



THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL

# *Mast Cell Activation Disorders: A Patient Guide*



Photo credit: Sam Kittner '85

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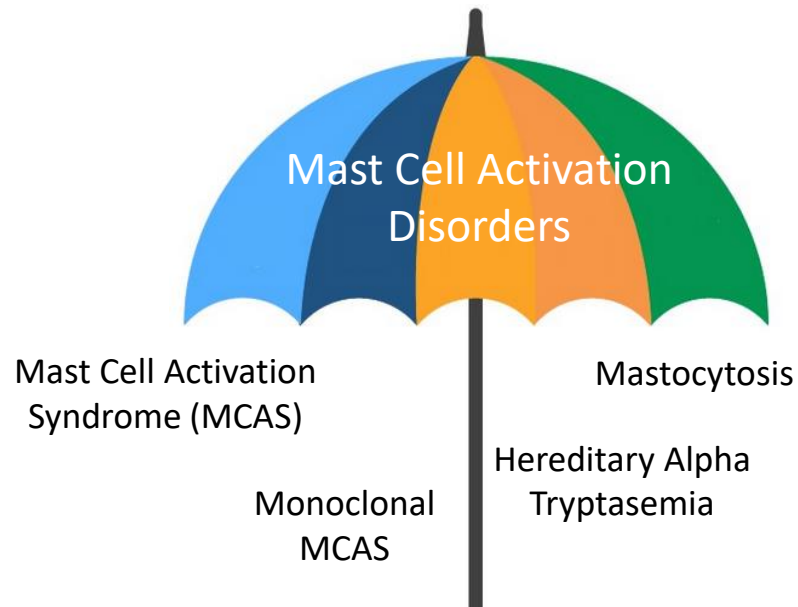
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# Why Do We Care About Mast Cell Activation Disorders?

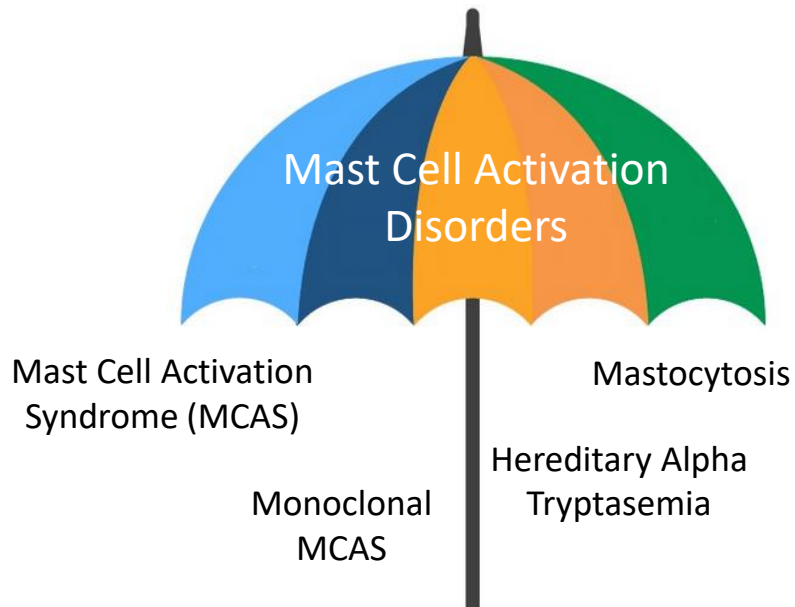
- They are complex diseases with many symptoms that often don't seem related.
- We want to understand how often these diseases occur, what other illnesses they may come with and how they make people ill.
- The disorders are ripe for new findings and progress
  - Create new drugs and other approaches for treatment
  - Refine our multiple specialist team approach for patient care
- Many of our patients are very ill and have seen many other doctors without identifying what is wrong. Many have trouble finding a doctor. Many have been sick for some time. We want to change this.

# What are Mast Cell Activation Disorders?



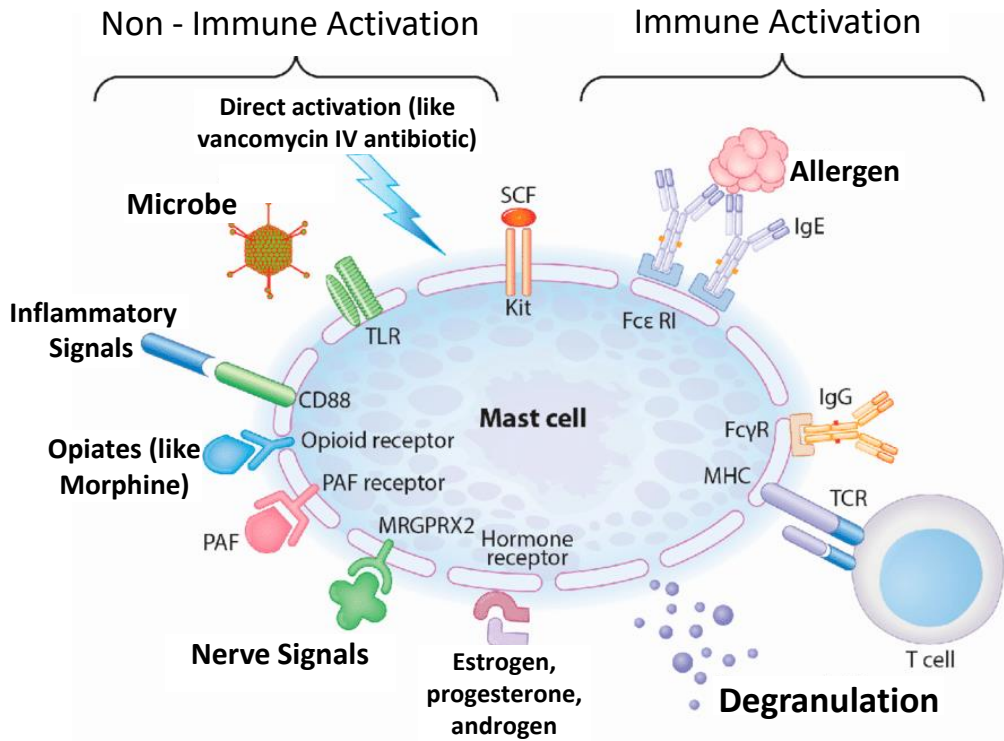
- Mast Cell Activation refers to mast cells that are misbehaving. They are active (or often overactive).
- Mast Cell Disorders refer to several illnesses with slightly different causes (see the umbrella).
  - They all cause similar symptoms. When a patient comes in, we run specific tests to figure out which Mast Cell Activation Disorder a person has.
  - Some Examples of Mast Cell Activation Disorders include:
    - Mast Cell Activation Syndrome (MCAS)
    - Monoclonal MCAS
    - Mastocytosis
    - Hereditary Alpha Tryptasemia
- People may have different types of symptoms. The severity of the symptoms can vary too.
- Symptom control and medication is often similar even if the type of mast cell disorder causing the symptoms differs from person to person. Some people have to be on more medication than others.
- **People have different “triggers.” We are not all the same.**

# Medications used in Mast Cell Activation Disorders



- We create a medicine regimen depending on the patient and symptoms. Medications we often use include:
  - Antihistamines
    - Long Acting Antihistamines like Allegra, Xyzal, and Zyrtec
    - Short Acting Antihistamines like Benadryl (these often make you drowsy)
    - Note: Patients often take higher amounts of Short Acting Antihistamines than a “normal” allergy sufferer. You can use **both** Long Acting **and** Short Acting at the same time!
  - Leukotriene Inhibitors
    - Singulair
    - Zflo
  - Mast Cell Stabilizers
    - Ketotifen
    - Cromolyn
  - Immune Modulators
    - Xolair
    - Plaquenil
  - Emergency Medication
    - Epinephrine
    - Inhalers
    - Steroids

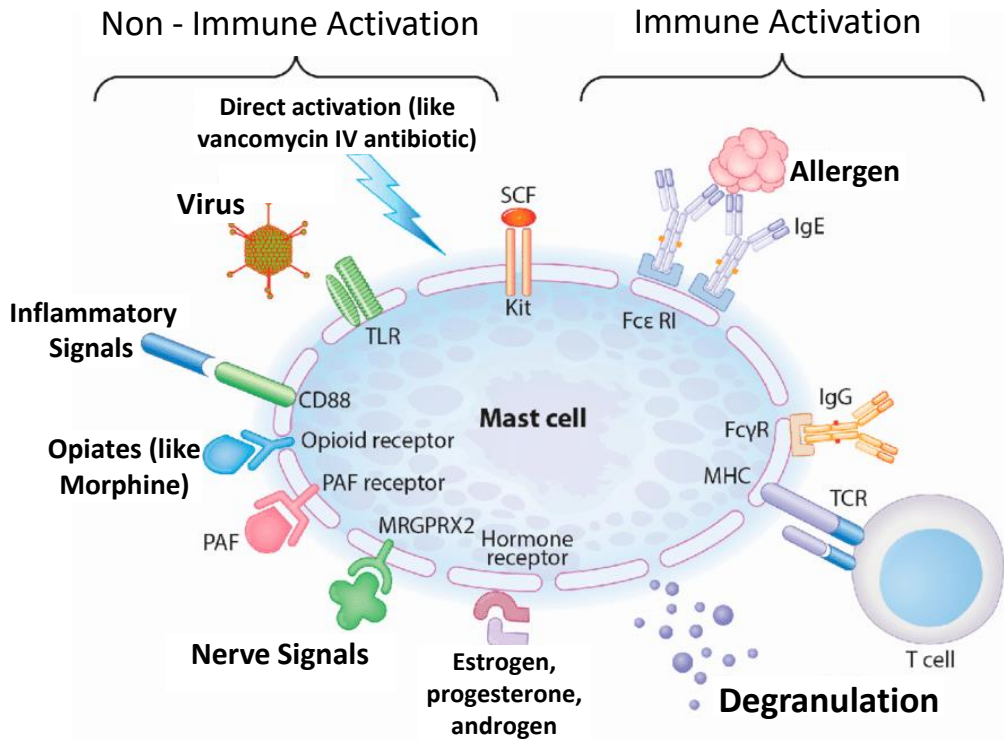
# What are Mast Cells?



- They live in tissues throughout the body
- They prefer to be at sites exposed to the outside world
  - Skin, Airways, Gut (like stomach, intestines)
- They have different sensors on their surface that can recognize:
  - Allergens (things your are allergic to)
  - Microbes (bacteria, viruses) and parasites (worms)
  - Nerve signals (such as pain, stress)
  - Inflammatory signals and toxins
  - Hormones (such as thyroid, menstruation)
- These items have the ability to “activate” or trigger mast cells. When they do, the cells “degranulate” releasing hundreds of mast cell chemicals into the body. Histamine, TNF-Alpha, other Cytokines, and Tryptase are just a few examples of mast cell chemicals also known as “mediators.”



# Mast Cell Activation and the Release of Mast Cell Chemicals are Triggered by Different Things:



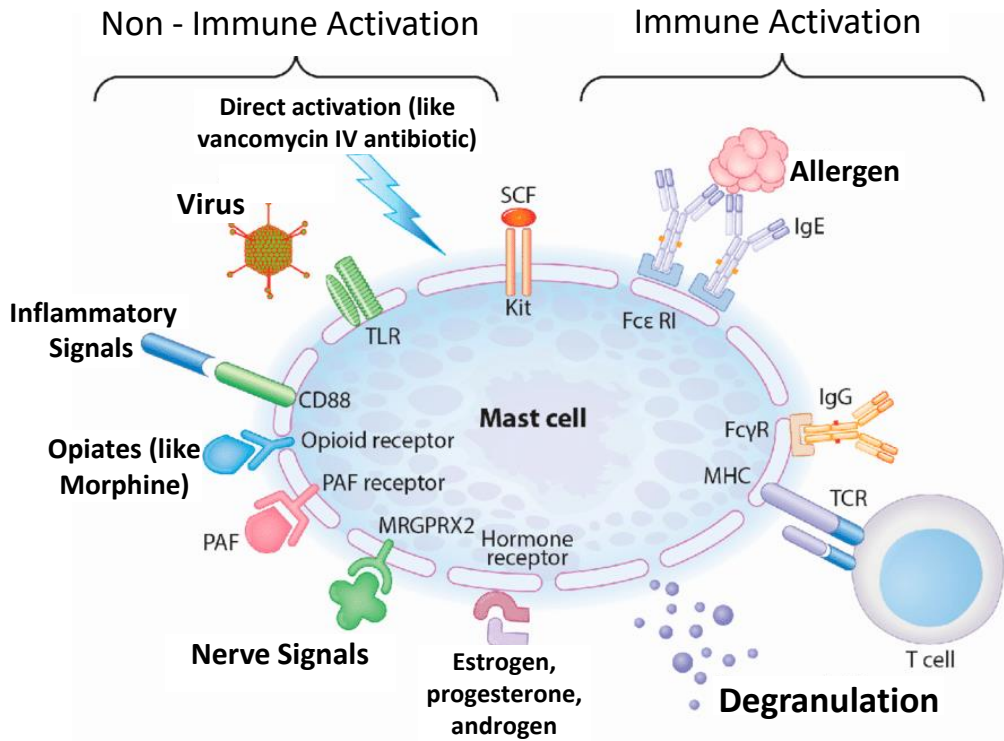
## Triggers that Cause Mast Cell Activation

*Note: Not everyone has the same triggers. What triggers one person, may be different from what triggers another person.*

1. Allergens (things you are allergic to)
2. Alcoholic drinks or Other Fermented Foods like Vinegar
3. Exercise or Physical Exertion
4. Viral or Bacterial Infections (getting sick)/Vaccines
  - We know that many vaccines will cause symptoms in the short term.
  - BUT in the long run, VACCINES are a GOOD idea for overall mast cell symptom control.
  - Vaccines reduce your risk of getting sick from the infections that can trigger mast cell flares.
5. Sensory/Nerve signals
  - physical pressure; temperature changes; pain; emotional trauma; stress

# Mast Cell Activation is Triggered by Different Things:

(continued)



## Mast Cell Triggers:

### 6. Autoimmune antibodies

- Like in Hashimoto's Thyroiditis, Lupus, Rheumatoid Arthritis.

### 7. Changes in hormone levels

- Some patients say they have more mast cell problems right before or at the beginning of their period.
- Some patients say when their thyroid hormones are off balance they have more symptoms.

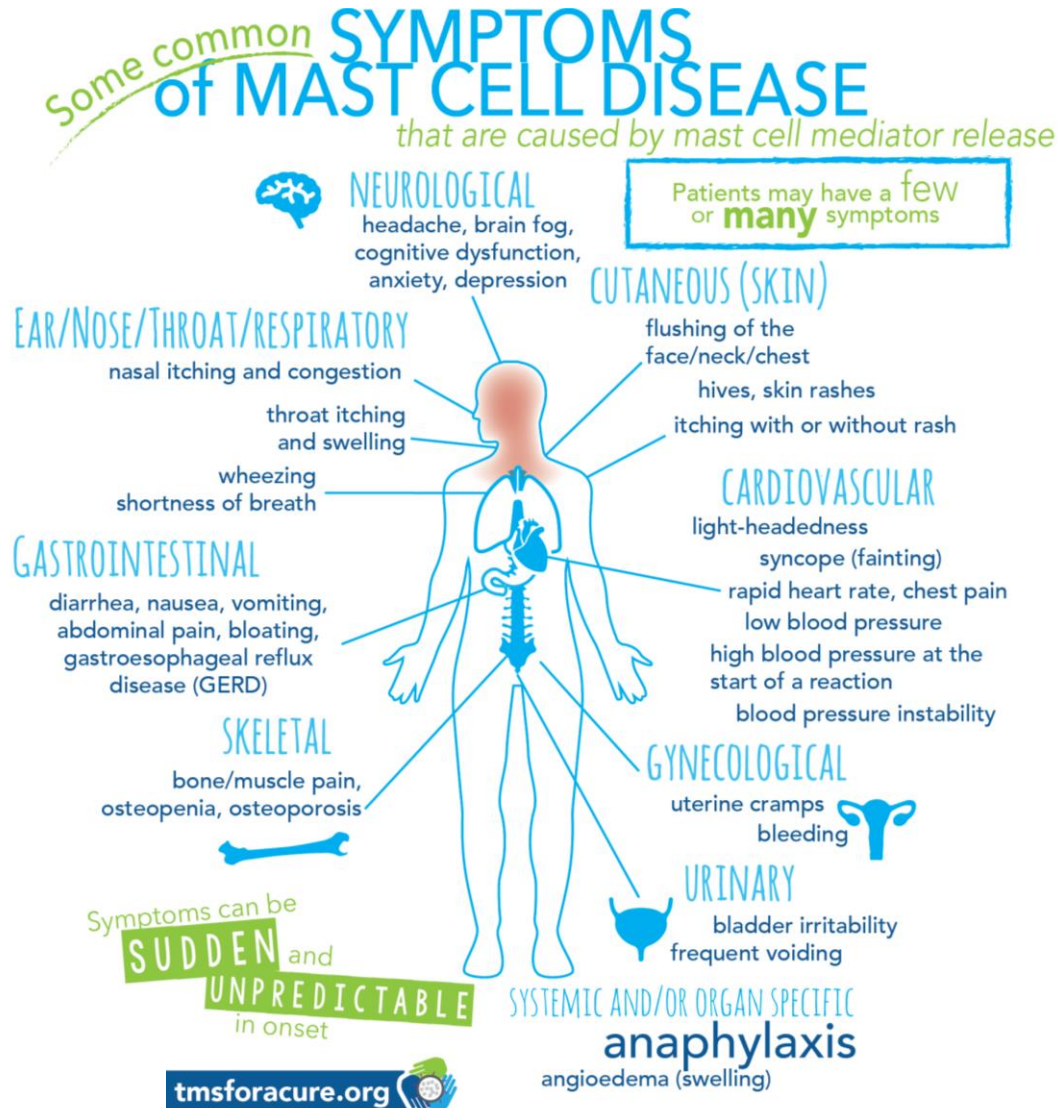
### 8. Medications (this can be different for each person)

- Many OPIATES – morphine, hydromorphone, codeine, fentanyl
- Some people can't tolerate NSAIDs (nonsteroidal anti-inflammatory drugs like ibuprofen and naproxen)

### 9. Cancer

- We worry about this more for patients 50 years and older.
- If we have their symptoms under control and then suddenly, none of the standard treatments seems to help, we look harder for possible cancers activating their mast cells.

# Mast Cell Chemicals Can Cause Many Different Symptoms



- When a mast cell degranulates, it causes different symptoms depending on the mast cell chemicals released.
- A few examples of the hundreds of mast cell chemicals:
  - Histamine
    - Can Cause Symptoms Like: Wheezing, low blood pressure, fast heart rate, abnormal heart beats, mucus production, heartburn, uterine contractions (and “spotting”), itching, hives
  - Tryptase
  - Leukotrienes
    - Can Cause Symptoms Like: Wheezing, mucus production
  - Prostaglandins
    - Can Cause Symptoms like: Flushing
  - TNF-alpha (Tumor Necrosis Factor)
    - Can Cause Symptoms Like: Fever, autoinflammatory disorders
  - Other Cytokines
    - Can Cause Symptoms Like: Fever, fatigue, loss of appetite, muscles and joint pain, nausea, vomiting, diarrhea, headache



# What is Flushing?

Flushing is blotchy redness, hot patches that come and go with mast cell activity. Often across the ears, face, neck, and chest. It is important to note that this is not a “hot flash.” Unlike a hot flash, there is no sweating involved. This is a dry heat.

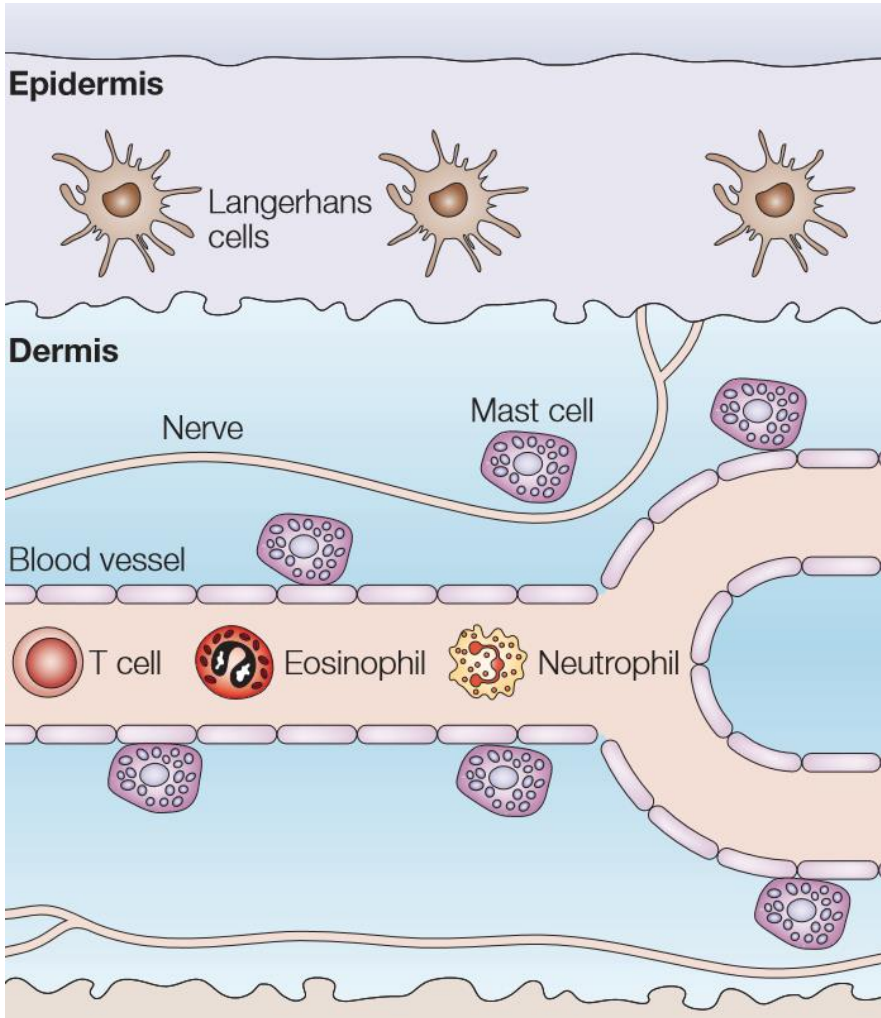


<https://www.medicalnewstoday.com/articles/323219>



Our research nurse, Claire Amelio

# Remember! Mast Cells are Found Close to Nerves and Blood Vessels



This is why we strongly believe, that in some patients, flawed nerves are bothering mast cells.

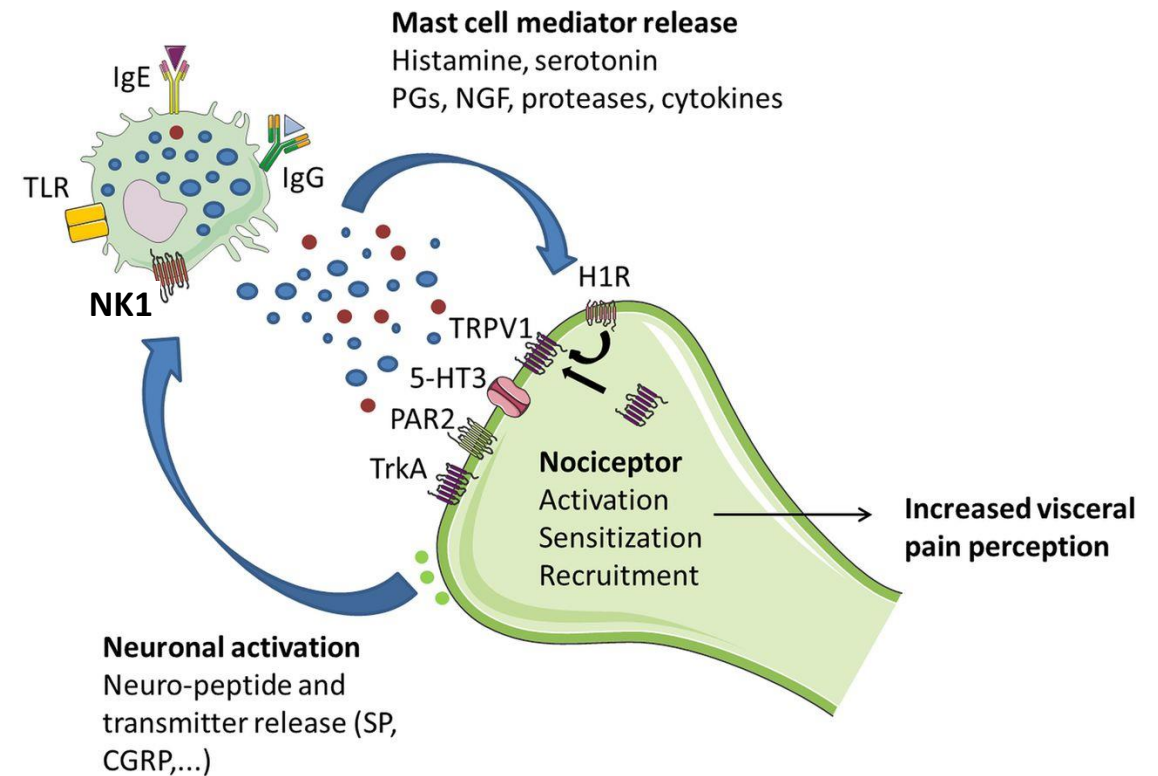
Then, bothered mast cells trigger nerves and you have a constant troublesome “feedback loop” where mast cells and nerves are irritating each other, back and forth all the time.

We think that some of the symptoms of pain and brain fog may be due to this feedback loop.

# Mast Cells Have Sensors for “Neurotransmitters”

(the chemicals nerves use to talk to each other)

- There is a back and forth crosstalk (Feedback Loop) between mast cells and nerves. This is how stress or temperature can trigger nerves and in turn cause mast cells to release their chemicals.
- Nerve sensors that mast cells can have on their surface include:
  - Neurokinin1 (NK1) sensors
    - Attaches to Substance P
    - Involved in sensory nerve communication, nerve inflammation, depression, anxiety
  - Beta-2 adrenergic sensors
    - Attaches to the neurotransmitter/hormone Epinephrine
  - Alpha-1 and beta-1 adrenergic sensors
  - Mas-related G protein-coupled sensors (Mrgpr)
    - Involved in itching and pain, as well as other sensory nerve communication
    - Attaches to Substance P
  - Calcitonin Gene-Related Peptide (CGRP) sensors
    - Involved in migraines



# Mast Cell Activation Disorders: Mastocytosis and Hereditary Alpha Tryptasemia

- **Mastocytosis** is the abnormal *accumulation* of genetically flawed mast cells in one or more body system. C-kit mutations are often present in these cells. These cells produce too many of themselves, they don't look like normal mast cells, and they don't behave like normal mast cells.
- **Hereditary Alpha Tryptasemia** is a genetic condition given to you by one of your parents where your mast cells produce too much **tryptase** (one of the mast cell chemicals released during activation). If you are not having a symptom flare, and we were to draw your blood tryptase level, a result of 8 or higher would make this diagnosis far more likely. In this case, we use a genetic test to confirm the condition.

My Favorite Mast Cell Activation Disorder:  
**Mast Cell Activation Syndrome (MCAS)**  
What's That?



# The Different Types of MCAS

## Two Types of Mast Cell Activation Syndrome (MCAS) Exist:

- Clonal (also called Monoclonal) MCAS
  - This means there is a **genetic mutation** in the mast cells, typically a c-kit mutation, causing the problem.
  - C-kit mutation can be found by a blood test or a test on a bone marrow biopsy.
- Non-Clonal MCAS
  - This means that there is **no** evidence of a genetic mutation in your DNA that would push your mast cells to act abnormally.

# What Causes MCAS?

## Why would someone get MCAS?

- Truth is, we don't know exactly why. We think the reasons may be different for different people. This is one of the things our research team is trying to sort out. Some things we are considering:
  - With some people it seems to run in their family. Is there a gene we aren't yet aware of? Are they born with MCAS or do they develop MCAS after a life event due to that unknown gene?
  - Certain other disorders may run in the family of a person with MCAS.
    - Autoimmune conditions
    - Hypermobile joints ("double jointed")
    - Other allergic conditions like chronic hives and swelling (urticaria and angioedema)
  - Insect or animal stings?
    - Patients get tick bites and develop Alpha-gal red meat allergy for example, and then go on to develop MCAS. Can bee or jellyfish stings or tick bites change their allergic cells?
  - Hormonal changes like puberty or pregnancy? MCAS is more common in females.
  - Has a viral infection changed their allergic cells? Was it a specific virus and specific strain of that virus or was the person predisposed in some way to develop MCAS with a particular virus?

# What Do We Mean By “Confirmed” MCAS?

## Criteria for MCAS Diagnosis:

- 1) Typical Symptoms: episodic symptoms (or episodic symptoms with some chronic symptoms) consistent with mast cell chemical release affecting two or more organ systems (skin, gut, cardiovascular, nervous system, airway, etc.)
- 2) Drugs that target mast cell chemicals improve symptoms to some degree or completely. These are the antihistamines, mast cell stabilizers, and others mentioned before.
- 3) Positive lab tests consistent with Mast Cell Activation (activity)
  - Tryptase: *Abnormal tryptase at baseline or (baseline tryptase x 1.2) + 2 ng/ml during a flare*
  - Mast cell chemicals and/or their metabolites in the urine:
    - 24 hour urine N-methyl histamine
    - 24 hour urine 11-beta-prostaglandin F2
    - 24 hour urine leukotriene E4
    - Random urine prostaglandin PGD2 (specimen must be frozen within 30 minutes of collection)
    - Note: **24 hour urine samples must be kept cold during the entire 24hr collection period until the time of running the test.** These chemicals disappear from the urine quickly unless kept refrigerated. It is important that the lab staff understand this when dropping off your specimen.

# What Do We Mean By “Probable” MCAS?

## Dr. Iweala’s Criteria for “Probable MCAS” Diagnosis:

- 1) Typical Symptoms: episodic symptoms (or episodic symptoms with some chronic symptoms) consistent with mast cell chemical release affecting two or more organ systems (skin, gut, cardiovascular, nervous system, airway, etc.)
- 2) Drugs that target mast cell chemicals improve symptoms to some degree or completely. These are the antihistamines, mast cell stabilizers, and others mentioned before.
- 3) Person **doesn’t** yet have tests that show Mast Cell Activation (activity)

*Note: As you can see, criteria 1 and 2 are checked off. Criteria 3 of testing has not yet come back as abnormal. We still treat these patients as though they have MCAS or an MCAS-like condition. The testing can be falsely negative sometimes OR we don’t yet have testing sensitive enough to detect the abnormal things happening in the body. We don’t let this stand in the way of helping a patient try to feel their best.*

# Criteria 1) What are Typical Symptoms?



- You have to have symptoms that match any of those listed in the chart to the right. You should have symptoms in at least 2 out of the 4 categories during the same reaction/flare. Two or more at the same time is critical to this diagnosis.

(This is actually the definition of Anaphylaxis. Not every anaphylactic episode looks the same in each person or each occasion.)

- Examples might include:**

- Fainting (or near fainting) PLUS Flushing
- Hives PLUS Diarrhea
- Hives PLUS Wheezing
- Facial Swelling PLUS Shortness of Breath
- Gut Pain PLUS Low Blood Pressure
- Skin Itching and hives PLUS Vomiting
- Rapid Heart Beat PLUS Flushing

**TABLE II.** Organ systems affected during anaphylaxis and associated symptoms of their involvement that are of diagnostic value for MCAS

<b>Cardiovascular</b> Hypotension Tachycardia Syncope or near syncope <sup>6,7,30,32</sup>	<b>Respiratory</b> Wheezing (inspiratory or expiratory) Shortness of breath Inspiratory stridor <sup>6,7</sup>
<b>Dermatologic</b> Flushing Urticaria <sup>6,7,30,32,34</sup> Pruritus Angioedema <sup>6</sup>	<b>Gastrointestinal</b> Diarrhea Nausea with vomiting Crampy abdominal pain <sup>6,7,10,28,30,32</sup>

As recommended for the working diagnosis of systemic anaphylaxis, symptoms affecting at least 2 of these 4 organ systems should occur concurrently.<sup>33</sup>



# You Can Have Mast Cell Activation / Activity Without Having Mast Cell Activation Syndrome (MCAS)

## How is Mast Cell Activation Different From Mast Cell Activation Syndrome?

- Mast Cell Activation is a term we use to describe a mast cell turning on or triggering. This happens in any “normal” allergic reaction. Mast cells are your allergic cells. So by having an allergic reaction, your mast cells are activating – but for a “true” reason (regular allergies)!
- Mast cell activity can occur with:
  - Food Allergies - we can measure blood IgE levels to diagnosis these
  - Environmental Allergies - we can measure blood IgE levels to diagnosis these
  - Chronic Inflammatory/Autoimmune Disorders (Lupus, RA, Atopic Dermatitis, Pulmonary Fibrosis)
  - Cancer
  - Chronic Hives or Angioedema - hives or swelling that occurs often, sometimes daily, but each individual rash on the skin usually improves within 24 hours or less. Sometimes things like vibration, cold/heat, exercise, water, or sunlight will cause them to appear again.
  - Infection – viral infections can activate mast cells, sometimes causing hives to show up during a viral illness. For most people the hives go away once your body clears the infection.



# You Can Have Mast Cell Activity Without Having Mast Cell Activation Syndrome (MCAS)

(Continued)

## How is Mast Cell Activation Different From Mast Cell Activation Syndrome?

- In Mast Cell Activation SYNDROME, the mast cells are “twitchy” to begin with.
- This means that allergic-like reactions can occur with or without a “true” allergy trigger.
- MCAS patients can have “true allergies,” meaning we sometimes find IgE allergy antibodies in their blood.
- But they can also experience anaphylaxis spontaneously or if exposed to a trigger even if their blood IgE level for that trigger is normal.
- Heat and exercise can also trigger allergic-like reactions.
- For example:
  - In Alpha-gal Allergy or Peanut Allergy, you have a reaction during an exposure to that food. You may flush, get hives and diarrhea for example. When that food is out of your system, the symptoms go away. Those mast cells calm down after the allergen leaves your system. **This is mast cell activation.**
  - In MCAS, you can have a similar reaction, even anaphylaxis, due to the trigger of stress or alcohol. You can have an allergic reaction on your own to no particular exposure at all. Your mast cells are behaving very badly. They are not calm and stable when they should be.



# What if I Don't Fit into the Probable or Confirmed MCAS Category, but I Have Some of the Symptoms?

- Some patients clearly have abnormal symptoms, but they don't fit completely with either the Probable or Confirmed MCAS category.
- Their symptoms don't match the symptoms of a typical MCAS patient.
- Some of these patients \*may\* get a little relief from antihistamines. Some don't.
- They also don't have the abnormal testing showing MCAS.
- There are a few other disease conditions we consider in these patients:
  - Undiagnosed food allergy such as Alpha-gal (anaphylaxis is quite common during exposure)
  - Chronic Hives or Angioedema
  - Chronic Inflammation/Autoimmune Disorders (Such as Lupus, RA, Psoriasis, Atopic Dermatitis)
  - Neuroendocrine Cancer: Pheochromocytoma; Carcinoid Syndrome; Vasoactive intestinal peptide secreting tumor
  - Problem with histamine elimination called "Histamine Intolerance"
    - Currently this is not a recognized disorder in the US. We also have no testing. Many foods we eat everyday have histamine in them. This is normal. Some patients eat histamine containing foods and then have allergic symptoms. The key here though is that they don't get those same symptoms with non-food items like heat or stress like a MCAS patient would. Anaphylaxis is uncommon in these patients.



# What if I Don't Fit into the Probable or Confirmed MCAS Category, but I Have Some of the Symptoms?

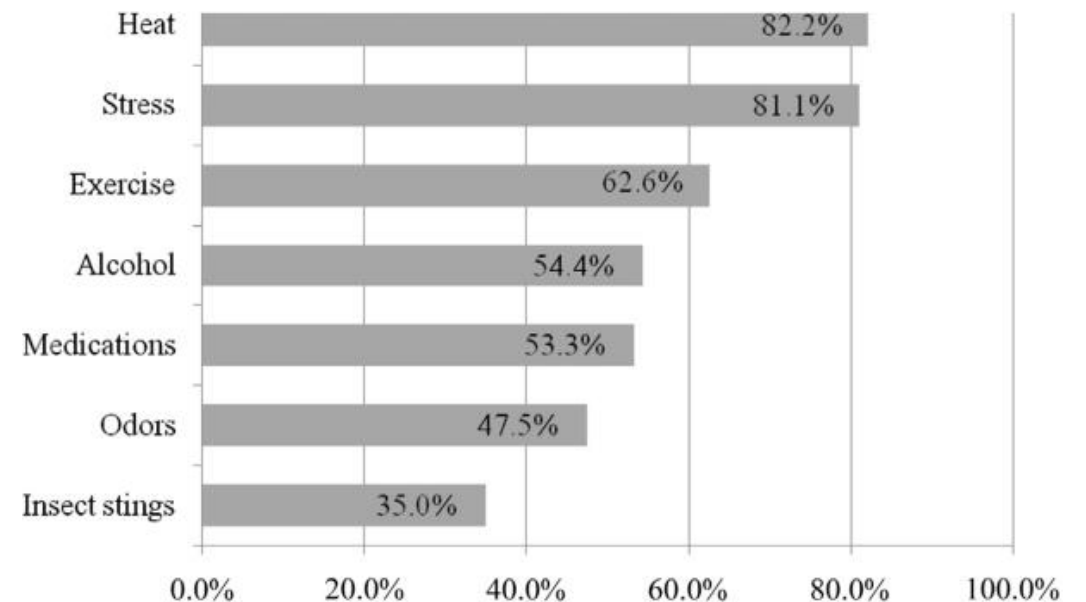
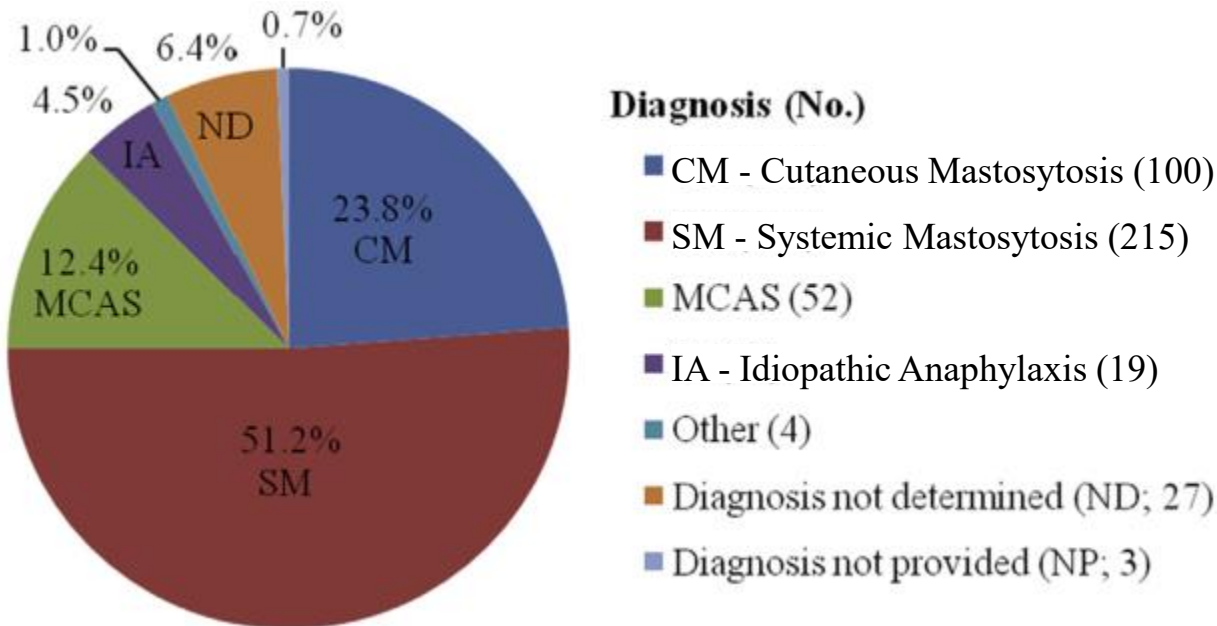
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- Other disease conditions I have to consider in these patients:
  - Dysautonomia/Dysfunctional Nerves (intrinsic or autoimmune)
    - POTS/other cardiovascular dysautonomia (**We have to send you to a Cardiologist to diagnose**)
    - Irritable Bowel Syndrome; gastric motility issues (**We have to send you to a Gastroenterologist to diagnose**)
    - Vocal Cord Dysfunction (**We have to send you to a Ear Nose Throat doctor to diagnose**)
    - Small Fiber Autonomic Neuropathy (**We have to send you to a Neurologist to diagnose**)
    - **Neurologically-mediated mast cell reactivity (NMMCR)** : you won't find this term anywhere else – this is a new term that we've created to describe what we think might be happening in many of our patients.
  - Alcohol Flush Reaction
    - This happens in people of Asian decent. It is a gene you inherit. In MCAS, the reaction to alcohol has its own characteristics. In this disorder though, the reaction to alcohol is different in timing and amount taken in. These patients can have anaphylactic reactions. It also only occurs with alcohol exposure, but not with some of the other MCAS triggers.
  - Asthma, Aspirin Exacerbated Respiratory Disease, NSAID Exacerbated Respiratory Disease

# Top Patient-Reported Triggers for Mast Cell Activation Disorders

(Combined Clonal and Non-Clonal MCAS)

- Results of an online survey conducted by The Mastocytosis Society (TMS) which included 420 participants
- TMS is a U.S.A. based organization that supports research and advocacy for patients with Mast Cell Activation Disorders of all types.

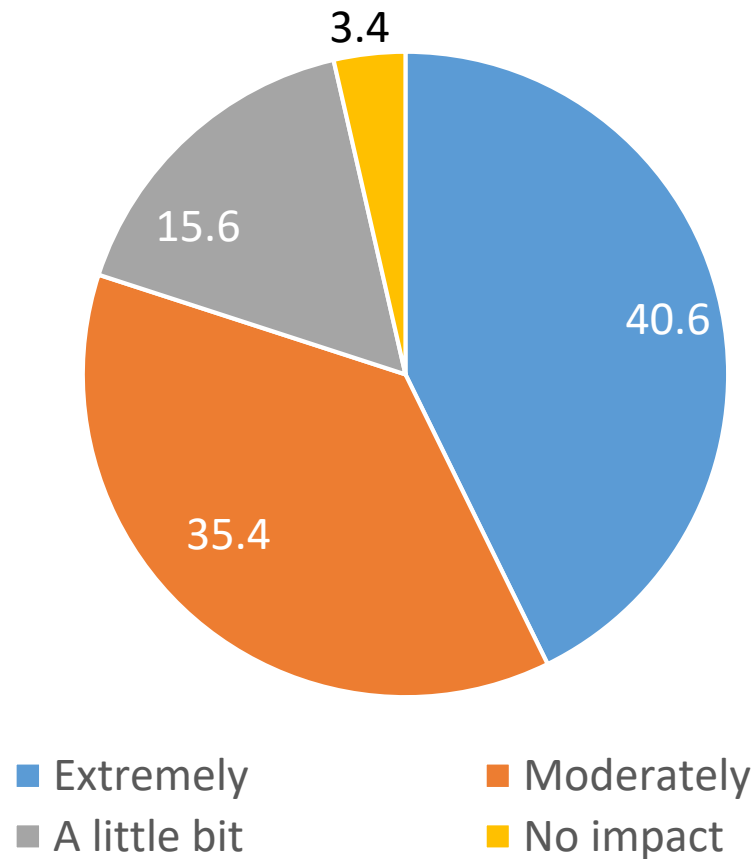




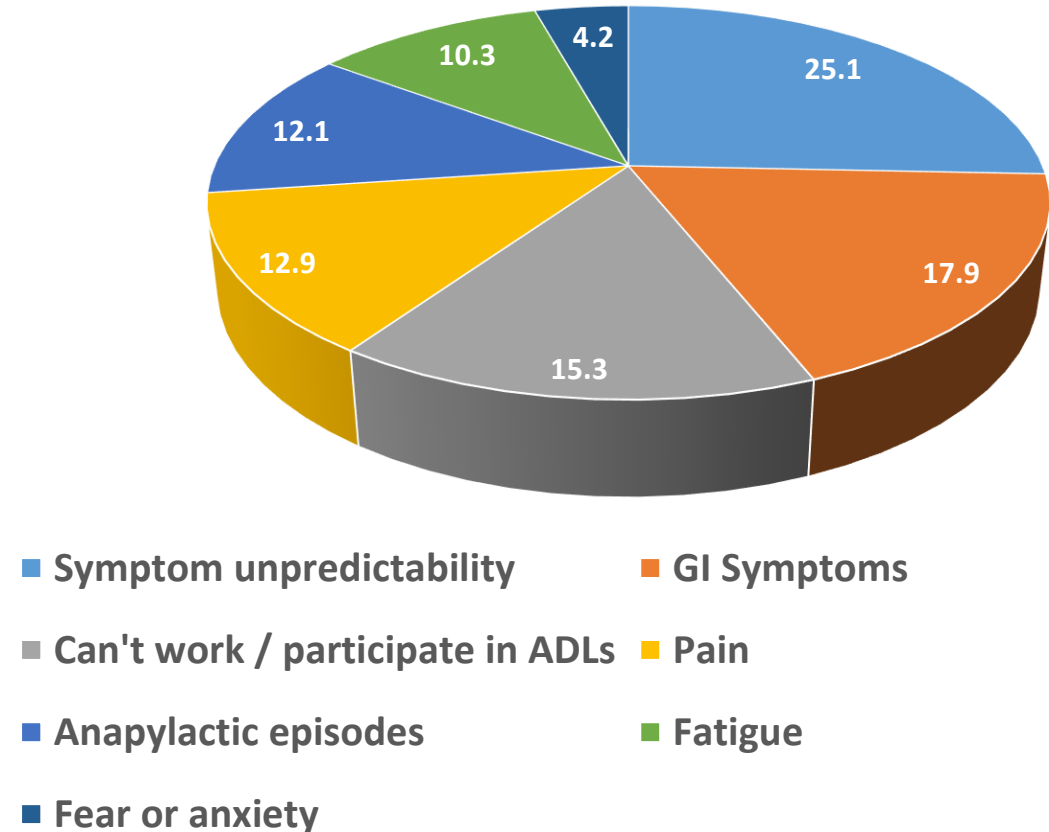
# Mast Cell Activation Disorders Affect Quality of Life

(Combined Clonal and Non-Clonal MCAS)

Emotional Impact of MCAD on patient life



Greatest Single Distress-Causing Aspect of Living with an MCAD



How do we manage patients with (Confirmed & Probable) MCAS?

# MCAS Management

## **Behavioral/Mental/Spiritual:**

- You will need support and understanding from loved ones. Family and friends need to understand your triggers and not purposefully put you in harms way.
- Avoid triggers whenever possible.
- Mindfulness, mind-body relaxation techniques, stress management - these can all lower the chance of a mast cell neurological trigger from anxiety and stress. Find a source of spiritual support. Prayer and mediation have been shown to lower stress levels and can play an important part in anxiety.
- Manage Your Expectations
  - Symptoms of MCAS (especially Non-Clonal MCAS) can be very difficult to treat. Complete resolution with medications alone is less common in Non-clonal MCAS than in Clonal MCAS. You have to get to a point where you accept a “new normal.” We have things to improve your baseline as well as your flares, but we have no cure yet.

## **Medications:**

- Medication regimen is a big part of total symptom control. This can take some time to figure out as we are all different.
- We put patients on multiple daily medicines and add more medicines to take as needed when you have a reaction or a symptom flare.



# MCAS Management

(Continued)

## **Doctors, Pharmacists, Care Management:**

- Your team may include: Primary Care, Allergy/Immunology, Hematology/Oncology, Cardiology, Pain Management, Psychiatry/Psychology, Geneticist, Neurology, Compounding pharmacy
- All parts of the team need to work together. We are lucky at UNC that we have teams already created and we all have mutual MCAS patients. No matter what though, you need to have your files shared between specialists, or you need to bring records so we can all work towards the same goals.

# MCAS Management

(Continued)

## **Low Histamine Diet:**

- I personally do NOT recommend this diet because there are no clinical trials saying that this diet is helpful and it's hard to do. If you are 18 years or older, I don't think it will hurt you. It is expensive and time consuming. Meat in particular is not flash frozen, vegetables often travel far. Foods at your local grocery store may not be as low histamine as you think.
- Our MCAS patients often have foods they can't eat since they react to them. Yet, those same items might be "okay" on the "Low Histamine Diet" list. To avoid triggers and also avoid the "high histamine" foods can severely restrict your diet.
- MCAS patients produce and release hundreds of mast cell chemicals that can trigger symptoms during a flare. Histamine is only one of them. The low histamine diet may not work for you, especially if you have non-food triggers as well.





# Many of My Patients have “MCAS *Plus*” Disorders

## New disease triad: POTS, EDS, and Non-clonal MCAS?

- Possible genetic basis – Lyons and colleagues at the National Institutes of Health (NIH) identified families with elevated baseline serum tryptase in the setting of dysautonomia, non-clonal MCAS, and joint hypermobility. They had **increased copy numbers of TPSAB gene** encoding alpha-tryptase (Nature Genetics 2016)
- Some of my other patients concerned about MCAS also seem to have a **multiple chemical sensitivity syndrome** - the side effects and responses they have to medications are *\*really\** different or more extreme or severe than your standard person.
- Because many patients with MCAS symptoms often have symptoms found in these other conditions, it can be challenging to get everything under control.
- It takes a lot of back and forth between you (the patient) and us (the providers) to come up with a treatment regimen that is right for you. This usually takes place over months or sometimes years.

# MCAS Management: Pharmacologic Therapy

## Iweala's MCAS Treatment Ladder:

### **Mast Cell Activation Syndrome Controller Regimen:**

1. - H1 (nondrowsy, 2<sup>nd</sup> generation) antihistamine: **examples: Zyrtec (cetirizine), Allegra (fexofenadine), Xyzal (levocetirizine), Claritin (loratadine), Clarinex (desloratadine)**
2. - H1 (DROWSY, first generation) antihistamine: **examples: Benadryl (diphenhydramine), Atarax or Vistaril (hydroxyzine), chlorpheniramine, bropheniramine, etc.**
3. - H2 (GI tract) antihistamine: **example – Pepcid (famotidine); Zantac (ranitidine, if it gets back on market), Tagamet (cimetidine, not my favorite because it can interact w/many meds)**
4. - Mast cell stabilizer: **examples: cromolyn and/or ketotifen**
5. - Leukotriene antagonist: **examples: Singulair (montelukast), Accolate (zafirlukast), Zyflo (zileuton)**
  - *Maybe Arachadonic acid inhibitor like aspirin (if patient already on and it's helping)*
6. - Natural supplements (act as mast cell stabilizers): Quercetin, vitamin C
7. - Immunomodulators: **examples – Plaquenil (hydroxychloroquine); Xolair (omalizumab);** other possibilities - Cyclosporine, methotrexate, dupilumab (if asthma and eczema or nasal polyps)
8. - Emergency medicines to use (in addition to controller medicines) during a flare: **epinephrine if history of anaphylaxis; otherwise diphenhydramine and steroids**

# MCAS Management: Pharmacologic Therapy

## Iweala's MCAS Treatment Ladder:

### **Mast Cell Activation Syndrome Controller Regimen:**

1. - H1 (nondrowsy)  
**(fexofenadine)** (Allegra), Allegra (fexofenadine)
2. - H1 (DROWSY)  
**Atarax or Vistarlin** (hydroxyzine), (hydroxyzine), (diphenhydramine), (diphenhydramine)
3. - H2 (GI tract)  
back on maintenance  
meds) (famotidine), (famotidine)
4. - Mast cell stabilizers
5. - Leukotriene modifiers  
**(zileuton)** (Accolate), (zileuton), (zileuton)  
  - Maybe Arava (leflunomide)
6. - Natural supplements (act as mast cell stabilizers): Quercetin, vitamin C
7. - Immunomodulators: examples – Plaquenil (hydroxychloroquine); Xolair (omalizumab);  
other possibilities - Cyclosporine, methotrexate, dupilumab (if asthma and eczema or nasal polyps)
8. - Emergency medicines to use (in addition to controller medicines) during a flare:  
**epinephrine if history of anaphylaxis;** otherwise diphenhydramine and steroids

We are willing to have you try medications #1-6 on the ladder, even if you don't have CONFIRMED mast cell activation syndrome because the side effects of the medicines are typically not TOO bad and usually go away once you stop the medication.