Histamine Receptors and Breakdown Pathways

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Histamine Intolerance

Reduced central or peripheral breakdown of histamine can lead to:

- Rashes
- Headaches
- Fatigue
- Hives or flushing
- Allergies
- Dysmenorrhea
- Estrogen dominance
- GI disturbances
- Dysrhythmias
- Arthritis
- Central, peripheral and/or autonomic neurologic disorders





Histamine Intolerance

Diagnosis

At least two typical symptoms of histamine intolerance
 Diamine oxidase (DAO) activity:

 <3 U/mL: likely
 <10 U/mL: possible
 >10 U/mL: improbable

Treatment

- Histamine-free diet for 4 weeks
- Daily symptom log
- Histamine capsule challenge with medical monitoring



Histamine Intolerance

Potential indirect causes of histamine intolerance due to reduced histamine breakdown:

- Low pyridoxal-5-phosphate reserves (active form of vit. B6).
- Low copper reserves.
- Low S-adenosyl methionine reserves (SAMe).
- Low methylation capacity (weak MTHFR or secondarily related genomic variants).
- Excess methylation demand (eg, chronic oxidative stress and inflammation, and/or chronic emotional stress).



Histamine Pathophysiology





Mastocytosis

- **Prevalence:** 1 in 10,000 (under-diagnosis suspected)
- **Prognosis:** worse for patients with widespread skin involvement, increased baseline tryptase levels, or extensive blistering.
- **Diagnosis:** based on bone marrow biopsy.
- **Conventional treatment options:** antihistamines, leukotriene antagonists (eg, montelukast), mast cell stabilizers (eg, cromolyn sodium), proton pump inhibitors, albuterol, corticosteroids

• **Integrative treatment options:** strategic nutrition-based food choices and dietary supplementation, exercise, stress reduction.



Mast cells and Irritable Bowel Syndrome

• Mast cell activation plays a role in post-infectious IBS. (1)

• Mast cell degranulation associates with cytokine alterations and intestinal hyperpermeability in patients with IBS. (2)

• Mast cell hyperplasia is seen in inflammatory bowel disorders. (3)

1. Grover M, et al. Postinfectious irritable bowel syndrome: mechanisms related to pathogens. *Neurogastroenterology and Motility*. 2014 Feb;26(2):156-67.

2. Matricon J, et al. Review article: associations between immune activation, intestinal hyperpermeability, and irritable bowel syndrome. *Alimentary Prhamacology and Therapeutics*. 2012 Dec;36(11-12):1009-31.

3. Beghdadi W, Blank U, et al. et al. Mast cells as cellular sensors in inflammation and immunity. *Frontiers in Immunology*. 2011;2:37-91.



Mast cells and Interstitial Cystitis/Bladder Pain Syndrome

• Current evidence from clinical and laboratory studies confirms that mast cells play a central role in the pathogenesis and pathophysiology of interstitial cystitis. (1)

• Mast cells promote cystitis pain and bladder pathology through separable actions of histamine and tumor necrosis factor. (2)

• Antigen ingress into the bladder submucosal layer results in mast cell degranulation. (3)

Sant GR, Theoharides T, et al. The mast cell in interstitial cystitis. *Urology*. 2007 Apr;69(4 Suppl):34-40.
 Rudick CN, et al. Mast cell-derived histamine mediates cystitis pain. *PLoS One*. 2008 May 7;3(5):e2096.
 Lu J, et al. MCP-1-induced histamine release from mast cells is associates with development of interstitial cystitis/bladder pain syndrome in rat models. *Mediators of Inflammatio*. 2012:358184.



Mast Cells and Coronary Artery Disease

Stress triggers mast cell release of inflammatory cytokines

- Mast cell activation plays a role in coronary inflammation, coronary disease, coronary hypersensitivity, and acute coronary syndromes.
- People with mastocytosis or myalgic encephaplitis/chronic fatigue syndrome are particularly prone to coronary hypersensitivity reactions.
- Stress precipitates and worsens activation of mast cells via activation of surface receptors by corticotropin releasing hormone (CRH) and other hypothalamic neuropeptide regulators.
- Mast cell stimulation by CRH and neurotensin triggers release of IL-6, which is an independent risk factor for myocardial ischemia.

Alivizos M, et al. Stress triggers coronary mast cells leading to cardiac events. *Annals of Allergy, Asthma, and Immunology.* 2014 Apr;112(4):309-316.



Mast Cells and the Blood-Brain Barrier

Acute stress triggers CRH production. CRH activates histamine release by mast cells, which leads to increased blood-brain barrier permeability. This implicates mast cells in neuroinflammatory disorders including multiple sclerosis, neuroborreliosis, and chronic inflammatory response syndrome related to poor biotoxin clearance.

Esposito P, Theoharides T, et al. Acute stress increases permeability of the blood-brain barrier through activation of mast cells. *Brain Research*. 2001;888(1):117-127.

Couturier N, Liblau RS, et al. Mast cell transcripts are increased within and outside multiple sclerosis lesions. *Journal of Neuroimmunology*. 2008 Mar;195(1-2):176-85.

image: learningneuroradiolgy.blogspt.com/2103/case-1430-choroid-plexus-xanthogranuloma



The Epigenetics of Mast Cell Activation Syndrome

- Aberrant activation of mast cells is a heritable trait.
- Epigenetic mechanisms are involved in nc-MCAS.
- nc-MCAS associates with alterations in DNA methylation related to genes responsible for DNA maintenance and repair.
- "Epigenetic processes could substantially contribute to the transgenerational transmission of nc-MCAS."

Haenisch B, et al. Evidence for contribution of epigenetic mechanisms in the pathogenesis of systemic mast cell activation syndrome. *Immunogenetics*. 2014 May;66(5):287-97.





When to Suspect MCAS

History

• Patient presents with a chronic (persistent or recurrent), waxing and waning or slowly progressive multisystem polymorbidity that is generally, but not necessarily, presents in a context of underlying chronic inflammation.

• Syndrome usually acquired early in life via interaction of environmental factors with heritable risk factors.

• Virtually all of the syndrome's manifestations are non-specific, leading to decades of unexplained illness and incorrect diagnoses that poorly respond to empiric therapies.

• Systemic MC disease of any form is not presently curable. The aim of therapy is to control symptoms through trigger avoidance, diet , lifestyle, supplements, and medications.

• Once MCAS suspected, a methodical, persistent trial-and-error approach usually leads to helpful therapy.

Molderings GJ, Afrin LB, et al. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *Journal of Hematology and Oncology*. 2011;4:10-29.



When to Suspect MCAS

Common Signs and Symptoms

• Skin: flushing, urticaria, pruritis, dermatographism, urticaria pigmentosa, angioedema, eczema.

- Gastrointestinal: abdominal pain, cramping, diarrhea, gas, bloating, reflux.
- Pulmonary: cough, wheezing, air hunger, shortness of breath.
- Upper Respiratory: nasal congestion, throat itching, soreness, or swelling.
- **Cardiovascular**: fatigue, rapid heart rate, low blood pressure, fainting, near-fainting.
- **Neurological**: headaches, difficulty concentrating, anxiety, irritability, fainting, near fainting.

Cardet JC, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Current Allergy and Asthma Reports.* 2013 Feb;13(1):10-18. Flow diagram slightly modified to include lifestyle-based therapies.



Predictors of clonal MCAS

- Male gender
- Absence of urticaria or angioedema
- Absence of near-fainting or fainting
- Serum total tryptase level >25 ng/mL

Bone marrow biopsy should be considered in patients with a serum total tryptase >20 ng/mL, or >11.4 ng/mL in patients with a history of significant blood pressure drops or fainting.

Alvarez-Twose I, et al. Clinical, biological, and molecular characteristics of of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *Journal of Allergy and Clinical Immunology*. 2010 Jun;125(6):1269-1278.



Treatment for MCAS

Avoid Known Triggers

- Temperature extremes, sunlight
- Mechanical irritation
- Alcohol, illicit drugs
- High histamine foods, food additives
- Stress
- Certain anesthetic agents
- Environmental biotoxins or man-made chemicals



Treatment for MCAS

Medications

• H1-histamine receptor antagonists (diphenhydramine, hydroxyzine, cetirizine, fexofenadine)

- H2-histamine receptor antagonists (ranitidine, famotidine)
- Mast cell stabilizers (NasalCrom, GastroCrom)
- Leukotriene inhibitor (Singulair, montelukast)



Treatment for MCAS

Supplements that Often Help

- **Neuroprotek** (quercetin, rutin, luteolin) *Algonot*
- **Histamine Block** (diamine oxidase)^{*} *Seeking Health*
- **ProBiota** (may reduce histamine in some people) *Seeking Health*
- Natural D-Hist (vit C, quercetin, nettles, bromelain, NAC) Orthomolecular
- Quercetin + C (from Saphora japonica and sago palm) TwinLabs
- Mangosteen (lowers histamine and prostaglandins) Source Naturals

* Use with caution if allergic to pork



Helpful Nutrients	Helpful Foods*	Harmful foods
antioxidants	<i>fresh</i> fruits	oxidized foods (fried, smoked)
bioflavonoids	<i>fresh</i> vegetables	processed foods
natural antihistamines	legumes (beans)	foods with additives
omega 3 fatty acids	<i>fresh</i> meats and fish	fermented foods
mangosteen	most leafy herbs	high histamine foods**

*Some persons may not tolerate helpful foods due to other types of reactivity.

**Highly aggressive restriction of histamine-containing foods may be counterproductive. The body needs histamine and may induce a compensatory increase in histamine synthesis when histamine support from food is very low.



Some high histamine foods

pickles	seeds	beer
mayonnaise	nuts	wine
sauerkraut	chocolate	champagne
vinegar	cocoa	shellfish
dried fruits	processed meats	tofu cheese
yeast	canned vegetables	mushrooms
food additives	egg whites	aged cheeses
tomatoes	spices	spinach

Keep meats and fish refrigerated! Eating meat or fish left out too long can cause histamine poisoning!



Some foods with anti-histamine effects

- Apples: rich in quercitin
- Carrots: rich in vitamin A
- Watercress: inhibits histamine release
- Broccoli: H2 receptor antagonist
- Ginger: H2 receptor antagonist
- Thyme: anaphylaxis inhibitor
- Fennel: antioxidants, antihistamine, anti-inflammatory
- Turmeric: stabilizes mast cells, inhibits histamine release

Visit www.lowhistaminechef.com to access some of the best information available on moderating mast cell activation through lifestyle change.



On low-histamine diets

You can't avoid histamine containing foods while on an otherwise toxic diet and expect to be well. The body works in conjunction with thousands of plant-based nutrients. If a low-histamine diet works it is in large part due to the multiple anti-inflammatory effects of whole foods. - Dr. Joel Fuhrman (food micronutrient expert)

I don't believe that any food list can address the mystery and beauty of nature, the body's relationship to this mystery, or the power of our minds to make us sick or well. Histamine-lowering foods work only when accompanied by an anti-inflammatory diet rich in whole foods, and a healthy, stress-reducing mind-body lifestyle.

- Yasmina Ykelenstam (The Low Histamine Chef)





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