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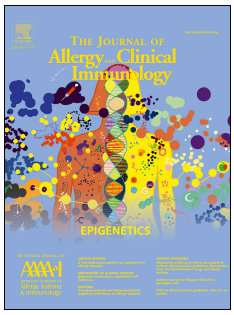

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PII: S0091-6749(19)31116-9

DOI: https://doi.org/10.1016/j.jaci.2019.08.023

Reference: YMAI 14160

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 25 June 2019

Revised Date: 20 August 2019

Accepted Date: 27 August 2019

Please cite this article as: Weiler CR, Austen KF, Akin C, Barkoff MS, Bernstein JA, Bonadonna P, Butterfield JH, Carter M, Fox CC, Maitland A, Pongdee T, Mustafa SS, Ravi A, Tobin MC, Vliagoftis H, Schwartz LB, AAAAI Mast Cell Disorders Committee Work Group Report: Mast Cell Activation Syndrome (MCAS) Diagnosis and Management *Journal of Allergy and Clinical Immunology* (2019), doi: https://doi.org/10.1016/j.jaci.2019.08.023.

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Disclosure of potential conflict of interest: LBS receives royalties for inventing the tryptase assay from Thermo Fisher, is a consultant for companies in the mastocytosis or anaphylaxis field, including Genentech, Deciphera, Blueprint Medicines, and Allakos, receives research support for a mastocytosis clinical trial from Deciphera, and receives honoraria from Up-To-Date and Cecil Medicine for writing about anaphylaxis and tryptase. CA consults for Novartis and Blueprint Medicines for tyrosine kinase inhibitors in mastocytosis and receives research support for a clinical trial in mastocytosis from Blueprint Medicines; AM is on the speakers' bureau for Sanofi/Regeneron and Genentech; SSM is on speaker bureaus

for Genentech, Teva, AstraZeneca, Regeneron and CSL Behring. The rest of the authors declare that they have no relevant conflicts of interest.

Keywords

mast cell activation syndrome; tryptase; hereditary alpha-tryptasemia; mastocytosis; anaphylaxis; Histamine; PGD2; LTC4; c-kit

Abbreviations

aspirin-exacerbated respiratory disease (AERD)

complement anaphylatoxins receptors (C3aR and C5aR)

gain-of-function (GOF)

leukotriene (LT)

mast cell (MC)

mast cell activation syndromes (MCASs)

Mas-related G protein receptor (MRGPRX2)

prostaglandin (PG)

postural orthostatic hypotension with tachycardia syndrome (POTS)

serum (or plasma) acute total tryptase level (sAT)

serum (or plasma) baseline tryptase level (sBT)

Stem Cell Factor (SCF)

systemic mastocytosis (SM)

ABSTRACT

Our current recommendations for diagnosing and treating primary MCAS make use of the latest studies and consensus guidelines for clinically recognizing systemic anaphylaxis in real time, regardless whether allergen-triggered an allergen-triggered IgE:FcεRI-mediated pathway or to ligands of G protein receptor pathways, or to intrinsic dysregulation of mast cells; our current understanding of the biomarkers secreted by activated mast cells that best discriminate this disorder from other conditions; and the therapeutic drugs that may selectively affect those mediators or mast cells themselves. Finding familial or somatic mutations of genes that cause mast cells to be hyper-activatable would extend our diagnostic tools and potentially indicate new therapeutic interventions, targeting either the mutated gene product or the associated molecular pathway. In conclusion, we trust that the clinical, laboratory and therapeutic criteria for primary MCAS(s) described herein will provide clinicians with practical criteria of sufficient sensitivity and specificity to diagnose most cases, without over-diagnosing the disorder in patients who likely have other conditions.

BACKGROUND

The last consensus report regarding mast cell (MC) disorders utilized the term mast cell activation syndromes (MCASs) to encompass all the current diagnoses in which MC activation plays a pivotal pathophysiologic role.[1] This included clonal and non-clonal MC disorders. The disorders were divided into primary, where MCs seem to be more activatable, either spontaneously or to a known or unknown external trigger, and secondary, where normal MCs are activated by an external trigger, typically an allergen via IgE:FcεRI, but also by antigens via IgG:FcγRI/IIa, a variety of ligands acting on GPCRs, or physical stimuli such as pressure, temperature, or vibration. Disorders associated with primary MCAS include systemic mastocytosis (SM),[1, 2] a clonal disease associated with a somatic gain-of-function (GOF) *KIT* mutation; clonal MCAS, associated with similar *Kit* mutations and/or aberrant expression of CD25, but lacking other criteria needed to diagnose SM by the WHO criteria;[1, 3] hereditary α-tryptasemia,[4, 5] associated with increased copy numbers of the *TPSAB1* gene encoding α-tryptase; and idiopathic MCAS, where neither a trigger, mutation nor genetic trait as yet has been identified.

The term, MCAS, is defined as a primary clinical condition in which patients present with spontaneous episodic signs and symptoms of systemic anaphylaxis, concurrently affecting at least two organ systems and resulting from secreted MC mediators. Symptoms occur in association with the secretion of MC products such as tryptase, histamine, prostaglandin (PG) D_2 and leukotriene (LT) C_4, leading to elevated levels in blood or urine of secreted mediators or of their metabolites,

including N-methylhistamine, 11β-$PGF_{2α}$ and LTD_4/LTE_4, and should improve with medications that block their binding to receptors or their production. Agents that block receptor binding include H1R and H2R antihistamines and CysLTR1 antagonists, while decreasing production occurs with inhibitors of cyclooxygenase for PGD_2 or of 5-lipoxygenase for LTC_4 or with mast cell stabilizers such as omalizumab that diminish mast cell activatability.

BASIC SCIENE OF MAST CELL DEVELOPMENT AND ACTIVATION (see Online Repository for further details)

Mast cell development, heterogeneity and activation are inter-related, likely affecting MC activation syndromes. Importantly, MCs develop from progenitors in the bone marrow that mature either in the bone marrow or after being recruited to their tissue site of residence under the influence of Stem Cell Factor (SCF) interacting with the Kit tyrosine kinase receptor on the surface of mast cells. The capacity of MCs to be activated and the mediator pathways elicited may vary among different types of mature and immature MCs. MC mediator secretion can follow engagement of FcεRI and FcγRI/IIa receptors as well as after stimulation of surface G protein-coupled receptors, including complement anaphylatoxins receptors (C3aR and C5aR) and Mas-related G protein receptor (MRGPRX2), and Toll-like Receptors. Depending on what activates MCs, differential secretion of granule mediators and newly-generated mediators can occur.

DIAGNOSIS OF MCAS: CLINICAL SIGNS AND SYMPTOMS

MCAS is a diagnosis that should be entertained in patients with an appropriate clinical and laboratory profile when other conditions have been excluded. Patients with MCAS can have a variable clinical phenotype, affecting multiple organ systems. **However, a key feature is recurrent episodes of systemic anaphylaxis with concurrent involvement of at least two of the four organ systems listed below.[1, 6] The clinical symptoms have to be associated with acute increase in specific biologic mediator levels[7] and patients should respond to therapy with mast cell mediator blocking agents and/or mast cell stabilizers.** The most validated mediators for their direct clinical impact include histamine, PGD_2 and LTC_4, while the metabolites of these mediators along with tryptase serving as biomarkers for mast cell activation.

As an example, a patient who presents with episodic symptoms affecting two or more organ systems such are syncope, wheezing, diarrhea and/or flushing should be evaluated for MCAS. The evaluation should include measuring mediator levels at baseline and during an acute episode (Table I). If the laboratory findings correlate with the presence of symptoms, then appropriate therapy(ies) should be implemented. The symptoms should resolve with therapies directed at the elevated mediator. If, for example, only urinary histamine products are elevated, then histamine blocking agents may improve the symptoms. If, on the other hand, prostaglandins are elevated, then aspirin (with appropriate precautions discussed later in the manuscript) will reduce prostaglandin levels and should alleviate symptoms. The presence of the specific symptom during which a mediator is

154 elevated and the clinical response to appropriate therapy are all prerequisites for
155 the diagnosis of MCAS.
156
157 Persistent symptoms, such as occurs in chronic urticaria or poorly-controlled
158 asthma, should direct the clinician to a different underlying diagnosis. Likewise,
159 chronic elevation of a mediator, such as tryptase, may reflect underlying SM[1, 2] or
160 hereditary α-tryptasemia,[4, 5, 8-11] disorders that can be but are not always associated
161 with MCAS, (Section 5a, Tryptase). Clinical symptoms of diagnostic value that are
162 frequently reported by patients with MCAS[12-14] include the following:
163
164 **Cardiovascular:** Hypotension, tachycardia and syncope or near-syncope.[7,
165 14-16]
166
167 **Dermatologic:** Urticaria, pruritus, and flushing[7, 12, 14-16] and angioedema,[6]
168 particularly of the eyelids, lips, and tongue.
169
170 **Respiratory:** Wheezing, shortness of breath and inspiratory stridor[6, 7]
171
172 **Gastrointestinal:** Crampy abdominal pain, diarrhea, nausea, vomiting. [6, 7,
173 12, 14-17]
174
175 **Importantly, two or more of the above organ systems being concurrently**
176 **involved in acute, recurrent clinical episodes, consistent with the working**
177 **diagnosis of systemic anaphylaxis recommendations,[18] would increase the**

likelihood of MCAS being culpable (Table II). Symptoms should be associated with acute elevations of mast cell mediators on two or more occasions to establish a diagnosis of MCAS.

Reported triggers or potentiating factors can include hot water, alcohol, drugs, stress, exercise, hormonal fluctuations, infection and/or physical stimuli such as pressure or friction.[14, 16, 19] A connection between such triggers and mast cell activation is generally inconclusive, except in rare monogenic disorders. However, an effort to examine whether biomarkers for mast cell activation are elevated when symptoms are triggered is encouraged.

CONDITIONS OR CLINICAL PRESENTATIONS THAT ARE NOT DIAGNOSTIC OF MCAS

Some publications[20, 21] and lay press information[22] have greatly broadened the clinical criteria for MCAS. Non-validated laboratory tests have been used to collate unrelated symptoms with non-validated laboratory findings to make a diagnosis of MCAS. This has caused confusion for patients and physcians alike.[23, 24] The misconceptions about diagnosing MCAS have affected many patients and impaired their quality of life.[25, 26] More concerning, however, is using the diagnosis of MCAS erroneously and missing a truly treatable underlying condition not related to mast cells.

Clinical criteria that lack precision for diagnosing MCAS, but nevertheless are in use include fatigue, fibromyalgia-like pain, dermographism, tired appearance,

chronically ill appearance, edema, rashes of many sorts, tinnitus, adenopathy, constipation, prostatitis, chronic low back pain, headache, mood disturbances, anxiety, post-traumatic stress disorder, weight change, hypothyroidism, hyperthyroidism, polycythemia, anemia, abnormal electrolytes, an elevated or decreased level of at least one immunoglobulin isotype and multiple psychiatric and neurologic disorders.[20, 22, 27] Also, some signs or symptoms that can occur with MCAS, do not support this diagnosis when they occur in isolation, like abdominal pain and diarrhea, or flushing, or when they are chronic rather than episodic.

Disorders that have been used to diagnosis MCAS with **no scientific basis for being associated with mast cell activation** include, but are not limited to, Ehlers-Danlos Syndrome,[28, 29] postural orthostatic hypotension with tachycardia syndrome (POTS),[30-32], sclerosing mediastinitis,[33] hematologic non-malignant disorders,[34-37] psychiatric and other idiopathic disorders,[38-41] solid organ tumors,[42-44] obesity, type 2 diabetes mellitus, atherosclerosis, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease, essential hypertension, pulmonary hypertension, chronic kidney disease, idiopathic non-ischemic cardiomyopathy, metabolic syndrome, attention deficit/hyperactivity disorder, depression, multiple chemical sensitivity syndrome, autoimmune disorders, endometriosis, polycystic ovarian syndrome, celiac disease and non-celiac gluten intolerance, migraine headaches, neurogenic pain syndrome, restless leg syndrome, and schizophrenia.[20] The use of those disorders to support the diagnosis of MCAS had led to the use of unorthodox and potentially harmful therapies such as chemotherapeutic agents[45] and tyrosine kinase inhibitors.[46, 47]

Notably, patients with hereditary α-tryptasemia can have the concomitant diagnosis of Ehlers Danlos syndrome and POTS, but neither of these manifestations are due to MCAS.[5, 8-11] Nevertheless, MCAS was reported in members of one extended family who have an α-tryptase gene quintuplication,[4] and can occur in those with this condition. But many affected hereditary α-tryptasemic family members do not have MCAS. More research needs to be performed in order to understand the relationship between hereditary α-tryptasemia, to MCAS and other manifestations of this genetic condition.

Our recommendation is that patients should undergo an appropriate workup for their symptoms or condition, and be treated according to evidence-based medical standards. Even with a precise diagnosis of MCAS based on the clinical and laboratory criteria discussed in this report, other conditions need to be correctly diagnosed and treated independently.

DIAGNOSIS OF MCAS: BIOMARKERS AND BONE MARROW BIOPSY/ASPIRATE (see Online Repository for additional details)

Preformed mediators in mast cell secretory granules

Preformed stored mediators in the cytoplasmic granules include histamine, heparin and chondroitin sulfate proteoglycans, α/β tryptases, and acid hydrolases in all mast cells, while chymase, carboxypeptidase A3, and cathepsin G are found in a subset (MC_{TC}) of mast cells.[48] Heparin and chondroitin sulfate E proteoglycans are mainly found in mast cells. Proteases are the major protein component of mast cell

250 secretory granules. Presently, there are no pharmacologic means for blocking the
251 production and storage of these mediators in mast cell secretory granules.
252
253 ***Histamine***
254 Histamine (2-[4-imidazolyl]-ethylamine) is synthesized from L-histidine by histidine
255 decarboxylase, which removes a carboxylic acid residue from this semi-essential
256 amino acid. Mast cells and basophils each store comparably large amounts of
257 histamine in their secretory granules, whereas other cell types, such as
258 lymphocytes,[49] neutrophils,[50] monocytes,[51] macrophages,[52] and keratinocytes[53]
259 synthesize and secrete histamine, but do not store it intracellularly. Both mast cells
260 and basophils release histamine when they are activated to degranulate.[54, 55]
261 Histamine can also be produced by bacteria colonizing mucosal surfaces[56] or
262 contaminating ingested foods.[57-61]
263
264 Once released, histamine is metabolized rapidly (half-life 1-2 minutes), primarily to
265 N-methylhistamine. Several investigations of urinary histamine metabolites have
266 demonstrated clear utility to aid in the evaluation and diagnosis of SM. However,
267 for investigating MCAS, measurement of urine N-methylhistamine has
268 demonstrated little clinical utility,[17, 62-64] perhaps because metabolites generated
269 just after mast cell activation were not collected. However it can be supportive if
270 elevated levels are found in conjunction with other mediators, such as PGD_2
271 metabolites. Further studies are needed to evaluate how measurement of urine N-
272 methylhistamine levels may optimally be used for the evaluation and management
273 of MCAS.

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Tryptase

The tryptase locus on human chromosome 16 normally contains two genes that encode α or β tryptases, TPSB2, expressing only β-tryptase, and TPSAB1, expressing either α- or β- tryptase.[65-68] Each is expressed as a 275 amino acid pretryptase that is rapidly converted to a 257 amino acid protryptase. One portion of these protryptases is continuously secreted by unstimulated mast cells, and is the form detected in serum or plasma collected under non-anaphylactic/baseline conditions for healthy, mastocytosis, or hereditary α-tryptasemia subjects, while another portion of the protryptases is converted to their 245 amino acid mature proteins, which when bound to heparin at acidic pH spontaneously form tetramers that are stored in secretory granules with histamine until the cells are activated to degranulate, thereby secreting them.[69] Homotetramers of β-tryptase are active proteases, while those of α-tryptase do not exhibit a known proteolytic activity. A new form of tryptase, α/β-tryptase heterotetramers, forms naturally in mast cells

298 and has a distinct substrate repertoire from either homotetramer.[70] In healthy
299 subjects α- and β- tryptases are only produced by mast cells, with one exception,
300 basophils, that contain less than 1% of that present in tissue-derived mast cells.[71,
301 72] The current commercial tryptase assay (ThermoFisher/Phadia Laboratory
302 Systems, Uppsala, Sweden) measures both mature and pro forms of α and β
303 tryptases, sometimes referred to as total tryptase.
304
305 Mature tryptases released during episodes of systemic anaphylaxis triggered by
306 insect stings result in elevated levels of total tryptase detected in serum or plasma
307 that correlate with the magnitude of hypotension during such reactions,[73-76] while
308 systemic anaphylaxis triggered by ingestion of a food allergen results in lower
309 elevations of mature and total tryptase. In experimental insect sting-triggered
310 anaphylaxis, peak levels of mature tryptase occurred 30 to 90 min after onset of
311 signs or symptoms, and then declined with a t½ of about 2 hours.
312
313 Optimal use of the total tryptase assay for diagnosing a mast cell activation event
314 requires an acute sample, optimally collected between 30 min and 2 hours after
315 onset, though a significant elevation in samples collected up to 4-6 hours after the
316 event still can be informative; and a baseline sample collected either before the
317 event or at least 24 hours after all signs and symptoms have abated (Table III).
318 Based on an analysis of retrospective data, a consensus conference of the European
319 Competence Network for Mastocytosis recommended that for a rise in the serum
320 (or plasma) acute total tryptase level (sAT) to be considered clinically significant,
321 the sAT should be greater than the serum (or plasma) baseline tryptase level (sBT)

according to the formula: sAT > 1.2xsBT + 2,[1] which has been validated in other studies.[77-80] Physicians should consider employing this assay and algorithm for any clinical event thought to be due to systemic activation of mast cells, particularly if signs or symptoms of hypotension are present, including in patients with hereditary α-tryptasemia or with a somatic *KIT* GOF mutation.

An elevated sBT value reportedly puts a patient at an increased risk for a variety of clinical problems such as anaphylaxis and food allergic reactions in children, adverse reactions to drugs, to radiocontrast media, to insect stings[81-83] and to venom immunotherapy.[84-86] However, it would be imprudent to conclude that tryptase itself increases this risk, as it also serves as a surrogate for other underlying factors such as GOF *KIT* mutations or elevated TPSAB1 α-tryptase gene copy numbers, each of which increase the burden and activatability of mast cells.

Hereditary α-Tryptasemia, an autosomal dominant disorder, has a clinical phenotype that may include dysautonomia with postural orthostatic tachycardia syndrome (POTS), flushing or gastrointestinal hypomotility, joint hyperextensibility with arthritis, vibratory urticaria, irritable bowel syndrome, retained primary dentition, and allergic disorders affecting the cutaneous, respiratory, or cardiovascular systems.[5, 8-10] This genetic defect involves one or more extra copies of the α-tryptase gene encoded by TPSAB1, resulting in overexpression of α-tryptase and increased mast cells in bone marrow biopsies. The precise role(s) played by increased expression of α-tryptase may relate in part to the increased formation of α/β-tryptase heterotetramers, which can make skin mast cells

susceptible to vibration-triggered degranulation and directly activate protease-activated receptor 2 on the surface of cells, which include nerves, smooth muscle and endothelium, and may impact the risk for severe systemic anaphylaxis.[70] Spontaneous bouts of hypotension due to POTS are not typically associated with a clinically significant sAT elevation and in such cases do not reflect mast cell activation. Nevertheless, systemic anaphylaxis with elevated sAT over sBT does occur in some α-tryptasemia patients, including spontaneous and insect venom-triggered episodes, making this condition an inherited risk factor for MCAS.[4, 5, 11]

Newly-generated mediators

As commercial assays are currently available for relatively stable metabolites of PGD_2 and LTC_4, these are the newly-generated mediators that will be discussed. Platelet-activating factor also has shown promise in food-induced anaphylaxis, but commercial assays are not yet available. Sphingosine-1-phosphate is secreted by mast cells along with other cell types, is rapidly metabolized, and lacks a stable metabolite of proven diagnostic utility. Also, pharmacologic agents are available to block the production of PGD_2 by inhibiting cyclooxygenases 1 and 2, and LTC_4 by inhibiting 5-lipoxygenase.

PGD_2 and its metabolites

PGD_2 is generated from arachidonic acid by the sequential actions, first of either cyclooxygenase 1 or 2 to PGH_2, and then of either the hemopoietic (H-) or lipocalin (L-) type of PGD synthase to PGD_2. While L-PGDS is expressed in both the CNS and cardiac tissue,[87] endothelial cells,[88] and osteoblasts,[89] H-PGDS is expressed by mast

370 cells, megakaryocytes,[90] microglia and astrocytes,[91] dendritic cells,[92] eosinophils,[93]
371 and Th2 lymphocytes,[94], but not by basophils.[95] Large amounts of PGD_2 can be
372 rapidly synthesized and secreted by mast cells activated when FcεRI is aggregated,
373 as long as Cox-1 and-2 have not been inhibited by aspirin or other NSAIDs.[96] What
374 activates clinically-significant PGD_2 synthesis and secretion from other cell types is
375 less obvious.
376
377 Once secreted, PGD_2 is metabolized by an aldoketoreductase, principally AKR1C3,
378 at the 11-ketone position to an 11β-hydroxyl moiety, or 9α,11β-PGF_2 (also called
379 11β-$PGF_{2\alpha}$). 11β-$PGF_{2\alpha}$ can then be metabolized by β-oxidation of its carboxyl-
380 terminal, shortening the molecules by 2 carbons, called 2,3-dinor-11β-$PGF_{2\alpha}$, and
381 then by ω-oxidation at the other end of the molecule to the 2,3,18,19-tetranor
382 metabolite (PGD-M). The dinor metabolite of PGD_2 seems to persist longer than the
383 parent and intermediate metabolites, and in urine may be the predominant marker
384 for PGD_2 production.[97] In any assay, these PGD_2-specific metabolites need to be
385 distinguished from metabolites of either PGE_2 or PGH_2 catalyzed by AKR1B1 9α,11α-
386 PGF_2 (also called $PGF_{2\alpha}$), and its dinor β-oxidation and tetranor ω-oxidation
387 metabolites, which is accomplished by liquid chromatography-tandem mass
388 spectrometry. Elevated levels of these metabolites in 24 hour urine collections,
389 normalized to the creatinine level, or in plasma can provide biochemical evidence
390 for mast cell activation as recommended by the ECNM consensus conference.[1]
391 Levels considered to be elevated are determined by each diagnostic laboratory. The
392 currently available commercial clinical tests for PGD_2 production are the urinary
393 levels of dinor 11β-$PGF_{2\alpha}$ and of PGD_2, with the metabolite being preferred because

most of the PGD_2 is converted to its metabolite before being excreted. Measurement of serum PGD_2 levels is also available commercially but has not been validated as a diagnostic marker for mast cell disorders.

In 1980 increased PGD_2 production in 2 patients with SM was reported, and inhibiting PGD_2 synthesis along with blocking histamine binding to its H1 receptor resulted in symptomatic improvement and decreased hospitalizations for hypotensive episodes.[98] In a retrospective study of 25 MCAS patients, baseline 24 hour urine 11β-$PGF_{2\alpha}$ levels were the most frequently elevated mast cell mediator, and flushing and pruritus had the greatest correlation with elevated baseline 11β-$PGF_{2\alpha}$ levels.[17] Eight of 9 patients with MCAS, who had elevated 11β-$PGF_{2\alpha}$ levels at baseline, underwent aspirin therapy.[17] Follow-up urinary 11β-$PGF_{2\alpha}$ levels normalized for patients on aspirin (1 patient did not have a follow-up urine study). Six of these 9 patients with MCAS who underwent aspirin therapy had symptomatic improvement.

Plasma 11β-$PGF_{2\alpha}$ levels were found elevated in systemic allergic reactions to venom in a small number of patients and seem to have promise as a marker of mast cell activation.[99] Another study of serum 11β-$PGF_{2\alpha}$ levels found them to be a more sensitive marker for systemic anaphylaxis than either tryptase or sulfidopeptide leukotriene levels in serum.[79] Questions regarding the time course of 11β-$PGF_{2\alpha}$ levels during anaphylaxis, whether there is a difference between serum and plasma, and what other conditions, if any, result in elevated levels remain to be answered. Thus, as noted above, more research on serum levels of PGD_2 or its

metabolites as a validated biomarker for mast cell activation would better inform its positive and negative predictive values.

LTC_4 and its metabolites

LTC_4 is generated when arachidonic acid bound to 5-lipoxygenase activating protein is converted by 5-lipoxygenase to LTA_4 followed by LTC_4 synthase conjugating LTA_4 with reduced glutathione to form bioactive LTC_4, which is then secreted via the ATP-binding cassette transporters-1 and -4. Secreted LTC_4 is rapidly metabolized to LTD_4 as γ-glutamyl transpeptidases remove glutamine, and then to LTE_4, a more stable metabolite, as dehydropeptidase I removes glycine. LTC_4 is produced directly by activated mast cells,[100, 101] basophils,[102] eosinophils,[103] monocytes and macrophages,[104] and indirectly by transcellular metabolism when LTA_4 is transferred from a cell lacking LTC_4 synthase to one that has LTC_4 synthase, which includes platelets.[105]

LTE_4, the most stable cysteinyl leukotriene, is used to monitor this pathway in plasma or urine, because its precursors, LTC_4 and especially LTD_4, are very transient. Urinary LTE_4 levels are often elevated at baseline in SM patients and clinical improvement may occur with montelukast.[106-109]

Using acute (2 hours after onset) and baseline blood samples of patients presenting to the emergency department with systemic anaphylaxis, cysteinyl leukotriene levels were measured by an immunoassay that detects LTC_4, D_4 and E_4, revealing that acute levels of cysteinyl leukotrienes were elevated above baseline in 6 of 8

patients, tryptase levels in 6 of 9 (by the algorithm) and 11β-$PGF_{2α}$ levels in 8 of 9.[79] One of the issues needing further study is whether LTC_4 is released into serum during blood clotting by cells such as eosinophils, basophils or monocytes, or by platelets through transcytosis, versus by tissue mast cells prior to the blood draw. In addition to SM, there are several studies showing the utility of measuring urinary leukotrienes in aspirin-exacerbated respiratory disease (AERD),[110, 111] and benefit from leukotriene-modifier drugs.[112] A study of urinary LTE_4 and 11β-$PGF_{2α}$ levels following anaphylaxis, measured by immunoassays and normalized to levels of creatinine, found that they correlated with one another and with anaphylactic severity.[113] Further, 11β-$PGF_{2α}$ levels peaked in the 0-3 hour urine collection, while LTE_4 levels were comparable in the 0-3 and 3-6 hour collections.

In summary, elevations of one or a combination of the above mediators is observed in a variety of mast cell activation disorders, including allergen-triggered systemic anaphylaxis as well as systemic anaphylaxis occurring in association with SM, MCAS, aspirin exacerbated respiratory disease (AERD) and hereditary α-tryptasemia (Table I). For MCAS, measuring secreted mast cell biomarkers shortly after the onset of a putative anaphylactic event is likely optimal for all mediators. Whether serum or plasma is the preferred fraction of blood for lipid mediators will depend on whether secretion or processing of the mediator occurs *in vivo* versus *ex vivo*, which should be more precisely examined. Comparing acute to baseline levels is optimal for tryptase, and is likely to be the case for histamine, another preformed mediator, but needs more research. Having a baseline level to compare to the

acute level may not be as critical for newly-generated lipid mediators or their metabolites, though additional research should help clarify this point.

Bone marrow biopsy/aspirate

A bone marrow biopsy and aspirate are needed to precisely diagnose and stage systemic mastocytosis, which if present would increase the possibility of an associated clonal MCAS. Also, the procedure can identify clonal mast cells with a GOF mutation in *KIT* in the absence of other criteria for diagnosing systemic mastocytosis, a mutation that might be missed in peripheral blood, and by itself would increase the likelihood of an associated clonal MCAS. Also, a patient with clonal MCAS associated with a GOF *KIT* mutation who does not adequately respond to anti-mediator, omalizumab, or other established preventative therapies, might respond to a tyrosine kinase inhibitor targeting the mutated Kit. However, a bone marrow biopsy or aspirate cannot *per se* identify mast cell activation. Also, a buccal swab rather than a bone marrow biopsy is needed to diagnose hereditary alpha-tryptasemia, another condition associated with MCAS.

TESTS THAT ARE NOT RECOMMENDED FOR THE DIAGNOSIS OF MCAS (see Online Repository)

Biomarkers for mast cell activation events, as discussed above, should include substances secreted by activated mast cells and for which assays are available with sufficient sensitivity and specificity to clearly distinguish levels during mast cell activation versus basal level and to distinguish mast cell

activation events from other acute conditions. Putative biomarkers of mast cell activation that are problematic include heparin,[37, 62, 114-116] which has not been validated as a marker of MC activation in blood, and chromogranin A,[117, 62, 118] which resides in neuroendocrine cells but not in mast cells. Also, for reasons discussed above, neither plasma nor urine histamine levels[119, 120, 121] are recommended over histamine metabolites.

MANAGEMENT AND THERAPEUTIC OPTIONS FOR PATIENTS WITH MAST CELL DISORDERS

MCAS presents with a constellation of symptoms related to mediators secreted by activated mast cells.[1] Treatment of MCAS patients is highly individualized, targeted to bothersome symptoms and the underlying pathology (Table IV). Other coexisting medical conditions need to be treated by an appropriate specialist.

Acute management of a mast cell activation attack corresponds to the acute management of systemic anaphylaxis. Hypotensive episodes should be managed by patients assuming the supine position, followed by administration of epinephrine IM. Laryngeal angioedema requires epinephrine IM; bronchospasm also can be treated with epinephrine IM or an inhaled rapidly-acting bronchodilator such as albuterol. Patients at risk for such events should carry an epinephrine autoinjector to avoid unnecessary and potentially detrimental delays in treating anaphylaxis. Among SM patients, 20%-50% experience systemic anaphylaxis,[122, 123] typically with hypotension, rarely with laryngeal angioedema, and should learn the

importance of supine positioning and should carry an epinephrine autoinjector. If epinephrine is used, the patient should strongly consider being taken to the emergency room via ambulance, while remaining in the supine position.

Prevention of future mast cell activation events first involves the *identification and avoidance* of the trigger(s), such as insect venoms, extremes of temperature, mechanical irritation, alcohol, or medications (e.g., aspirin, radiocontrast agents, certain anaesthetic agents). The second step is to attenuate the clinical response to mast cell activation by reducing mast cell mediator production or by blocking the action of mast cell mediators with appropriate medical therapy. The third step may involve reducing the ability of mast cells to respond to activation triggers or, possibly, to reduce mast cell numbers. A SM patient sensitive to insect venom, particularly with a history of systemic anaphylaxis to a prior insect sting, should undergo lifelong venom immunotherapy. Using omalizumab during immunotherapy appears to reduce the risk of anaphylaxis to venom immunotherapy.[124] Eliminating additives in drugs used to treat or prevent anaphylaxis by compounding them is not recommended. Although additives have not been evaluated for MCAS patients, for 100 chronic urticaria patients, 43 of whom complained of additive allergies, single or double blind challenges were used to rule this out in all of these patients.[125]

Mediator inhibitors

Histamine:

H1R and H2R antagonists

Recommendations for antihistamine therapy for mast cell activation disorders are based on expert opinion. The objective is to relieve symptoms from secreted histamine.[126-128] H1R and H2R anti-histamine receptors work better as prophylactic than acute treatment, because once signs or symptoms of histamine-mediated effects are apparent, it is too late to block the binding of histamine to its receptors. H1R blockers in patients with MCAS reduces dermatologic manifestations such as flushing and pruritus, along with tachycardia, and abdominal discomfort. These medications, particularly later generation non-sedating H1R antihistamines such as fexofenadine and cetirizine, are often used at 2-4 times FDA-approved doses. First generation H1R antihistamines include diphenhydramine, hydroxyzine, and chlorpheniramine. A limitation of these medications is their associated sedation, impairing driving ability and leading to cognitive decline, particularly in elderly patients, and there is some concern in MCAS patients prone to cardiovascular events.[129] Cyproheptadine has dual function as a sedating H1R blocker and a serotonin-receptor antagonist and has been used to treat diarrhea and nausea in the setting of MCAS. Ketotifen, also sedating, is now available as a compounded medication in the USA and is used to treat dermatologic, gastrointestinal, as well as neuropsychiatric symptoms.[130] Rupatadine, an H1R blocker that also blocks PAF binding to its receptor, is approved for use in many countries, but not in the USA. In patients with mastocytosis,[131] rupatadine improved control of pruritus, flushing, tachycardia, and headache, but not gastrointestinal symptoms. Studies of rupatadine for treating MCAS, as for other antihistamines, were promising, but not conclusive.[132]

H2R-blocking agents are commonly used to treat abdominal and/or vascular signs or symptoms of MCAS. Options include ranitidine, famotidine, and cimetidine. Much like H1R blockers, most of the data to support the use of H2R blockers is limited to case reports and case series.[133] However, H2R anti-histamines prevent histamine-mediated acid secretion from parietal cells and blunt the vasoactive effects of iv-infused histamine if combined with an H1R antagonist.[134] Importantly, H1R and H2R blocking agents, especially those with anticholinergic effects, can be associated with cognitive decline that is worse in the elderly populations.[135-139]

H3R and H4R antagonists

Therapeutic antagonists for these receptors are in development, and beyond the scope of this current communication, but may have novel clinical value, particularly H4R antagonists that reduce pruritus and inflammation occurring in atopic dermatitis.[140]

LTC_4

Cysteinyl leukotriene receptor antagonists or 5-lipoxygenase inhibition

Other therapies for MCAS include cysteinyl leukotriene receptor blocking agents such as montelukast and zafirlukast, or the 5-lipoxygenase inhibitor, zileuton. These medications may work best in conjunction with H1R antihistamines, being most efficacious for dermatologic symptoms.[106, 108]

PGD_2

584 Aspirin has been used to attenuate refractory flushing and hypotensive spells
585 associated with PGD_2 secretion by inhibiting its synthesis.[64, 141, 142] Aspirin should be
586 introduced in a controlled clinical setting because of the risk of triggering mast cell
587 degranulation.[64, 143]
588
589 **Cromolyn**
590 Oral cromolyn is used predominately for gastrointestinal symptoms, though its
591 mechanism of action is not known.[144, 145] Cromolyn taken orally or applied topically
592 also may reduce pruritus.[146] Patients should be counseled that the onset of action
593 can be delayed, and should be taken for at least one month before deciding
594 whether it is helping. It should be introduced at the lowest dose and the dose
595 gradually increased to 200 mg four times a day, given before each meal and at
596 bedtime.
597
598 **Glucocorticosteroids**
599 Systemic steroids may help some patients as indicated in case reports, but should
600 be tapered as quickly as possible in order to limit its numerous adverse effects.
601
602 **Anti-IgE therapy**
603 Omalizumab binds free IgE, preventing its binding to FcεRI, and has been approved
604 for treating poorly-controlled moderate to severe atopic asthma and anti-histamine-
605 resistant chronic urticaria. The mechanism of action of omalizumab remains
606 incomplete, but may affect the activation threshold of mast cells when surface
607 levels of FcεRI are reduced by blocking IgE binding. For example, omalizumab

608 reduces the severity and frequency of allergic reactions during aeroallergen rush
609 immunotherapy and insect venom immunotherapy in mastocytosis patients.[147-151]
610 Omalizumab also prevents spontaneous episodes of anaphylaxis in case reports and
611 case series.[152-155] Omalizumab is an expensive therapeutic option, though case
612 reports support its benefit in prevention of anaphylaxis, emergency room visits and
613 lost time from work. Therefore, it should be considered in cases of MCAS resistant
614 to mediator-targeted therapies.
615
616 **Cytoreductive Therapies**
617 For patients with clonal MCAS in advanced SM (aggressive SM, mast cell leukemia
618 or sarcoma, SM associated with a non-MC hematologic clonal disorder, and in some
619 cases of smoldering SM) with signs and symptoms refractory to anti-mediator
620 therapy, cytoreductive therapy should be considered. Two of the most commonly
621 used agents have been **IFN-α** and **cladribine**. Commonly-observed adverse events
622 of IFN-α include flu like symptoms, depression, hypothyroidism and a variety
623 autoimmune disorders.[156] Cladribine can be efficacious in advanced SM patients
624 with severe life-threatening or disabling anaphylaxis,[157, 158, 159] but is associated
625 with an increased risk of infection.
626
627 Signal transduction inhibitors have been considered for MCAS that cannot be
628 adequately controlled by safer interventions. Based on laboratory studies, inhibitors
629 of Kit tyrosine kinase decrease mast cell activatability and survival, and thus may
630 be helpful in MCAS.[160] **Midostaurin** is a multi-kinase inhibitor (Tyr and Ser/Thr
631 kinases) with activity against wild type and D816V Kit and has been approved for

treating advanced SM. [161-167] Although nausea, vomiting, and cytopenias are relatively common, for most patients nausea can be controlled by taking ondansetron 30-60 min prior to midostaurin, and cytopenias can be managed by adjusting the dose of midostaurin. This agent may replace IFN-α and cladribine in the treatment paradigm for clonal mast cell disorders.

Masitinib is a tyrosine kinase inhibitor with activity against wild type Kit and Lyn tyrosine kinase and has been used to treat mediator related symptoms in MCAS, but asthenia is a common side effect.[168] **Imatinib** has been used but is not indicated if the D816V mutation or another mutation at this position is present, which causes resistance to this agent.[169] **Ibrutinib** (used to treat mantle cell lymphoma, chronic lymphocytic leukemia and Waldenstrom macroglobulinemia) decreases IgE-mediated reactivity, but not non-IgE mediated mast cell activation.[170] Patients with advanced SM, including those with mast cell leukemia, were treated with a more selective D816V Kit inhibitor, **avapritinib,** in a Phase 1 trial and experienced rapid and durable responses with manageable side effects.[167, 171] Another inhibitor of D816V Kit, DCC2618, is in a Phase 1 trial for smoldering and advanced SM.[172]

Current studies, using a monoclonal antibody targeting **Siglec-8** reported that in humanized mice eosinophil numbers in the circulation and mast cell activation tested by passive cutaneous anaphylaxis were both reduced,[173, 174] but data in humans has not yet been published.

Whether such newer therapies targeting signaling pathways will have a favorable long-term benefit to toxicity ratio for treating MCAS remains to be determined, but may depend in part upon whether such drugs inhibit mast cell activation at substantially lower concentrations than those causing cytoreduction.

Prognosis and length of therapy

There are no specific studies evaluating the prognosis of patients with MCAS. Some with clonal MCAS may progress to SM, most likely indolent. None of the patients in the Mayo Clinic cohort followed[17] for over 15 years developed mastocytosis. However, data regarding patients with indolent SM demonstrate a normal life expectancy.[17, 175-180] We propose treatment based on symptoms and elevated levels of mast cell mediators. For example, if a patient with MCAS has elevated urinary LTE_4 levels, then leukotriene antagonists are recommended; if elevated urinary PG metabolite levels, then treatment with aspirin may help. Therefore, the therapeutic intervention should be adjusted to fit each patient.

DIFFERENTIAL DIAGNOSIS

Clinical presentations of patients with MCAS are discussed in section 4 and outlined in Table II. It should be noted that there is a wide differential diagnosis. For example, flushing is not limited to mast cell disorders, but is a hallmark of other conditions as well.[181-184] These include benign flushing,[185-188] familial flushing and endocrine disorders[189] such as hyperthyroidism and hormone withdrawal.[190-192] Neuroendocrine tumors such as carcinoid[193-196] and pheochromocytoma[197, 198] cause spells and flushing as well. Dermatologic conditions such as rosacea,[188]

680 medications,[199, 200] reduced alcohol metabolism,[201] and other less common
681 conditions[202-204] are also associated with flushing. It is beyond the scope of this
682 communication to discuss the diagnostic workup and treatment of all conditions
683 that might clinically mimic certain signs or symptoms of MCAS.
684
685 **CURRENT CLASSIFICATION AND UNMET NEEDS**
686 Our current recommendations for diagnosing MCAS make use of the latest studies
687 and consensus guidelines for clinically diagnosing systemic anaphylaxis in real time,
688 regardless whether allergen-triggered through the IgE pathway or via other
689 pathways; our current understanding of the mediators secreted by activated mast
690 cells that best discriminate this disorder from other conditions; and the drugs that
691 may selectively affect those mediators or mast cells themselves. Whether precise
692 measurement of additional mediators will provide complementary and clinically
693 useful insight, such as platelet-activating factor, heparin, chymase or
694 carboxypeptidase A3, requires further research. Also, our recommendations do not
695 address the occurrence of local mast cell activation. An increase in the number of
696 mast cells in the gastrointestinal tract or elsewhere, by itself, does not diagnose
697 mast cell activation or indicate that mast cell activatability is affected. Whether the
698 plasticity of human mast cells, governed largely by their local tissue or
699 inflammatory environment, might affect their activation in a clinically-significant
700 manner needs to be better understood. The detection of an activating KIT mutation
701 such as D816V in peripheral blood or tissues, demonstrates clonality; surface
702 expression of CD25 on mast cells is a surrogate marker for clonality; and the
703 presence of dense aggregates of spindle-shaped mast cells suggests underlying

mastocytosis. Finding familial or somatic mutations of other genes that identify hyper-activatable mast cells would extend our diagnostic tools and potentially indicate new therapeutic interventions, targeting either the mutated gene product or the associated molecular pathway. In conclusion, we trust that the clinical, laboratory and therapeutic criteria for primary MCAS(s) described herein will provide clinicians with practical criteria of sufficient sensitivity and specificity to diagnose most cases, without over-diagnosing the disorder in patients who likely have other conditions. We propose a modified algorithm for the diagnosis of patients with suspected MCAS in Fig 1.

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FIG 1. Algorithm for Diagnosing MCAS

GOF, gain of function.

*Somatic *KIT* mutation assays have limited sensitivity;[205-210] germ line TPSAB1 α-tryptase CNV test is available from GenebyGene (Houston, TX). If peripheral blood allele-specific D816V *KIT* mutation is negative, perhaps due to a low allelic *KIT* mutation burden[211] or to a different GOF *KIT* mutation, but REMA[212] (gender; sBT; pruritus, hives or angioedema; presyncope or syncope) or NIH[213] (similar to REMA plus allele-specific D816V *Kit* PCR on peripheral blood) score is positive, then a bone marrow study for a GOF *KIT* mutation should be considered.

Table I: Mast cell serum tryptase and urinary mediators in different disorders

Disorder	Serum Tryptase (ng/mL)	Urinary Mediators		
		NMH**	11β-$PGF_{2\alpha}$†	LTE_4‡
SM (baseline)	>20 (75% of cases)[77, 214-217]	+++[217-221]	++/-[219, 222]	++/-[107, 109, 219]
MCAS (acute)	>sBT*1.2 + 2[17, 77]	-[17]	+++[17]	-/+[219]
α-Tryptasemia (baseline)	>8[5, 9, 11]	?	?	?
AERD* (acute aspirin or NSAID SA reaction)	>sBT*1.2 + 2	?	?	+/+++[223-225]

*, AERD, Aspirin exacerbated airway disease; **, NMH, N-methylhistamine, †, 11β-$PGF_{2\alpha}$, ‡, LTE_4; sBT, serum baseline tryptase level (ng/mL); +, mildly elevated (10-30% above upper limit of normal range); ++, moderately elevated (31-70% above upper limit of normal range); +++, highly elevated (>70% above upper limit of normal range); ?, unknown.

TABLE II. Organs systems affected during anaphylaxis and the associated symptoms of their involvement which are of diagnostic value for MCAS

Cardiovascular Hypotension Tachycardia Syncope of near syncope[6, 7, 14, 16]	**Respiratory** Wheezing (inspiratory or expiratory) Shortness of breath Inspiratory stridor[6, 7]
Dermatologic Flushing Urticaria[6, 7, 14, 16, 126] Pruritus Angioedema[6]	**Gastrointestinal** Diarrhea Nausea with vomiting Crampy abdominal pain[6, 7, 12, 14, 16, 17]

As recommended for the working diagnosis of systemic anaphylaxis, symptoms affecting at least 2 of these 4 organ systems should occur concurrently.[18]

Table III. Tryptase algorithm for diagnosing systemic anaphylaxis:[1, 77, 78, 80, 226]
sAT > (1.2*sBT) + 2

1. Neither an sBT nor an sAT by itself has sufficient sensitivity to assess a MC activation event, regardless if outside of or within the normal range.
2. Sensitivity increases with clinical severity, primarily correlating with hypotension.
3. The optimal time to collect an acute blood sample, based on experimental insect sting-triggered anaphylaxis, is 30 to 120 min after onset of symptoms; sensitivity diminishes outside of this range.
4. The optimal time to collect a baseline blood sample is either prior to the event or at least 24 hours after all signs and symptoms have resolved.
5. This test has high specificity (>90%), while sensitivity varies with time of collection, clinical severity, and the trigger.

1402 **Table IV.** Treatment Interventions for MCAS

Intervention	**Comments**
Prevention	
Avoidance of known triggers	
Pharmacologic Agents for Prevention	
H1R Antihistamines*	Non-sedating H1 histamines are generally preferred and may be increased to 2-4 times the standard dose; sedating H1 antihistamines may acutely cause drowsiness and impair driving ability, and chronically lead to cognitive decline, particularly in the elderly.
H2R Antihistamines	Can be utilized as first line therapy for GI symptoms and may help H1R antihistamines attenuate cardiovascular symptoms
Cromolyn sodium (oral formulation)	May reduce abdominal bloating, diarrhea and cramps. Benefit may extend to neuropsychiatric manifestations. Divided dosing and weekly upward titration to reach desired target dose may improve tolerance and adherence
Doxepin*	Potent H1 + H2 antihistamine with tricyclic antidepressant activity may reduce the CNS manifestations in MCAS or SM, but may cause drowsiness and cognitive decline, particularly in the elderly, and may increase suicidal tendencies in children and young adults with depression
Aspirin	May reduce flushing and hypotension in some patients, particularly those with elevated urinary 11β-$PGF_{2\alpha}$, but contraindicated in those with allergic or adverse reactions to NSAIDs. Clinical improvement may require dosing increase up

	to 650 mg twice daily as tolerated. Use with caution.
Steroid taper/Steroid burst	May be useful for refractory signs or symptoms. Initial oral dosage of 0.5 mg/kg/day followed by a slow taper over 1-3 months. May be helpful to give Prednisone 50 mg 13, 7 and 1 hour prior to radiologic or invasive procedures where mast cell activation has been problematic. Steroid side effects dampen enthusiasm for long term use
Omalizumab	Cases indicate prevention of anaphylactic episodes in some MCAS or SM patients, or in those who cannot otherwise tolerate needed insect venom immunotherapy.
Cysteinyl leukotriene inhibitor (e.g., montelukast) or 5-lipoxygenase inhibitor (zileuton)	May reduce bronchospasm or gastrointestinal symptoms in MCAS or SM, particularly if urinary LTE_4 is elevated, but not well-studied.
Cyproheptadine	Sedating H1 antihistamine with extended anticholinergic and antiserotonergic activities. May help GI symptoms.
Ketotifen	This sedating H1R antagonist is approved in the USA for allergic eye disease, but can be compounded as tablets. Whether beneficial beyond other antihistamines, like diphenhydramine, is unproven.
Acute Management	
Epinephrine autoinjector	Patients with a history of systemic anaphylaxis or airway angioedema should be prescribed this device and instructed how and when to use it
Supine positioning	Those with recurrent hypotensive episodes should be trained to assume a supine position as soon as possible, using a bedpan for diarrhea and an emesis basin after rolling on to their side or

	abdomen
Bronchodilator (albuterol)	This can be inhaled by nebulizer or MDI to treat symptoms or signs of bronchospasm

*Cognitive decline has been reported for H1 blockers that have anticholinergic effects. This is especially worrisome in the elderly population.[135-139, 227]