Mast Cell Activation Syndrome

Diagnosis: Mast cell activation syndrome (MCAS) is a condition where benign but highly sensitive inflammatory/allergic cells are located in a variety of areas of the body and release chemicals (mediators) which work cause many symptoms. The diagnostic work up can be complex and relatively expensive depending on insurance coverage for lab tests. One approach is to look for mast cells by gastrointestinal biopsies and see if the symptoms respond to treatment. If biopsies have been obtained in the past, we can get the “cell blocks” (not the slides) to stain the tissue for mast cells. Most allergists however believe that it is necessary to document that these mediators are documented to be elevated in the blood or urine prior to making the diagnosis. There is a good rationale to this in that there is some controversy about the number of mast cells that are needed to make the diagnosis. Experts in the field often try to detect chemical evidence of the disease to support abnormal biopsies from the gastrointestinal tract.

Laboratory test to look for evidence of mast cell activation include: 1) serum chromogranin A and tryptase and plasma heparin, histamine and prostaglandin; and 2) 24-hour urine collections for N-methylhistamine, 2,3 dinor 11-beta-PGF2-apha, and leukotriene E4. These tests may be normal because: 1) mast cells live in tissues and may be locally active locally and thus do not secrete enough chemicals to be picked up by blood or urine tests, 2) mast cells secrete mediators intermittently, or 3) the blood or urine is not handled properly since these chemicals are sensitive to heat. The tryptase blood level is usually normal in 85% of patients but seeing normal or low levels is helpful to exclude another cause of mast cell activation symptoms known as mastocytosis. The lab should keep your blood cold at all times (including their use of cold centrifuge). You and the lab should keep the urine cold at all times. Lab tests can be expensive and you should check with your insurance company if they will cover the costs of the tests.

Small intestinal bacterial overgrowth (SIBO), imbalanced microbiome of the colon, Helicobacter pylori infection of the stomach, mold exposure, and Lyme disease may be triggering factors for MCAS and may need to be excluded with special tests.

Scientific definition of MCAS: Criteria proposed to define mast cell (MC) activation syndrome when all other diagnoses that could better explain the full range and chronicity of the findings in the case have been excluded (modified from Afrin 2014). The diagnosis *mast cell activation syndrome* is made upon fulfilment of the major criterion plus at least one minor criterion.

Major criteria: 1. Clinical complaints attributable to pathologically increased MC activity (MC - mediator release syndrome)

Minor criteria: 1. Multifocal or disseminated infiltrates of MCs in marrow and/or extra-cutaneous organ(s) (e.g., gastrointestinal or genitourinary tract; >19 MCs/high power field)

2. Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of abnormal levels of MC mediators including: tryptase, histamine or its metabolites (e.g., *N*-methylhistamine), heparin, chromogranin A (note potential confounders of cardiac or renal failure, neuroendocrine tumors, or recent proton pump inhibitor use), other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D_2, its metabolite 11-β-$PGF_{2\alpha}$, or leukotriene E4)

3. Symptomatic response to inhibitors of MC activation or MC mediator production or action

(and/or three other uncommonly found and/or measured biological changes)

4. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extra-cutaneous organ(s)

5. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)

6. MC genetic changes (e.g., activating KIT codon 419, 509 or 560 mutations) shown to increase MC activity

Treatment: Therapy for mast cells can be challenging in that patients often require multiple medicines usually given in a step-wise manner. Patients may react to the medications and/or the fillers/additives/coatings in medications. Medications, natural therapies (over the counter), and diet can be helpful. More aggressive MCAS usually requires more aggressive therapy. In general avoid live vaccines and watch for drug side effects owing to dyes, filler, preservatives and certain medicines which trigger MCAS (see section below). Gluten, dairy, and histamine-containing foods can be problems for MCAS patients. For highly sensitive patients a good compounding pharmacy can be very important.

Education: Watch Dr. Afrin on YouTube: Afrin and MCAS, other MCAS posts on YouTube:
http://www.paediatrics.uct.ac.za/scah/clinicalservices/medical/allergy,
Dr. Afrin's book "Never bet against Occam: a mast cell book review and call to action"
Listen to: https://drruscio.com/mast-cell-activation-syndrome-clinician-researcher-dr-lawrence-afrin/

MCAS Dietary Approaches: This is a baseline starting point for of all of the "MCAS Step Therapies" discussed below. For one month exclude gluten, yeast, and cow milk protein-containing foods. A low histamine diet is recommended long-term. A FODMAP-free diet can help especially when SIBO or dysbiosis is present. It is important to looking for food triggers.

MCAS Step 1 – Anti-histamine and Natural Therapy: Start with over-the-counter H1 blockers (Zyrtec, Claritin, or Allegra) and H2 blockers (Zantac or Pepcid) are reasonable to start early on. See last page. Quercetin 500 mg 2 - 3x/day (at GNC, health food stores or online), Vitamin C (sustained - slow release) 500 mg once a day (some patients benefit with 750 – 1000 mg daily), Vitamin D 1000 units (or more depending on blood level) and probiotic therapy that includes Lactobacillus *rhamnosus* (Culturelle) and Bifidobacter species.

Note about all medicines including H2 blockers – one will be tolerated whereas another in the same drug category will not. This could be due to the chemical shape or the fillers in the pill/capsule. There are 4 over-the-counter H2 blockers and the doses for these should start low and increase gradually. Liquid versions often used for children may be good for people who are sensitive for medications. Some patients need the H2 blockers 3 times a day. Some may need double the normal dose. See second to last page.

If these fail to help, add DAO Enzymes with meals (UmbrelluxDAO), CBD oil (can be obtained locally at Mr. Nice Guy shops), alpha lipoic acid 600 mg daily, omega-3 fatty acids (fish oil, krill oil), N-acetylcysteine (NAC).

Many people have benefited from CBD alone or with THC – this is also in combination with low dose naltrexone (see Step 2). Ellajeans Organics is one option of CBD alone – available online

Additional natural therapies that could help include:

1. Adrenal support:
    a. DHEA - for general health
    b. Ashwagandha herb - helps sleep and may decrease histamine
    https://www.puritan.com/ashwagandha-1012?&scid=42614&cmp=msn-_-Bing_NB_Cat_Supplements_Alpha-_-ashwagandha

2. Gut health
    a. EndoZin from Klaire.com – my code is F11 to order. This helps heal the leaky gut – zinc-carnosine and L-glutamine – with meals 2x/day. Zinc can also reduce mast cell activity.

MCAS Step 2 Therapy

A. H2 blockers: Zantac (start at 150 mg and increase to 300 mg twice a day) or Pepcid (start at 20 mg and work up to 40 mg twice a day). See last page.
B. H1 blockers: Zyrtec 10 mg (or either Claritin 10 mg or Allegra 60 mg) 2 times per day. Some people do better on one H1 blocker than another. Benadryl is a sedating H1 blocker and should be used at night or for severe histamine activity.
C. Quercetin (herbal mast cell stabilizer available at GNC or online) 500 mg – 1000 mg twice a day.
D. Vitamin C (sustained - slow release) 500 mg once a day (some patients benefit with 750 – 1000 mg daily)
E. Vitamin D 1000 units (or more depending on blood level)
F. Low dose naltrexone (LDN): I generally recommend LDN to reduce inflammatory proteins that can trigger mast cell activation. LDN cannot be used in the setting of chronic narcotic use. For LDN start at 1 mg and gradually increase dose up to 4.5 mg each morning (this needs to be made at a compounding pharmacy).

If tolerating the above, yet symptoms are not substantially improved then the next 3 options are substitutes for Quercetin and include:

Singulair (montelukast) 10 mg per day (if there is asthma, interstitial cystitis, chronic prostatitis, pain, or brain fog, I will start this early on in the treatment).

Ketotifen 2 mg one to two capsules 1-2x/day (start at night since it may be sedating) - this needs to be made at a compounding pharmacy and is not covered by insurance.

Cromolyn - start at 1 ampule 2-4 times a day and then slowly increase to 2 ampules 4 times a day. See last page.

CBD oil can help painful conditions and can work hand in hand with LDN.

MCAS Step 3 Therapy

Ziluten 600 mg twice a day (this is especially good when there is asthma and/or interstitial cystitis). Accolate is another option. Low doses of aspirin can be tried but this should be closely monitored since allergic responses may occur (start at 81 mg and increase to 650 mg twice a

day). Short term use of steroids can be used for severe attacks of pain or hives. Benzodiazepines can be helpful.

MCAS Step 4 Therapy

In severe cases, the following medications may be used: Xolair subcutaneous injections (FDA-indication is for hives, angioedema and asthma; risk of anaphylaxis is 1/1000 and is riskier for those who have many allergies and drug reactions), Imatinib (Gleevec; FDA approved for CML; clinical experience with MCAS), immune globulin injections (FDA-indication for IVIg included hives and angioedema), Tofacitinib pills (Xeljanz; FDA-indication is for rheumatoid arthritis; case reports for MCAS), and hydroxyurea (FDA-indication, leukemia, sickle cell – helpful for MCAS with deep muscle and bone pain – case reports for MCAS).

MCAS – Dietary supplementation

Options to improve nutrition include: Physicians' Elemental Diet by Integrative Therapeutics (tolerable oral nutrition). In severe cases feeding tube placement into the small intestine with an elemental diet is required: Neocate Jr. or Elecare Jr. can be used in place of Vivonex which is standard.

MCAS - Drug Triggers

Avoid drugs that can trigger mast cell release - narcotics, muscle relaxants, certain antibiotics, anti-seizure, local anesthetics, IV dye, ACE inhibitors, and beta-adrenoceptor antagonists. When Xolair is considered, beta-blockers should be stopped.

MCAS - Periodic, symptom specific therapy

Abdominal pain: butylscopolamine, proton pump inhibitor (PPI), steroids, Ativan, Xanax

Anemia: iron (in particular IV) must be given cautiously due to risk for potentially intense mast cell activation; alternatively, red blood cell transfusion should be considered

Angioedema: tranexamic acid; icatibant

Arthralgias: celecoxib

Brain fog: nasal Cromolyn

Conjunctivitis (after exclusion of a secondary disease) preservative-free eye drops with H_1-antihistamine, Cromolyn, ketotifen, or glucocorticoid (brief courses)

Chest pain: extra H_2 blocker, PPI

Colitis: budesonide; prednisone

Diarrhea: cholestyramine; nystatin; montelukast; ondansetron; aspirin (50–350 mg/day w extreme caution (in steps test each drug for 5 days until improvement of diarrhea)

Fatigue – see below

Gynecologic disorders:

Chronic vaginitis and dyspareunia: diphenhydramine (25 mg) or Cromolyn (20-50 mg) vaginal suppository, low dose naltrexone

Heavy periods and pain: diphenhydramine (25 mg) virginal suppository, birth control pills (a number may need to be tried before the right one is found; low dose naltrexone; evening primrose oil the days before and during menses; naprosyn

Hypercholesterolemia: atorvastatin

Itching: palmitoylethanolamine (PEA), Cromolyn-containing ointment

Insomnia: triazolam, doxepin - * see section on fatigue below

Interstitial cystitis: pentosan (Elmiron), low dose naltrexone, antibiotics for small intestinal bacterial overgrowth, amphetamines

Muscle spasm: sinemet (25/100), cyclobenzaprine

Nausea: dimenhydrinate; lorazepam; ondansetron; aprepitant (Emend); additional anti-histamines, CBD and THC, marijuana (best in edibles), prucalopride (Resolor) (0.5-2.0 mg typical dosage range), low dose erythromycin (50-100mg) before meals, mestinon. ginger products (Motility Activator by ITI, Motil-Pro from Pure Encapsulations), Iberogast herbal therapy, visceral manipulation, yoga breathing techniques, and meditation.

Neuropathy: alpha lipoic acid, low dose naltrexone

Osteoporosis, bone pain ⇒ bisphosphonates (Vitamin D plus calcium is second-line Rx d/t limited reported success and an increased risk for stones); calcitonin; teriparatide (with caution; cases of cholestatic liver failure reported); denosumab (dental clearance required prior to Rx with bisphosphonates and anti-RANKL therapies)

Respiratory mucus and obstruction: montelukast; Ziluten; urgent: albuterol

Rib pain (associated with Ehlers Danlos): compounded topical Rx (Ketoprofen 10%, Ketamine 5%, Gabapentin 5%, Phenytoin 5%, Cyclobenzaprine 2%, Mexiletine 2%, Bupivacaine 1.0%, Clonidine 0.2%, Menthol 0.25%)

Tachycardia: ivabradine

Fatigue – this is the second most common problem in MCAS, This disorder is often associated with postural orthostatic tachycardia syndrome and Ehlers Danlos syndrome.

Causes for Fatigue in patients with MCAS, postural orthostatic tachycardia syndrome (POTS) and Ehlers Danlos syndrome (EDS)

1. MCAS - release of histamine, cytokines, and many other chemical inflammatory mediators
2. Medications – including antihistamines.
3. Hormonal malfunction in women

4. Hypothalamic-pituitary-adrenal axis alterations – affected by hypoperfusion or by inflammation from small intestinal bacterial overgrowth.
5. Sleep problems
    a. Restless legs syndrome – common in MCAS
    b. Obstructive sleep apnea – can be in thin EDS or overweight MCAS patients. Snoring is common – start out using the SnoreLab App on the phone.
    c. Upper airway resistance syndrome – can be in underweight hypermobile teens and adults with EDS - heavy, labored breathing during sleep. Sufferers of UARS often describe their breathing effort as "trying to breathe through a straw."
    d. Poor sleep hygiene – staying up late, caffeine excess, working with electronics
    e. Nonrestorative sleep owing to sympathetic overdrive.
6. Narcolepsy, dissociation, and depersonalization disorders
7. Anxiety disorders
8. POTS patients have inadequate blood flow to the brain with poor oxygen delivery
9. EDS patients can have:
    a. Postural muscles because of ligament laxity. The muscles are made up of weak connective tissue.
    b. Craniocervical instability (CCI)
10. Secondary mitochondrial dysfunction

Healthcare Team: It is important to build a team of doctors to help take care of your total health. In addition to your primary care doctor, specialists can be helpful. This is especially the case when there is the addition of two common syndromes associated with MCAS: postural orthostatic tachycardia syndrome (POTS) and hypermobile Ehlers-Danlos syndrome (EDS).

MCAS – for this condition allergists can be helpful: Private Practice: Jeffrey Tillinghast, MD - 314-542-0606; Barbara Jost, - MD314-868-6260; University care: W.U.: 314-996-8670 - Jennifer Dy, MD, Jennifer Monroy, MD; SLU: M. Dykewicz, MD

For those with POTS – a cardiologist and a neurologist can be helpful: Private Practice: Craig Reiss, MD, University care: W.U.: Mitchell Faddis, MD, Neurology Laurence Kinsella, MD

EDS – for this connective tissue syndrome, a physical therapist, pain management doctor, and orthopedic doctor can be helpful

Detailed Advice on Mast Cell Triggers and Anti-histamines

It is essential to identify substances, activities, and/or physical forces which trigger flares of mast cell activation. These include infections, mold, dust, pollen, temperature or humidity changes, stress, and foods. Gluten, lactose, yeast, and histamine foods are common triggers. Medication product excipients such as fillers, binders, dyes, or preservatives which are listed as “inactive ingredients” in the product labelling can be triggers. A pharmacist-assisted review of the ingredient list of a poorly tolerated product may help identify a potential triggering excipient, whereupon a trial of an alternative formulation of the product not containing that excipient can be pursued to confirm (or refute) the suspicion.

The next step is to identify the optimal and specific anti-histamine regimen, meaning the particular histamine H1 receptor antagonist (“H1 blocker”) and the particular histamine H2 receptor antagonist (“H2 blocker”) which clearly improves symptoms better than the other blockers. These medicines do two things for MCAS: 1) they reduce the effect of histamine on the mast cell and thus reduce the output of other chemicals; and 2) they bind to histamine receptors in the body that cause symptoms such as itching, pain, hives, and acid reflux. Antihistamines bring significant (if usually incomplete) improvement to the majority of MCAS patients, and they are inexpensive and appear safe for chronic use in the vast majority of patients, making them an excellent choice for first-line pharmacologic intervention. Because the disease very frequently causes chronic fatigue, H1 blocker trials in MCAS patients typically focus on the non-sedating H1 blockers, though sedating H1 blockers (e.g., diphenhydramine - Benadryl) do have roles to play, typically in management of acute flares.

Try the non-sedating H1 blockers (typically as a two-week-long trial of each drug tried at its standard dose, taken twice daily), most MCAS patients indeed can identify a specific H1 blocker which is more helpful than the other H1 blockers, and after starting regular use of the most helpful H1 blocker, similar rotating trials of the H2 blockers are added, whereupon most MCAS patients again manage to identify a particular H2 blocker which helps more than the others. Since H1 and H2 blockers, at routine doses, usually are very well-tolerated drugs, an adverse reaction of any sort to the first formulation tried (name-brand or generic; gelcap, capsule, tablet, liquid, etc.) of any of these H1 or H2 blockers almost certainly is an issue of excipient-directed reactivity, not drug-directed reactivity, creating an excellent opportunity for identifying, and thus avoiding, yet another of the patient’s triggers. No methods exist for predicting which drugs will provide the most benefit in the individual MCAS patient. No methods exist for predicting which classes of therapy will best help the individual patient. There are not yet even any clear patterns as to which symptoms will necessarily be helped by which interventions. Thus, there is much “trial and error” at present in managing this disease, but most MCAS patients do seem to be able to eventually identify a particular MC-targeted regimen which allows them to reach the above-stated goal.

H1 Blockers

- **Claritin** (loratadine) – Dose 10 – 20 mg twice a day.
- **Zyrtec** (cetirizine) – Dose 10 – 20 mg twice a day.
- **Allegra** (fexofenadine) – Dose is 180 mg once a day.

- **Astelin** (azelastine) – Potential benefit for this over the counter nasal spray is the lack of binders or chemicals that one might be reactive. Dose is 1 – 2 sprays in each nostril twice a day.
- **Ketotifen** – this requires a prescription for the medicine at a compounding pharmacy. Dose is 2 -4 mg twice a day

H2 Blockers

- **Pepcid** (famotidine) – this is over the counter but if it works well I can prescribe it so that it might lead to insurance covering it or it could be used for tax deductions in this way. Pepcid is easy to be compounded in pure form with non-allergic binders in case this is a concern. Dose is 20 – 40 mg twice a day
- **Zantac** (ranitidine) – also over the counter and prescription. Dose is 150 – 300 mg twice a day.
- **Axid** (nizatidine) – also over the counter and prescription. Dose is 150 – 300 mg twice a day.

Detailed Advice on Cromolyn

Cromolyn is well recognized to have potential to aggravate mast cell activation in the first few days of use, but when that happens, it tends to lessen within 2-5 days of onset. If it is started at cautious dosing and the patient is still -- a week after having started the medicine -- experiencing significant aggravation of symptoms shortly after each dose, then the explanation is (1) unusually prolonged reactivity, (2) fundamental intolerance of the drug (also unusual), or (3) excipient (other chemicals in the mixture) reactivity. Therefore, try switching to an alternative formulation if the initial formulation is still proving substantially problematic after a week.

Some patients can "get through" the reactions just with some extra antihistamines, or possibly even with some steroids on board for the first few days.

When switching formulations, it's reasonable to switch to *any* alternative formulation, though it's my own personal preference to have the patient switch from the generic they were (almost certainly) initially issued to brand-name Gastrocrom (if accessible). Although I've seen switches to alternative generic formulations, and even switches to compounded formulations, prove successful in some patients, and though I've even *very* occasionally seen Gastrocrom prove problematic in patients who then successfully switched to a generic formulation, *most* of the time where I've seen a switch like this prove successful is when they switch from a generic to Gastrocrom.

Leonard Weinstock, MD – edited 2/7/18; adapted from Dr. Molderings and Dr. Afrin's articles