

Approach to Mast Cell Activation Syndrome

Diagnosis: Mast cell activation syndrome (MCAS) is a condition where benign but highly sensitive inflammatory/allergic cells are in a variety of areas of the body and release chemicals (mediators) which can cause many symptoms. The diagnostic work up can be complex and relatively expensive depending on insurance coverage for lab tests. Although a positive biopsy can be helpful, demonstrating laboratory evidence of overactive mast cells is very important. If biopsies have been obtained in the past, we can get the “cell blocks” or unstained 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.

Laboratory tests to look for evidence of mast cell activation include: 1) serum chromogranin A and tryptase, 2) plasma histamine and prostaglandin; and 3) 24-hour urine collections for N-methylhistamine, 2,3 dinor 11-beta-PGF₂-alpha, 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 MCAS patients but seeing normal or low levels is helpful to exclude another cause of mast cell activation symptom known as mastocytosis or genetic cause of high tryptase. Many physicians believe that an increased tryptase is required for the diagnosis of MCAS but that is incorrect.

The lab should always keep the plasma cold (including their use of cold centrifuge and then it should be frozen afterwards). You and the lab should always keep the urine cold. Lab tests can be expensive, and you should check with your insurance company if they will cover the costs of the tests. Getting the blood work during an attack increases the likelihood of getting a positive test.

Small intestinal bacterial overgrowth (SIBO), imbalanced microbiome of the colon, *Helicobacter pylori* infection of the stomach, mold exposure, tick and insect born infections, and chemical exposures including heavy metals may trigger MCAS.

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. The diagnosis *mast cell activation syndrome* is dependent upon fulfillment 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 – see the 5-page questionnaire)

Minor criteria:

1. Abnormal levels of MC mediators in blood or urine
2. Symptomatic response to inhibitors of MC activation or MC mediator production or action
3. Infiltrates of MCs in gastrointestinal biopsies ≥ 20 MCs/high power field

And exclusion of other syndromes better suited to explain the symptoms

Education:

Watch YouTube videos: my webinar is <https://www.youtube.com/watch?v=2-b0r7l6b5A>

Also search [Afrin and MCAS](#) and [Theoharides and MCAS](#) posts

Listen: <https://drruscio.com/mast-cell-activation-syndrome-clinician-researcher-dr-lawrence-afrin/>

Read: “Never bet against Occam: a mast cell book review and call to action” (Dr. Afrin)

Websites: <http://mastcellmaster.com/index.php>;
<http://www.paediatrics.uct.ac.za/scah/clinicalservices/medical/allergy>

Support and Join: MCAS Facebook Support Group

Treatment: Therapy for mast cells can be challenging since patients often require multiple medicines usually given in a stepwise manner. Patients may react to the medications and/or the fillers/additives/coatings in medications. It is important to look for reactions to medicines whether it is the first time you take it or if you take the same medicine from a different manufacturer. One example is if you are sensitive to pine tree pollen then taking medicine with a methyl-cellulose filler will cause a reaction.

Medications, natural therapies (over the counter), and diet can be helpful. More aggressive MCAS usually requires more aggressive therapy. In general, avoid live vaccines. Gluten, dairy, and histamine-containing foods can be problems for MCAS patients. A good compounding pharmacy for highly sensitive patients can be very important.

MCAS Dietary Changes and Reducing Triggers: This is a baseline starting point for all the “MCAS Step Therapies” discussed below. For one month exclude gluten, yeast, and cow milk protein-containing foods. A low histamine diet is recommended – this may or may not be required long-term (<https://histaminefriendlykitchen.com/>). Download the Food Intolerance app on your phone. A FODMAP-free diet can help especially when SIBO or dysbiosis is present. A high protein ketogenic diet can be helpful. See: <https://mastcellactivationssyndrome.org/foods-to-avoid-worst-foods-for-mcas/>.

What can you eat? Check out www.whatTheBleepCanIEat.com (what the bleep can I eat)

Good foods and supplements include apples, Brazil nuts, Chamomile, high fiber diet, galangal (Thai ginger), moringa, nettle tea, onions (can also be bad), peaches, turmeric, vitamins C and D, watercress:

It is important to look for all triggers: stress, environmental factors (mold, heat, atmospheric changes, certain types of electricity), tick-borne infections including the Lone Star tick which can cause alpha gal syndrome (allergy to meat from mammals), heavy metals (including dental fillings), and chemical triggers (including odors). Hair coloring and tattoos are other potential issues. Note that pills and capsules contain dyes, preservatives, and binders that MCAS people can react to. Mold is a common problem in many parts of the country (see SurvivingMold.org). This can be tested via www.mymycolab.com – blood tests for antibodies against mycotoxins.

I do not believe in the urine tests via Great Plains Laboratory or Real Time Lab. Rarely, respiratory allergy triggers can be so severe that a mask may be needed (<https://cambridgemask.com/>). Some people need an air purifier (example: <https://austinair.com/>)

MCAS Step 1 Therapy

- A. H2 blockers: Pepcid or famotidine (start at 20 mg twice a day and work up to 20 mg three times a day or if needed 40 mg twice a day) or Nizatidine (start at 150 mg and increase to 150 mg twice a day) See last page of this handout.
- B. H1 blockers: Claritin 10 mg, Xyzal 5 mg, or Zyrtec 10 mg twice a day. Allegra 180 mg is good at 1 to 2 times per day. Some people do better on one H1 blocker than another. See section towards the end of this document. Some people do well with generics. Benadryl is a sedating H1 blocker and should be used at night or for severe reactions.
- C. Flavonoids (food-based mast cell stabilizers available online). Options include luteolin available from Algonot online and Isoquercetin which is more well absorbed than quercetin.
- D. Vitamin C (sustained - slow release) 500 mg once a day (some patients benefit with 750 – 1000 mg daily). Regular vitamin C can irritate the stomach and blood levels are not sustained.
- E. Vitamin D 1000 - 5000 units per day (depending on blood level)

And I often add one prescription medicine early on:

- 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). See www.gidoctor.net; www.LDNresearchtrust.org, and www.LDNscience.org

These medicines should be added one at a time roughly every four days to check for tolerance.

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

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 1/2 ampule daily and over a matter of weeks slowly increase to 2 ampules 4 times a day. Some patients react to tiny amounts of the plastic that may be released into the liquid. See last page of the handout. The form used as nasal cromolyn can help brain fog. All cromolyn preparations on the market have 2 ingredients lists: cromolyn and water. However, the plastic vials, the water used, the air in the manufacturing plant, etc. may all be different and can impact the patient's reaction to it. In general, Wallace brand seemed to be preferred by many of my patients, but I believe it is on backorder. Some of my patients are on Rising brand and a small number on Microlab. Woodard 's cromolyn seems to be least tolerated. Compounded cromolyn is a good option to sort these issues out.

Singular (montelukast) 10 mg per day (if there is asthma, interstitial cystitis, chronic prostatitis, pain, or brain fog, I will start this early in the treatment). It can work better twice a day in some patients. There is a warning for this drug of rare but serious emotional problems.

MCAS Step 2 Therapy

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). Zileuton 600 mg twice a day (this is especially good when there is asthma and/or interstitial cystitis. Benzodiazepines can be helpful to stabilize the mast cells.). Accolate is another option. Short term use of steroids can be used for severe attacks of pain or hives. Short term use of the non-systemic steroid budesonide can be used for colitis/diarrhea.

MCAS Step 3 Therapy

- 1) Xolair subcutaneous injections (FDA-indication is for hives, angioedema and asthma (prescribed by an allergist); risk of anaphylaxis is 1/1000 and is riskier for those who have many allergies and drug reactions); Hydroxyurea (Droxia) (FDA-indication, leukemia, sickle cell – helpful for MCAS with deep muscle and bone pain – case reports for MCAS);
- 2) Imatinib (Gleevec; FDA approved for CML; clinical experience with MCAS); immune globulin injections (FDA-indication for IVIg included hives and angioedema; this can be helpful when there is co-morbid autoimmune POTS); Tofacitinib pills (Xeljanz; FDA-indication is for rheumatoid arthritis; case reports for MCAS).

Regarding Imatinib: first check for tolerance by getting a few and pay cash (Costco Pharmacy). If it is tolerated get a full prescription which will ultimately require preauthorization. If insurance does not pay it then get it via CostPlus mail order pharmacy.

With refractory, severe anaphylaxis or hives, continuous diphenhydramine infusions can be given but few insurance companies and infusion companies will be cooperative.

Other options for refractory hives are Cyclosporin and CellCept.

MCAS – Dietary supplementation

Options to improve nutrition include Physicians' Elemental Diet by Integrative Therapeutics (tolerable oral nutrition – online or locally at Colonial Hills Pharmacy in Webster). Orgain vegetable protein powder is a well-tolerated product (see ingredients which differ between the flavors to look for issues. 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 or Vital HN which are standard formulations of tube feeding. A number of patients will tolerate these.

MCAS - Drug Triggers

Avoid drugs that can trigger mast cell release - narcotics, muscle relaxants, certain antibiotics, anti-seizure, local anesthetics, IV dye, and certain blood pressure medicines such as ACE inhibitors and beta-adrenoceptor antagonists. When Xolair is considered, beta-blockers should be stopped (and should not be used in patients who have been on steroids long enough to cause adrenal insufficiency). Excipients are chemicals in pills/capsules and include food colors, preservatives, and fillers – the following websites could be helpful:

<https://dailymed.nlm.nih.gov/dailymed/index.cfm>

<https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>

This one is more for drug interactions

<https://www.webmd.com/interaction-checker/default.htm>

Note there are blood pressure medicines that could actually help MCAS: angiotensin II receptor blockers (candesartan, losartan, and valsartan).

Natural Therapies that can be used include:

1. Use the strength of your brain overcome chronic illness -
Dynamic Neural Retraining System (DNRS) <https://retrainingthebrain.com>, "the Gupta program," the "Acceptance and Commitment Therapy" (ACT) program, the "Curable" program, and the "Accelerated Resolution Therapy" (ART) program.
2. Alpha stim (www.alpha-stim.com) – vagal stimulation that could decrease anxiety, pain, depression, abdominal symptoms, fibromyalgia pain, and insomnia.
3. Gut health
 - a. Probiotic therapy that includes *Lactobacillus rhamnosus* (Culturelle) and *Bifidobacter* species. Symprove has multiple organisms and is an expensive option.
 - b. EndoZin from Klaire.com – use code F11. This helps heal the leaky gut – zinc-carnosine and L-glutamine – with meals 2x/day. Zinc can also reduce MC activity.
4. DAO Enzymes with meals (UmbrelluxDAO) – this prevents histamine release by high histamine foods
5. Alpha lipoic acid 600 mg daily. Some patients have had measurements of their ALA level and addition of this compound if low has been helpful
6. Omega-3 fatty acids (fish oil, krill oil)
7. N-acetylcysteine (NAC)

8. Mitochondrial support – L-Carnitine (usually 2000 mg twice a day or 50 mg per kilogram twice a day) and CoQ10 (usually 200 mg twice a day or 5 mg per kilogram twice a day)
9. CBD oil can help painful conditions and can work hand in hand with LDN.
 - a. CBD can be obtained locally at Mr. Nice Guy shops or online.
 - b. Populum - Full spectrum organic hemp oil. Products offer sweet orange oil. Gluten-free versions. Use grape seed oil and coconut oil as carriers
 - c. Ellajans Organics
 - d. Hemp Meds -imported from UK. Have multiple formulations.
 - e. Ananda Hemp
 - f. CW hemp – 100% organically grown full spectrum Hemp from Colorado. Charlotte's Web. Carrier is coconut oil or organic extra virgin olive oil
 - g. Delta Botanics – offer multiple flavors. Full spectrum. European hemp. GMO free, organically grown. Gummies
 - h. CBD Fx – organically grown hemp from Europe. Full spectrum CBD. Use coconut and MCT oil as carrier. Vegan gummies available. Use the code: SUP-10
 - i. NuLeafnaturals.com
 - j. Theramu – 2 strengths for the tinctures (300mg/ 1-ounce bottle or 750mg/1-ounce bottle) and the cream.
10. THC – There are receptors for THC and CBD on mast cells. Modulation of the mast cell can reduce inflammation. THC is often helpful for nausea and pain. A physician must be licensed to prescribe medical marijuana – a reasonable diagnosis is chronic fatigue.
11. Adrenal support:
 - a. DHEA - for general health
 - b. Rholiola (may also inhibit histamine formation)
 - c. Ashwagandha herb - helps sleep and may decrease histamine
<https://www.puritan.com/ashwagandha>

Periodic or symptom specific therapy

Anaphylaxis: EpiPen

Abdominal pain: butylscopolamine, proton pump inhibitor (PPI), steroids, Ativan (lorazepam), low dose naltrexone, antibiotics for SIBO, antifungals for SIFO

Anemia: iron (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

Anxiety: Dihydrohonokiol for those who want to take a herbal anxiety medicine

Brain fog: Nasal Cromolyn, BrainGain (algonot.com/braingain/), Neuroprotek, DIM (dindolyl methane) – OTC or via Internet; or DNRS - <https://retrainingthebrain.com/>

Burning mouth syndrome: swishing 25 mg liquid solution of dye free Benadryl in mouth and then spitting out; clonazepam 0.1 mg/mL solution swish with 5 mL for 5 minutes and spit two to four times daily; fat soluble thiamine (benfotiamine), 100 mg twice a day with food until symptoms remit, then once a day maintenance; injectable peptide called ARA290

Chest pain: extra H₂ blocker, PPI, oil of peppermint

Colitis: budesonide

Conjunctivitis: (after exclusion of a secondary disease) Cromolyn, ketotifen, or glucocorticoid (brief courses), and Cetirizine eye drops, in a preservative free dispenser (Zerviate: Eyevance, <https://eyevance.com/>)

Constipation: ginger products (Motility Activator by Immune Therapeutics, Motil-Pro from Pure Encapsulations), Motegrity (1-2 mg in the morning), Zelnorm 6 mg twice a day, various treatment for methane intestinal overgrowth if present. Visceral Manipulation for Constipation (<https://www.barralinstitute.com>): Helen Bayer Tel: 314.434.6794; Michael Nobs Tel: 314.651.5155; Samuel Rotman Tel: 314.803.4990; Complementary treatments: Soaking a flannel rag with castor oil, placing it over the belly, putting a plastic bag over it and then covering it with a heating pad for one hour. Treading water in the deep end of a pool allows for added value by forces of hydrostatic compression; Magnesium Plus TM: <https://www.amazon.com/Biotics-Research-Acti-Mag-PlusTM-Bioavailable/dp/B07TV78SBW>

Dental and oral problems including burning mouth, sores, cavities, and gum disease: Swish and spit liquid color free diphenhydramine, Swish and swallow cromolyn, See a Biologic Dentist (Dr. Rehm – father and son on Ballas). Quercetin and green tea have been well studied and found positive effects for shifting gum disease by doing a swish and swallow. Toothpaste with hydroxyapatite can mineralize teeth at the same rate as fluoride.

Diarrhea: budesonide steroid, cholestyramine; nystatin; montelukast; ondansetron; aspirin (50–350 mg/day w extreme caution (in steps test each drug for 5 days until improvement of diarrhea); Thorn Dipan- 9 - pancreatic enzymes - <https://www.amazon.com/Thorne-Research-Pancreatic-Digestive-Capsules/dp/B000FGZF04>;

Cellulose allergic patients --- <https://enzymedica.com/collections/enzymes/products/digest-spectrum-digestive-enzymes?variant=720040805> – This as a digestive enzyme that has a vegetarian capsule that has cellulose in the wrapper only – if you open it and takes it that way with no problems

Fatigue: see section 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) vaginal 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

Hair loss: A diphenhydramine (Benadryl) shampoo can be made by taking a small bottle of liquid dye-free diphenhydramine and pouring it in to a mostly full bottle of shampoo that is currently tolerating and then mix it up and use it daily. The same approach can be taken with a bottle of nasal cromolyn spray. Each drug can be applied to the scalp separately from the shampoo. Do this after the shampooing. The following could help.

<https://www.healthfulelements.com/store/reversing-alopecia-masterclass>.

For severe hair loss consider: baricitinib and tofacitinib

<https://jddonline.com/articles/dermatology/S1545961618P0800X>

Other options:

1) 200 mg of compounded Benadryl or dye free Benadryl liquid in a spray bottle. Filled it up with water about 1/2 of the way. Shake it well and then spray over scalp. The compounded powder can get stuck in the plastic tube after a few days so transferred it into an eye drop bottle (see below) which is better for treating spots that needed more attention.

2) https://www.amazon.com/Benadryl-Relief-Spray-Extra-Strength/dp/B015JL83WG/ref=sr_1_5?dchild=1&keywords=benadryl+spray&qid=1603492320&sr=8-5

3) Mix basil oil with Jojoba oil for a spray

https://www.amazon.com/Miracle-Botanicals-Tulsi-Basil-Essential/dp/B01IPZLQHM/ref=sr_1_5?dchild=1&keywords=miracle%2Bbotanical%2Btulsi%2Bholy%2Bbasil&qid=1603492484&sr=8-5&th=1

3) Trader Joe's Jojoba Oil - mix the oil with water and massaged into scalp about an hour before washing my hair. With significant loss of hair washed it every 3rd day).

4) Once hair started to grow back, try L'Oreal shampoo – it might thicken hair

Headaches: <https://www.migrelief.com/> can be helpful for some patients.

If these are postural and severe need to look for spinal fluid leaks

Hypercholesterolemia: atorvastatin, lovastatin

Hypertension: blood pressure medicines that could actually help MCAS include angiotensin II receptor blockers (candesartan, losartan, and valsartan). See end of document for dos and don'ts

Inhaled sensitivities: nebulized cromolyn; air mask ("Cambridge mask")

Insomnia: triazolam, doxepin, CBD, THC - * see section on fatigue below. Doxepin, ketotifen and other H1 blockers, additional H2 blocker, Remeron, quetiapine for severe cases (12.5-25 mg), estrogen + progesterone or progesterone only in a woman who is deficient helps sleep. Supplements can help including melatonin, inositol, L-theanine, Mirica, ParaSym Plus, and ashwaganda. BDNF may help: <https://www.researchednutritionals.com/product/bdnf-supplement-essentials-for-nueroplasticity-and-brain-health-support/>

Interstitial cystitis: pentosan (Elmiron), low dose naltrexone, antibiotics for small intestinal bacterial overgrowth, amphetamines. Freeze dried Aloe via Internet can help. Biofilm therapy and repeating the culture could help - <https://icwellness.org/biofilms-and-ic/>

Itching: palmitoylethanolamine, Cromolyn-containing ointment (<http://www.mastokids.org/magic-masto-lotion>), higher dose antihistamines

Joint and muscle pain: palmitoylethanolamine (PEA), celecoxib, low dose naltrexone, CBD cream. Try BenGay for localized pain (contains aspirin)

Muscle spasm: Sinemet (25/100), cyclobenzaprine

Nasal congestion: nasal cromolyn, ketotifen eye drops placed in the nose

Nausea: 1) Medications: cyproheptadine, dimenhydrinate (Dramamine), scopolamine ear patch, lorazepam, ondansetron (Zofran), additional anti-histamines including diphenhydramine, prucalopride (Resolor or Motegrity - 0.5-2.0 mg typical dosage range), Mestinon, Aprepitant (Emend), Tricyclic anti-depressants, mirtazapine (Remeron); and 2) Natural: CBD and THC, marijuana (best in edibles without dyes), ginger products (Motility Activator by Immune Therapeutics, Motil-Pro from Pure Encapsulations), vitamin B6, Calamus Root, Iberogast herbal therapy, yoga breathing techniques, meditation.

Nausea with slow stomach (gastroparesis): low dose octreotide, low dose erythromycin (50-125 mg) before meals, vagal stimulus (GammaCore device - especially with complex migraine), endoscopic ultrasound with celiac plexus block (consider liposomal bupivacaine)

Neuropathy: alpha lipoic acid, low dose naltrexone, vitamins B6 and B12, methylated folate

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; Zileuton; 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%), binding by a physical therapist – see educational PowerPoint:

Skin – Dry skin: GentleDerm – on Internet; stretchmarks: PracaSil-Plus

Sweating - low-dose glycopyrrolate

Tachycardia: metoprolol; if POTS is present there are many medicines to try, increased salt intake, support stockings, and recumbent exercises

Tinnitus: This may improve with usual MCAS treatments. Persistent tinnitus or vertigo can be treated with either using a few drops of dye free Benadryl or cromolyn- either the oral formulation if the patient happens to already have oral cromolyn or try over the counter Nasal cromolyn

Vertigo: vertigo and tinnitus using a few drops of cromolyn- either the oral formulation if the patient happens to already have oral cromolyn or try over the counter nasal cromolyn

Fatigue: This is the second most frequent 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 or any chronic inflammatory condition.
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 – Metoprolol can help.
 - f. Nocturnal hypertension – check blood pressure at night.
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)

c. Spinal fluid leak

10. Secondary mitochondrial dysfunction

Medical treatments for fatigue: naltrexone, Stimulants (Adderall, Concerta, Ritalin, Nuvigil, Provigil), DNRS: <https://retrainingthebrain.com/>

Detailed Advice on Mast Cell Triggers

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, chemicals, heavy metals, physical conditions, 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.

GI disorders – celiac disease, Helicobacter pylori, small intestinal bacterial overgrowth, yeast/candida, imbalanced bacteria (dysbiosis), parasites

Autoimmune disorders – thyroid and others

Mold (mycotoxins) – via blood test - MyMycoLab.com. See Dr. Jill Crista's book "Break the Mold".

Tick and insect born infections – diagnosis via at Immunosciences Lab Lyme panel, Western Blot blood work, ArminLab, or Igenex

COVID-19 infection – this can exacerbate MCAS and can trigger a MCAS-like illness in previously healthy people – see

<https://reader.elsevier.com/reader/sd/pii/S1201971221007517?token=DB5AF102E2CC780DF1641422716AC096DC5083D1B1CE84B2E8475F3A66C646CBBE00A78F07D1683C2D8ADE48E835B006&originRegion=us-east-1&originCreation=20210924131217>

Other infections

Chemical and food sensitivity – see TILResearch.org and take the QEESI test; consider hair dyes, tattoos, heavy metals (potentially including metal cavity fillings), herbicides (glyphosate, atrazine). Heavy metals in dental cavity fillings (amalgam) may be a trigger to MCAS. Measuring metals by using an EDTA challenge test is an option, though controversial. Silicone leak or plastic from breast supplements can be a trigger. Mesh from hernia surgery may also be a trigger. For inhaled chemical problems try the Austin Air Filter.

Stress – look into yoga, meditation, self-hypnosis, Dynamic Neural Retraining (www.retrainingthebrain.com)

Poor motility and Pain – problems with the vagus nerves:

<https://elemental.medium.com/science-confirms-that-the-vagus-nerve-is-key-to-well-being-c23fab90e211>

<https://zenfounder.com/managing-stress/hacking-the-system-what-you-need-to-know-about-the-vagus-nerve/>

Detailed Advice on Antihistamines

The next step is to identify the optimal and specific antihistamine 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 most 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; gel cap, 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 MC-targeted regimen which allows them to reach the above-stated goal.

Notes on Antihistamine Therapy: Start with over-the-counter H1 blockers (Claritin, Xyzal, Zyrtec, or Allegra) and H2 blockers (Pepcid or Axid) early on in MCAS therapy

H1 Blockers

- **Claritin** (loratadine) - Dose 10 – 20 mg twice a day.
- **Xyzal** (levocetirizine) - Dose 5 mg twice a day.
- **Zyrtec** (cetirizine) - Dose 10 – 20 mg twice a day.
- **Allegra** (fexofenadine) - Dose is 180 mg once a day.
- **Desloratadine** - requires a prescription – 5 – 10 mg once a day
- **Cyproheptadine** - requires a prescription
- **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

- There are three 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.
- **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
- **Axid** (nizatidine) – also over the counter and prescription. Dose is 150 – 300 mg twice a day
- **Tagamet** (cimetidine) – 400 mg is the starting dose

Dry eye issues occur with antihistamines but need to exclude Sjogren's syndrome and other specific eye disorders (mast cell activation syndrome per se, rosacea, allergic conjunctivitis, vasomotor conjunctivitis, etc.).

There is less of an issue with H2 antihistamines which alone can help MCAS before trying H2 blockers again. When using H1 agents try the ones that seem to show the least antimuscarinic effects. All the H1 antihistamines have some anticholinergic, antimuscarinic effects clinically (including fexofenadine & cetirizine, even though it was not detected in the preclinical research cited). Start with low dosage (1/4 to 1/2 of the usual dosage) & see how it goes, work up as necessary and tolerated. Sometimes the drying is not as problematic as anticipated & occasionally large benefits occur for the problem under treatment even with low doses. Levocetirizine and ketotifen seem to product the least anticholinergic effects relative to their H1 blocking effects in many patients.

Note: Olopatadine eye drops can help allergic and vasomotor conjunctivitis. Many treatments are available for ocular rosacea, but it also responds to treatment for small intestinal bacterial overgrowth when present. Ketotifen eye drops can help allergic conjunctivitis and mast cell activation syndrome. Cromolyn and Cetirizine eye drops, in a preservative free dispenser (Zerviate: Eyevance, <https://eyevance.com/>) are also good.

Note about all medicines– one will be tolerated whereas another in the same drug category will not. This could be due to the chemical shape or the fillers/dyes/preservatives in the pill/capsule.

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, first try the compounded version to see if it even works. If it does see if the brand name drug via the normal pharmacy works (Gastrocrom) – currently not available.

Pre-op and Pre-procedure Advice

There are many considerations based on MCAS and co-morbid POTS and EDS – see separate handouts. A good basic approach is listed on www.tms4acure.org

In general, intravenous diphenhydramine (Benadryl), famotidine (Pepcid), midazolam (Versed), and in very reactive patients, steroids should be given at the time of the procedure.

Patients with one of the Ehlers-Danlos Syndromes need to take several precautions: see www.hypermobilitymd.com

Patients with Postural Orthostatic Tachycardia Syndrome need to take several precautions.

Perioperative Management in MCAS

Pre-medication for major and minor procedures and for radiology procedures with and without dyes may include:

- Prednisone 50 mg orally (20 mg for children under 12) 24 hours and 1-2 hours prior to surgery/ procedure
- Benadryl (Generic: diphenhydramine) 25-50 mg orally (12.5 mg for children under 12) or Atarax (Generic: hydroxyzine) 25 mg orally, 1 hour prior to surgery/procedure •
- Pepcid (Generic: famotidine) 20 mg orally (10 mg for children under 12) 1 hour prior to surgery/procedure

- Singular (Generic: montelukast) 10 mg orally (5 mg for children under 12) 1 hour prior to surgery/procedure

Drugs to be avoided whenever possible:

- Aspirin and non-steroidal anti-inflammatory medications (unless patient are already taking)
- Aspirin should be tried when the prostaglandin tests are positive
- Opioids/opiates (e.g.: Morphine, hydrocodone, oxycodone, codeine, etc.)
- Vancomycin
- Beta and Alpha-adrenergic blockers --- sometimes beta blockers are important for POTS
- Procaine, Benzocaine (some people with EDS are resistant to the effects and will achieve better results with Mepivacaine)
- Lidocaine maybe tolerated by some patients but not by others

Emergency Management

For symptoms including flushing, rash, hives, swelling, abdominal pain, nausea, vomiting, shortness of breath, wheezing or hypotension:

- Epinephrine 0.3 cc of 1/1000 and repeat 3x at 5-minute intervals if BP < 90 systolic (0.1 cc for children under 12)
- Benadryl (Generic: diphenhydramine) 25-50 mg (12.5-25 mg for children under 12) orally, intra-muscular or intravenously (slow IV push) every 2—4 hours or Atarax (Generic: hydroxyzine) 25 mg (12.5 mg for children aged 2-12) orally every 2—4 hours
- Solu-Medrol (Generic: methylprednisolone) 120 mg (40 mg for children under 12) IV/IM
- Oxygen by mask or nasal cannula 100%
- Albuterol nebulization

More information can be found at <https://tmsforacure.org/perioperative-management>

Blood pressure and Anti-hypertension Medicine Advice

A subset of mast cell disease patients (about 20 to 40%) suffer from night-time hypertension which is often missed because normally blood pressure is not determined during the night. The blood pressure often already starts to rise in early evening (7-8 p.m.), reaches its maximum (not uncommonly up to 200/130 mm Hg) at 3-4 a.m. and then slowly returns to normal values at 7-8 a.m. and then remaining normal throughout the day. In cases e.g., of headaches resistant to analgesics or sleep disturbances the patients should measure blood pressure during the night when awake. Also 24-hour monitoring of blood pressure would make sense. This form of presumably mast cell-induced/associated hypertension is difficult to treat. One should determine Brain Natriuretic Peptide and perform echocardiography.

Some of the follow comments apply to the severe case of mast cell disease - mastocytosis
Anti-hypertensives which should not be used in mastocytosis patients:

- β -blockers (not only because the potential blockade of the effect of the epi-pen, but also

because as already said above, β -adrenoceptors are the last mechanism of the organism to control, i.e. reduce, the activity of mast cells – these drugs can activate mast cells

- ACE inhibitors; if activated mast cells of the individual patient form and release bradykinin, you will enhance its symptoms because ACE is the main enzyme for metabolism of bradykinin;

Anti-hypertensives which are problematic in mastocytosis patients:

- Diuretics because they often increase uric acid, disturb the mineral balance (which is often already disturbed by the mastocytosis) and may injure the kidney (thiazides) which are frequently already impaired by the mastocytosis (reflected by an increased CK value)

- Calcium channel blockers can be used but often induce a considerable retention of water in the body which limits its antihypertensive effects after a relative short time;

- Alpha-adrenoceptor blockers can be used but in my hands are without effect on blood pressure in mastocytosis patients.

Anti-hypertensives which can be used in mastocytosis patients:

- ARB Saran family; these compounds are in the majority of the patients ineffective in reducing the increased blood pressure but they protect the kidney which is frequently impaired by the mast cells;

- Clonidine (or moxonidine) is (are) effective and does not affect the mast cells; the dose has to be specified individually; contraindication is a low heart rate;

- Renin antagonists may be effective, since mast cells are known to release renin.

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.

MCAS: Jennifer Monroy, MD (314-996-8670); Jeffrey Tillinghast, MD (314-542-0606); Mark Dykewitz, MD (314-977-9050)

POTS: Neurology Laurence Kinsella, MD (636-496-3900); Cardiology: Patricia Clark, NP at St. Luke's (314-692-2807); Mitchell Faddis, MD at WU (314-362-1291).

PT program at St. Luke's Hospital for POTS with safe endurance exercise routine and other programs (Madeline.Wagner@stlukes-stl.com)

EDS: Physical therapy: 1) W.U. PT: Jennifer Miller or Linnette Koos-Summers (314-286-1580), 2) TC with Advanced Training Rehab in Crestwood (314-729-9300). Pain management doctor and orthopedic doctor can be helpful.

Tick borne , Mold, Heavy Metal Diseases: Christian Wessling, MD and/or Cindy Willebrand, ND (314-961-6631); Scott Jamison, MD (314-801-8898); Michael Schoenwalder, DO (314-721-2140); Asia Muhammad, ND (314-409-8834); specifically for tick born disease: Charles Crist, MD (Ashland, MO). Jessica Jellison in KC for Bartonella.

Dietician: Amy Schleper, MS,RDN, CDE; amy@redonutrition.com (takes some insurance); Local is Nancy Bradley, RD

Updated 6-27-22

Copyright 2022