Mast Cell Activation Syndrome;

Mast Cell Activation and Triggers

Mast cells can be activated to release mediators by multiple triggers. Possible triggers of mediator release are shown below in Figure 1. Please note that any patient with a mast cell disorder can potentially react to any trigger, and triggers can change over the course of the disease. In addition, patients may experience reactions to virtually any medications, including medications that they have tolerated previously. Common medication reactions in mast cell disorder patients include, but are not limited to: opioids, antibiotics, NSAIDs, alcohol-containing medicines and intravenous vancomycin. Use with caution. More information related to drug hypersensitivity in mast cell disorders is available in a position paper by European specialists.[1]

Figure 1. Some *Potential* Mast Cell Triggers[2-5]

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
- Exercise
- Fatigue
- Food or beverages, including alcohol
- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)
- Infections (viral, bacterial or fungal)
- Mechanical irritation, friction, vibration
- Sun/sunlight

Mast Cell Mediator Symptoms

The myriad symptoms patients with mast cell disorders experience during mast cell activation can wreak havoc on patients on a daily basis, and multiple organ systems, including pulmonary, cardiovascular, dermatologic, gastrointestinal, musculoskeletal, and neurologic can be involved. Table 1 lists some potential effects linked to specific mediators.[5-13] Symptoms (Table 2) may include, but are not limited to: flushing of the face, neck, and chest; headache; tachycardia and chest pain; abdominal pain, bloating, gastroesophageal reflux disease (GERD), diarrhea, vomiting; uterine cramps or bleeding; rashes, including maculopapular cutaneous mastocytosis (MPCM)/urticaria pigmentosa (UP), telangiectatic lesions; bone/muscle pain, osteosclerosis, osteopenia, osteoporosis; itching, +/- rash; blood pressure instability; brain fog, cognitive dysfunction; anxiety/depression; lightheadedness, syncope; and anaphylaxis. These symptoms may appear as acute (as in anaphylaxis, see Table 3) or as chronic conditions. It should be noted that the manifestation of anaphylaxis or similar symptoms among infants and preschoolers may be more difficult to identify.

Table 1. Possible Effects of Some Mast Cell Mediators[13, 14]

MEDIATOR	POSSIBLE EFFECTS
Histamine	Flushing, itching, diarrhea, hypotension
Leukotrienes	Shortness of breath
Prostaglandins	Flushing, bone pain, brain fog, cramping
Tryptase	Osteoporosis, skin lesions
Interleukins	Fatigue, weight loss, enlarged lymph nodes
Heparin	Osteoporosis, problems with clotting/bleeding
Tumor Necrosis Factor-α	Fatigue, headaches, body aches

This list is by no means complete and serves as an example. Mast cells secrete many mediators responsible for numerous symptoms within different organ systems.

Table 2. Mast Cell Mediator Symptoms[12, 13]

MAST CELL MEDIATOR SYMPTOMS
Anaphylaxis
Flushing of the face, neck, and chest
Itching, +/- rash
Hives, skin rashes
Angioedema (swelling)
Nasal itching and congestion
Wheezing and shortness of breath
Throat itching and swelling
Headache and/or brain fog, cognitive dysfunction, anxiety, depression
Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)
Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis
Light-headedness, syncope/fainting
Rapid heart rate, chest pain
Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability

Uterine cramps or bleeding	

Table 3. When Does this Become Anaphylaxis?

(Taken from the American Academy of Allergy, Asthma and Immunology (AAAAI) Anaphylaxis Emergency Action Plan[15] and the Anaphylaxis Guidelines Pocketcard[16])

Anaphylaxis is an acute life-threatening systemic reaction that results from the sudden, rapid, systemicrelease of mediators.

MOUTH	Itching, swelling of lips and/or tongue
THROAT*	Itching, tightness/closure, hoarseness
SKIN	Itching, hives, redness, swelling
GUT	Vomiting, diarrhea, cramps
LUNG*	Shortness of breath, cough, wheeze
HEART*	Weak pulse, dizziness, passing out

*Only a few symptoms may be present. Severity of symptoms can change quickly. *Some symptoms can be life-threatening. ACT FAST! Use your anaphylaxis action plan! An AAAAI Anaphylaxis Card in English and Spanish is also available.*

First and foremost, a careful examination of the skin should be undertaken, looking for characteristic lesions of mastocytosis. If lesions are found, the physician should stroke the lesion firmly with a tongue depressor 5 or 6 times to see if it urticates (Darier's sign). However, flushing and systemic low blood pressure can result from attempts to identify Darier's sign in young children who have cutaneous mastocytoma or a polymorphic variant of maculopapular cutaneous mastocytosis with nodular lesions, such that this test should be avoided in these patients.[1,2] Darier's sign is positive in almost all children and most of the adults who have skin involvement in mastocytosis. An international consensus task force of mast cell disorder specialists has recently proposed that Darier's sign be included as part of the major criterion for diagnosing skin involvement in mastocytosis patients.[2] Clear areas of skin can be stroked in the same way noted above to check for dermatographism, or skin writing, in which the area stroked becomes inflamed. Darier's sign and dermatographism are characteristic cutaneous symptoms in mast cell disorders.

Information on tests for children with mast cell disorders is also available on this website. Click here for more information .

Tests for Mast Cell Activation and Mast Cell Activation Syndrome (MCAS)

An increase in the serum level of tryptase, above baseline and within a narrow (generally accepted as one to two hour) window of time after a symptomatic episode, is proposed as the preferred method for providing evidence of mast cell involvement.[3-5] An international consensus article provides a method for calculating the required minimum rise in serum tryptase:[5]

After a reaction, a level of serum tryptase that is a minimum of 20% above the basal serum tryptase level, *plus* 2 ng/ml, will meet the second criterion for a mast cell activation event. For example, if a patient had a basal (baseline level, at least 24 hours after a reaction) serum tryptase level of 8 ng/ml, a 20% rise, plus 2 ng/ml, would be 11.6 ng/ml. To meet the above criterion for serum tryptase, the patient would need a post-reaction serum tryptase level *above* 11.6 ng/ml. The calculation would be conducted as follows:

(8 ng/ml x 1.2) + 2 ng/ml = 11.6 ng/ml

(basal level, plus 20%) + additional 2 ng/ml = the serum tryptase level, after a reaction, that must be exceeded in order to meet a rise in serum tryptase considered a mast cell activation event

Consensus members also agreed that when serum tryptase evaluation is not available or when the tryptase level does not rise sufficiently to meet the required increase for the co-criterion, other mediator tests could suffice. A rise in urinary n-methyl histamine, prostaglandin-D_2, or its metabolite, 11β-prostaglandin-$F_{2\alpha}$ (24-hour urine test for any of the three), is considered an alternative for the co-criterion related to a requirement for a mast cell mediator level rise during a systemic mast cell activation event.[5, 6] Some practitioners currently utilize other tests to make a diagnosis of mast cell activation. While we strongly recognize that we are limited in that there are many mast cell mediators, and yet we have commercial tests available for less than five of them here in the US, The Mastocytosis Society, Inc. (TMS) cannot endorse the use of other mediator markers as diagnostic tools until they have been adequately evaluated and proven as valid for mast cell disorders in sound, scientific research. TMS strongly supports and currently funds research to identify *better* markers for mast cell activation.

TMS does recognize, however, that capturing a mediator rise is not always easy, and depends on many factors, internal and environmental. We have seen 24-hour urine samples test negative simply because the lab technician did not refrigerate the sample in a timely manner (when the test was repeated and handled properly, the result was positive). Therefore, we support the use of a clinical diagnosis and advise that the patient continues to be treated when the following criteria have been met:[7]

- An exhaustive work-up has ruled out other medical conditions with similar symptoms and presentations
- The patient has exhibited consistent symptoms of mast cell activation in 2 or more organ systems during the same period of time, such as skin, gastrointestinal tract, central nervous system, etc.
- The patient responds to antimediator therapy

- The patient is monitored on a regular basis, with testing for mediator rises performed periodically, by a mast cell or other specialist and/or in conjunction with an established local allergist or other physician
- The patient is evaluated for other disease processes on an ongoing basis in order to be inclusive of any new changes in the patient's condition

Routine and Follow-up Testing for MCAS

In patients who demonstrate a mediator rise, mediator testing should be repeated periodically. In addition, a complete blood count (CBC) with differential, blood chemistries, immunoglobulin levels, liver function tests, DEXA scans for bone density, and other testing may all be done as part of the routine exam, depending on the patient's age, presenting symptoms, coexisting conditions and medication profile.[8]

Tests for Clonal Mast Cell Disorders Such as Systemic Mastocytosis or Monoclonal MCAS

Bone Marrow Biopsy

Standard technique can be used to obtain an iliac crest bone marrow biopsy and aspirate smear for diagnosis. Aspirated bone marrow should be allocated for flow cytometry to assess for the presence of mast cells with aberrant phenotype (i.e., co-expression of CD25). *KIT* mutation testing (see below) can also be performed on bone marrow aspirate. Immunohistochemistry for *KIT*, mast cell tryptase, and CD25 should be performed on sections of the biopsy.[1, 9-12]

KIT Mutation Testing[13]

To understand why *KIT* testing is necessary, one must first understand the difference between clonal and non-clonal mast cell disorders. Clonal means that there is a defect in a person's mast cell DNA, which results in their mast cells having abnormal characteristics. Although the most common defect seen in mast cell disease is *KIT* D816V, it is not the only one that can result in an abnormal disease process. Numerous other mutations in *KIT* have been associated with mastocytosis, and in the absence of a *KIT*D816V mutation, other testing can be performed to identify them, including *KIT* sequencing. If you have *no change* (no mutation, such as a KIT mutation) identified in your mast cell DNA, but experience mast cell activation, then you may have non-clonal disease, such as idiopathic mast cell activation syndrome.

There has been a peptide nucleic acid mediated PCR based test available for years that can identify the *KIT* D816V mutation in peripheral blood, and it has been able to detect the mutation in 44% of systemic mastocytosis patients tested.[14] A newer test, an allele-specific oligonucleotide qPCR test, has proven to be much more sensitive and reliable. Patients with indolent systemic mastocytosis with skin involvement, for example, were found to have the *KIT* D816V mutation 92% of the time using the newer allele-specific qPCR blood test.[14]

Although the more sensitive test for the *KIT* D816V mutation (the allele-specific qPCR, with a sensitivity of 0.01%) that can be performed in peripheral blood samples has been developed, is not yet widely available here in the US. However, Mayo Clinic in Rochester, MN can perform the allele-specific oligonucleotide PCR (ASO-PCR) test for KIT D816V and the test may be available through several other labs in the US. Currently in the US, the result is often reported as either positive or negative, although in a research setting, results can be presented in more detail as an "allelic frequency", which is essentially a measure of the extent to which the mutation is present versus KIT without that mutation (the allelic frequency can help in determining disease prognosis). It is important to note that receiving a negative test does not rule out a mast cell disorder.[13, 15] If an adult with systemic mastocytosis does not test positive for the KIT D816V mutation using sensitive testing methods, then sequencing of *KIT* might be considered.

Knowing the *KIT* mutation status can be very important when considering therapeutic options such as new medications and chemotherapy. The development of the allele-specific qPCR test will make peripheral blood *KIT* testing more widely available in the near future. More information on the use of KIT mutation testing in mast cell disorders (including potential use in prognosis and is available in published recommendations from the European Competence Network on Mastocytosis (ECNM).

Routine and Follow-up Testing for Systemic Mastocytosis (SM) and Smoldering SM

Examinations should occur periodically and include:[13]

- Dermatological exam (with stroking for Darier's sign)
- Careful palpation of the liver, spleen and lymph nodes
- A full neuropsychological evaluation
- CBC with differential
- Serum tryptase and 24-hour urines for N-methyl histamine, prostaglandin D2 (PGD2), 11β-prostaglandin $F_{2\alpha}$
- Liver function tests, serum albumin, serum LDH, and serum alkaline phosphatase[16]
- Blood chemistries
- Total immunoglobulins or total IgE, if indicated by previous testing
- DEXA scans for bone density; nuclear medicine bone scan, if indicated
- Bone marrow biopsy with flow cytometry and cytology, when indicated
- Allele-specific qPCR for *KIT* D816V mutation in peripheral blood/bone marrow, if not already performed; *KIT* sequencing, if indicated[13]
- CT scan/ultrasound, if indicated
- Other tests may be performed, as indicated, if there is a suspected hematologic disorder or to evaluate the individual patient's symptoms.

NOTE: More information on the use of the above tests and examinations can be found in Table 3 of the ECNM recommendations.[13] The Mastocytosis Society, Inc. has removed serum β2-microglobulin from the above list after a survey of some of our medical specialists indicated that this test is not routinely ordered to evaluate mastocytosis in the US.

Diagnostic Workup for Advanced Systemic Mastocytosis Variants or Associated Hematological Disorders[1, 13, 17, 18]

When advanced disease or an associated hematological disorder is suspected, further evaluation of the patient beyond a bone marrow biopsy and aspirate with flow cytometry may include:

- Comprehensive bloodwork
- X-ray or CT scan of the chest, looking for evidence of significantly enlarged lymph nodes (greater than 2 cm in diameter)
- X-ray, nuclear medicine bone scan of the skeletal system, or bone density scan looking for osteoporosis, osteosclerosis, or areas where calcium has been completely lost from bone
- CT scan or ultrasound of the abdomen, looking for enlarged liver or spleen,[16] enlarged lymph nodes, or the collection of fluid
- Endoscopy/colonoscopy and biopsy of the gastrointestinal tract, looking for evidence of mast cell infiltration, ulcers, or areas of bleeding. Mast cell infiltration can be identified by aggregates of 15 or more abnormal mast cells, or sheets of mast cells. Abnormal mast cells can be identified by the presence of CD25 on these cells.[19]
- Other tests may include next-generation sequencing and myeloid gene panels for additional genetic lesions.

TREATMENTS FOR MAST CELL DISORDERS

Mast Cell Activation/Mediator Release Symptoms

Controlling symptoms of mast cell activation/mediator release starts with avoiding the very triggers which we know will initiate mast cell activation in us, and the triggers can be very individual. Avoiding heat, cold, abrupt changes in temperature, sunlight, strong odors/perfumes and chemical smells can help many patients. Caution must be taken around venomous creatures such as bees, wasps, hornets, spiders, jellyfish and snakes, etc. Stress and fatigue can be major triggers for many patients, as can viruses, bacterial and fungal infections. Sometimes a simple change in routine can trigger us!

Many foods can trigger mast cells to activate and release their mediators; shellfish, peanuts, nuts, citrus, and high histamine foods are high on the list of potential triggers known to bother some people, but not others. Medications to be taken with caution include NSAIDs such as ibuprofen, toradol, aspirin (this can be confusing, because aspirin can also be used as a treatment for those with high prostaglandin levels; when used as a treatment it must be started under the supervision of a physician!), opioid narcotics, alcohol, the intravenous form of vancomycin (the oral form is usually fine), some anesthetics, some antibiotics, and topical agents, like benzocaine. However, everyone is different, and *anyone can react to anything*, *and you can even react to something that you have never reacted to before*, so always proceed with caution. Always have someone with you when taking a new medication, starting a new treatment, or traveling to a new place.

The most irritating thing can be that sometimes we do not even know what the trigger was that sent us into a mast cell frenzy! In that case, treat the symptoms, get some rest, and then review the last few days to see if you can spot a culprit. Also, remember that your response may be delayed. You may have an alcoholic drink on Saturday, and then be symptomatic several days later. Keeping a food, medicine and symptom diary can help you connect the dots!

Treatment of mastocytosis depends on the symptoms and the classification of disease.[1-3] Symptoms of mast cell activation/mediator release are treated with H1 and H2 antihistamines, mast cell stabilizers, leukotriene inhibitors, and possibly aspirin (under *direct supervision* of a physician). All mast cell disease patients should carry *two doses* of self-injectable epinephrine, unless otherwise contraindicated (glucagon may need to be administered for patients on beta-blockers). Patients should also be instructed on how to self-administer the epinephrine while lying down, to maximize rapid absorption of the drug. Every patient should carry a physician-signed American Academy of Allergy, Asthma and Immunology Anaphylaxis Action Plan at all times.

Treatment of MCAS is similar to that listed above for mastocytosis symptoms *related to mast cell activation and mediator release*.[4-6]

There has been growing recognition of the detrimental effects on cognition (mental clouding and other cognitive impairments) caused by long term use of antihistamines.[7] A high risk group of patients 65 years and older (defined as patients taking 50 mg per day for 3 years diphenhydramine or doxepin or 25 mg for 6 years), were found to have a significant association between diphenhydramine use and cognitive impairment.[8] Similarly, high doses of sedating antihistamines such as diphenhydramine can cause increased seizure activity, seen mostly in children. In addition, a tolerance to or a dependence upon diphenhydramine may result in a need for even higher doses.[7] Caution and restraint must be used when taking antihistamines long term in order to help preserve neurological function. While these drugs are critical to us for their antimediator effects, we must work with our physicians to titrate them to the lowest dose necessary to achieve control of mast cell activation symptoms.

Additional Symptoms of Indolent Systemic Mastocytosis

A suggested order of treatment options for adult patients with indolent systemic mastocytosis, aimed at symptom control, and including suggested therapies for osteoporosis, can be found in Table 3 of this article from the American Journal of Hematology.[9]

More on Medications to Treat Mast Cell Disorders

Advanced Disease

Therapies exist for smoldering systemic mastocytosis (SSM) and advanced systemic mastocytosis, and promising new treatments are being developed. Prominent among these

newer treatments are tyrosine kinase inhibitors (TKIs) targeting the *KIT* kinase[10, 11] (e.g., midostaurin[10, 12]). Imatinib is approved therapy for adult aggressive systemic mastocytosis (ASM) patients lacking the *KIT* D816V mutation or if mutation status is unknown. Additional standard therapies for advanced variants are interferon, the chemotherapeutic agent cladribine, and tyrosine kinase inhibitors such as midostaurin.[9, 12] These chemotherapeutic agents are used in combination with antimediator therapy to control symptoms and reduce the overall mast cell burden. In patients with systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD)/systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), therapy selection usually depends on the associated disease, which is commonly more aggressive than the SM part. Mast cell leukemia and sarcoma require a polychemotherapy approach. More information on therapies for advanced systemic mastocytosis variants can be found here.

More on Medications to Treat Mast Cell Disorders

Probiotics;
The following strains may be helpful because they have been found to break down or reduce the formation of histamine:
Lactobacillus plantarum
Lactobacillus rhamnosus
Bifidobacterium infantis
Bifidobacterium lactis
Bifidobacterium longum
These strains should be avoided because they produce histamine in the GI tract:
Lactobacillus brevis
Lactobacillus casei
Lactobacillus delbrueckii
Lactobacillus fermentum
Lactobacillus helveticus
Lactobacillus hilgardii
Lactobacillus lactis
Enterococcus faecium
Streptococcus thermophilus

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