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AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management

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Our current recommendations for diagnosing and treating primary mast cell (MC) activation syndrome make use of the latest studies and consensus guidelines for clinically recognizing systemic anaphylaxis in real time, regardless of whether allergen-triggered or other pathways are involved; our current understanding of the biomarkers secreted by activated MCs that best discriminate this disorder from other conditions; and the therapeutic drugs that might selectively affect those mediators or MCs themselves. Finding familial or somatic mutations of genes that cause MCs to be hyperactivatable 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 MC activation syndromes described herein will provide clinicians with practical criteria of sufficient sensitivity

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and specificity to diagnose most cases without overdiagnosing the disorder in patients who likely have other conditions. (J Allergy Clin Immunol 2019;144:883-96.)

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The last consensus report regarding mast cell (MC) disorders used 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 nonclonal MC disorders. The disorders were divided into primary disorders, in which MCs seem to be more activatable, either spontaneously or to a known or unknown external trigger, and secondary disorders, in which normal MCs are activated by an external trigger, typically an allergen through IgE/FcεRI but also by antigens through IgG/FcγRI/IIa, a variety of ligands acting on G protein–coupled receptors, 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, which is associated with similar *KIT* mutations and/or aberrant expression of CD25 but lacking other criteria needed to diagnose SM based on the World Health Organization criteria[1,3]; hereditary α-tryptasemia,[4,5] which is associated with increased copy numbers of the *TPSAB1* gene encoding α-tryptase; and idiopathic MCAS, in which neither a trigger, mutation, nor genetic trait has been identified.

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 2 organ systems and resulting from secreted MC mediators. Symptoms occur in association with secretion of MC products, such as tryptase, histamine, prostaglandin (PG) D_2, and leukotriene (LT) C_4, leading to increased levels in the blood or urine of secreted mediators or of their metabolites, including N-methylhistamine, 11β-$PGF_{2\alpha}$ and LTD_4/LTE_4. These symptoms should improve with medications that block binding of these products to receptors or their production. Agents that block receptor binding include H1 histamine receptor (H1R) and H2 histamine receptor (H2R) antihistamines and type 1 cysteinyl leukotriene receptor antagonists, and decreases in production occur with inhibitors of COX for PGD_2 or 5-lipoxygenase for LTC_4 or with MC stabilizers, such as omalizumab, which diminish MC activatability.

BASIC SCIENCE OF MC DEVELOPMENT AND ACTIVATION

For more information on the basic science of MC development and activation, see this article's Online Repository at www.jacionline.org for further details.

MC development, heterogeneity, and activation are interrelated, likely affecting MCASs. Importantly, MCs develop from progenitors in the bone marrow that mature either in the bone marrow or after being recruited to the tissue site of residence, and do so under the influence of stem cell factor interacting with the Kit tyrosine kinase receptor on MC surfaces. The capacity of MCs to be activated and the mediator pathways elicited can vary among different types of mature and immature MCs. MC mediator secretion can follow engagement of FcεRI and FcγRI/IIa receptors, as well as stimulation of surface G protein–coupled receptors, including complement anaphylatoxin receptors and Mas-related G protein receptor, and Toll-like receptors. Depending on what activates MCs, differential secretion of granule mediators and newly generated mediators can occur.

Abbreviations used
GOF: Gain of function
H1R: H1 histamine receptor
H2R: H2 histamine receptor
LT: Leukotriene
MC: Mast cell
MCAS: Mast cell activation syndrome
PG: Prostaglandin
POTS: Postural orthostatic tachycardia syndrome
sAT: Serum (or plasma) acute total tryptase
sBT: Serum (or plasma) baseline tryptase
SM: Systemic mastocytosis

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 2 of the 4 organ systems listed below.[1,6] The clinical symptoms have to be associated with an acute increase in specific biologic mediator levels,[7] and patients should respond to therapy with MC mediator blocking agents, MC stabilizers, or both. The most validated mediators for their direct clinical effect include histamine, PGD_2, and LTC_4, with the metabolites of these mediators (along with tryptase) serving as biomarkers for MC activation.

As an example, a patient who presents with episodic symptoms affecting 2 or more organ systems, such as 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).[5,8-25] If the laboratory findings correlate with the presence of symptoms, then appropriate therapies should be implemented. The symptoms should resolve with therapies directed at the increased mediator. If, for example, only levels of urinary histamine products are increased, then histamine-blocking agents might improve the symptoms. If, on the other hand, PG levels are increased, then aspirin (with appropriate precautions discussed later in the article) will reduce PG levels and should alleviate symptoms. The presence of the specific symptom during which levels of a mediator are increased and the clinical response to appropriate therapy are all prerequisites for the diagnosis of MCAS.

Persistent symptoms, as seen in patients with chronic urticaria or poorly controlled asthma, should direct the clinician to a different underlying diagnosis. Likewise, chronic increases in levels of a mediator, such as tryptase, might reflect underlying SM[1,2] or hereditary α-tryptasemia,[4,5,8,9,26,27] disorders that can be but are not always associated with MCAS (see the "Tryptase" section). Clinical symptoms of diagnostic value that are

TABLE I. MC 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)[11,14-17]	+++[17-21]	++/−[19,22]	++/−[12,13,19]
MCAS (acute)	>sBT*1.2 + 2[10,11]	−[10]	+++[10]	−/+[19]
α-Tryptasemia (baseline)	>8[5,8,9]	?	?	?
AERD (acute aspirin or nonsteroidal anti-inflammatory drug-triggered systemic anaphylaxis)	>sBT*1.2 + 2	?	?	+/+++[23-25]

sBT levels are shown in nanograms per milliliter.
+, Mildly increased (10% to 30% above upper limit of normal range); ++, moderately increased (31% to 70% above upper limit of normal range); +++, highly increased (>70% above upper limit of normal range); *?*, unknown.

frequently reported by patients with MCAS[28-30] include the following:

- *cardiovascular*—hypotension, tachycardia, and syncope or near-syncope[7,30-32];
- *dermatologic*—urticaria, pruritus, and flushing[7,28,30-32] and angioedema,[6] particularly of the eyelids, lips, and tongue;
- *respiratory*—wheezing, shortness of breath, and inspiratory stridor[6,7]; and
- *gastrointestinal*—crampy abdominal pain, diarrhea, nausea, and vomiting.[6,7,10,28,30-32]

Importantly, 2 or more of the above organ systems being concurrently involved in acute recurrent clinical episodes, which is consistent with the working diagnosis of systemic anaphylaxis,[33] would increase the likelihood of MCAS being culpable (Table II).[6,7,10,28,30,32,34] Symptoms should be associated with acute increases in levels of MC mediators on 2 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.[30,32,35] A connection between such triggers and MC activation is generally inconclusive, except in patients with rare monogenic disorders. However, an effort to examine whether levels of biomarkers for MC activation are increased when symptoms are triggered is encouraged.

CONDITIONS OR CLINICAL PRESENTATIONS THAT ARE NOT DIAGNOSTIC OF MCAS

Some publications[36,37] and lay press information[38] have greatly broadened the clinical criteria for MCAS. Nonvalidated laboratory tests have been used to correlate unrelated symptoms with nonvalidated laboratory findings to make a diagnosis of MCAS. This has caused confusion for patients and physicians alike.[39,40] The misconceptions about diagnosing MCAS have affected many patients and impaired their quality of life.[41,42] More concerning, however, is using the diagnosis of MCAS erroneously and missing a truly treatable underlying condition not related to MCs.

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, posttraumatic stress disorder, weight change, hypothyroidism, hyperthyroidism, polycythemia, anemia, abnormal electrolytes, an increased or decreased level of at least 1 immunoglobulin isotype, and multiple psychiatric and neurologic disorders.[36,38,43] Also, some signs or symptoms that can occur with MCAS do not support this diagnosis when they occur in isolation, such as 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 MC activation include, but are not limited to, Ehlers-Danlos syndrome,[44,45] postural orthostatic tachycardia syndrome (POTS), typically with hypotension,[46-48] sclerosing mediastinitis,[49] hematologic nonmalignant disorders,[50-53] psychiatric and other idiopathic disorders,[54-57] solid organ tumors,[58-60] obesity, type 2 diabetes mellitus, atherosclerosis, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease, essential hypertension, pulmonary hypertension, chronic kidney disease, idiopathic nonischemic cardiomyopathy, metabolic syndrome, attention deficit/hyperactivity disorder, depression, multiple chemical sensitivity syndrome, autoimmune disorders, endometriosis, polycystic ovarian syndrome, celiac disease and nonceliac gluten intolerance, migraine headaches, neurogenic pain syndrome, restless leg syndrome, and schizophrenia.[36] Use of those disorders to support the diagnosis of MCAS has led to use of unorthodox and potentially harmful therapies, such as chemotherapeutic agents[61] and tyrosine kinase inhibitors.[62,63]

Notably, patients with hereditary α-tryptasemia can have the concomitant diagnosis of Ehlers-Danlos syndrome and POTS, but neither of these manifestations are caused by MCAS.[5,8,9,27] 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. However, many affected hereditary α-tryptasemic family members do not have MCAS. More research needs to be performed to understand the relationship between hereditary α-tryptasemia and 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

For more information on the diagnosis of MCAS and biomarkers and bone marrow biopsy/aspirate, see this article's Online Repository for further details.

Preformed mediators in MC secretory granules

Preformed stored mediators in cytoplasmic granules include histamine, heparan and chondroitin sulfate proteoglycans, α/β

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

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

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

tryptases, and acid hydrolases in all MCs, whereas chymase, carboxypeptidase A3, and cathepsin G are found in a subset (tryptase and chymase double-positive MCs) of MCs.[64] Heparan and chondroitin sulfate E proteoglycans are mainly found in MCs. Proteases are the major protein component of MC secretory granules. Presently, there are no pharmacologic means for blocking the production and storage of these mediators in MC secretory granules.

Histamine. Histamine (2-[4-imidazolyl]-ethylamine) is synthesized from L-histidine by histidine decarboxylase, which removes a carboxylic acid residue from this semiessential amino acid. MCs and basophils each store comparably large amounts of histamine in their secretory granules, whereas other cell types, such as lymphocytes,[65] neutrophils,[66] monocytes,[67] macrophages,[68] and keratinocytes,[69] synthesize and secrete histamine but do not store it intracellularly. Both MCs and basophils release histamine when they are activated to degranulate.[70,71] Histamine can also be produced by bacteria that colonize mucosal surfaces[72] or contaminate ingested foods.[73-77]

Once released, histamine is metabolized rapidly (half-life, 1-2 minutes), primarily to N-methylhistamine. Several investigations of urinary histamine metabolites have demonstrated clear utility to aid in the evaluation and diagnosis of SM (for more information, see this article's Online Repository). However, for investigating MCAS, measurement of urine N-methylhistamine levels has demonstrated little clinical utility,[10,78-80] perhaps because metabolites generated just after MC activation were not collected. However, it can be supportive if increased levels are found in conjunction with other mediators, such as PGD_2 metabolites, even though cell source might be ambiguous. Further studies are needed to evaluate how measurement of urine N-methylhistamine levels might be optimally used for the evaluation and management of MCAS.

Tryptase. The tryptase locus on human chromosome 16 normally contains 2 genes that encode α- or β-tryptases: *TPSB2*, expressing only β-tryptase, and *TPSAB1*, expressing either α- or β- tryptase.[81-84] 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 MCs and is the form detected in serum or plasma collected under nonanaphylactic/baseline conditions for healthy subjects, patients with mastocytosis, or patients with hereditary α-tryptasemia. However, another portion of the protryptase 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.[85] Homotetramers of β-tryptase are active proteases, whereas those of α-tryptase do not exhibit a known proteolytic activity. A new form of tryptase, α/β-tryptase heterotetramers, forms naturally in MCs and has a distinct substrate repertoire from either homotetramer.[86] In healthy subjects α- and β-tryptases are only produced by MCs, with the exception of basophils, which contain less than 1% of the levels present in tissue-derived MCs.[87,88] The current commercial tryptase assay (Thermo Fisher/Phadia Laboratory Systems, Uppsala, Sweden) measures both mature and pro forms of α- and β-tryptases, sometimes referred to as total tryptase.

Mature tryptases released during episodes of systemic anaphylaxis triggered by insect stings result in increased levels of total tryptase detected in serum or plasma that correlate with the magnitude of hypotension during such reactions,[89-92] whereas systemic anaphylaxis triggered by ingestion of a food allergen results in lower increases in mature and total tryptase levels. In experimental insect sting–triggered anaphylaxis, peak levels of mature tryptase occurred 30 to 90 minutes after onset of signs or symptoms and then decreased with a half-life of about 2 hours.

Optimal use of the total tryptase assay for diagnosing an MC activation event requires an acute sample optimally collected between 30 minutes and 2 hours after onset, although a significant increase in samples collected up to 4 to 6 hours after the event can still be informative, and a baseline sample collected either before the event or at least 24 hours after all signs and symptoms have abated (Table III).[1,11,93-95] Based on an analysis of retrospective data, a consensus conference of the European Competence Network for Mastocytosis recommended that for an increase in the serum (or plasma) acute total tryptase level (sAT) to be considered clinically significant, the sAT should be greater than the serum (or plasma) baseline tryptase level (sBT) according to the following formula:

$$sAT > (1.2*sBT) + 2,$$[1]

which has been validated in other studies.[11,93,94,96] Physicians should consider using this assay and an algorithm for any clinical event thought to be due to systemic activation of MCs, particularly if signs or symptoms of hypotension are present, including in patients with hereditary α-tryptasemia or a somatic *KIT* GOF mutation.

An increased sBT value reportedly puts a patient at increased risk for a variety of clinical problems, such as anaphylaxis, food-induced allergic reactions in children, and adverse reactions to drugs, radiocontrast media, insect stings,[97-99] and venom immunotherapy.[100-102] However, it would be imprudent to conclude that tryptase itself increases this risk because it also serves as a surrogate for other underlying factors, such as GOF *KIT* mutations or increased *TPSAB1* α-tryptase gene copy numbers, each of which increase the burden and activatability of MCs.

Hereditary α-tryptasemia, an autosomal dominant disorder, has a clinical phenotype that can include dysautonomia with 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.[5,8,26,27] This genetic defect involves 1 or more extra copies of the α-tryptase gene encoded by *TPSAB1*, resulting in overexpression of α-tryptase and increased numbers of MCs in bone marrow biopsy specimens. The precise role or roles played by increased expression

TABLE III. Tryptase algorithm for diagnosing systemic anaphylaxis[1,11,93-95]: sAT > (1.2*sBT) + 2

1. Neither an sBT nor an sAT by itself has sufficient sensitivity to assess an MC activation event, regardless of whether it is 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 minutes after onset of symptoms; sensitivity diminishes outside of this range.
4. The optimal time to collect a baseline blood sample is either before the event or at least 24 hours after all signs and symptoms have resolved.
5. This test has high specificity (>90%), whereas sensitivity varies with time of collection, clinical severity, and trigger.

of α-tryptase might relate in part to the increased formation of α/β-tryptase heterotetramers, which can make skin MCs susceptible to vibration-triggered degranulation and directly activate protease-activated receptor 2 on cell surfaces, which include nerves, smooth muscle, and endothelium, and might affect the risk for severe systemic anaphylaxis.[86] Spontaneous bouts of hypotension caused by POTS are not typically associated with a clinically significant sAT increase and in such cases do not reflect MC activation. Nevertheless, systemic anaphylaxis with increased sAT over sBT does occur in some patients with α-tryptasemia, including spontaneous and insect venom–triggered episodes, making this condition an inherited risk factor for MCAS.[4,5,9]

Newly generated mediators

Because 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 patients with food-induced anaphylaxis, but commercial assays are not yet available. Sphingosine-1-phosphate is secreted by MCs along with other cell types, is rapidly metabolized, and lacks a stable metabolite of proved diagnostic utility. Also, pharmacologic agents are available to block PGD_2 production by inhibiting COX-1 and COX-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 COX-1 or COX-2 to PGH_2 and then of either the hemopoietic or lipocalin type of PGD synthase to PGD_2. Although lipocalin-type PGDS is expressed in both the central nervous system and cardiac tissue,[103] endothelial cells,[104] and osteoblasts,[105] hemopoietic PGDS is expressed by MCs, megakaryocytes,[106] microglia and astrocytes,[107] dendritic cells,[108] eosinophils,[109] and T_H2 lymphocytes[110] but not by basophils.[111] Large amounts of PGD_2 can be rapidly synthesized and secreted by MCs activated when FcεRI is aggregated as long as COX-1 and COX-2 have not been inhibited by aspirin or other nonsteroidal anti-inflammatory drugs.[112] What activates clinically significant PGD_2 synthesis and secretion from other cell types is less obvious.

Once secreted, PGD_2 is metabolized by an aldo-keto reductase, principally AKR1C3, at the 11-ketone position to an 11β-hydroxyl moiety or 9α,11β-PGF_2 (also called 11β-$PGF_{2\alpha}$). 11β-$PGF_{2\alpha}$ can then be metabolized by means of β-oxidation of its carboxyl terminal, shortening the molecules by 2 carbons, called 2,3-dinor-11β-$PGF_{2\alpha}$, and then by ω-oxidation at the other end of the molecule to the 2,3,18,19-tetranor metabolite (PGD-M). The dinor metabolite of PGD_2 seems to persist longer than the parent and intermediate metabolites and in urine might be the predominant marker for PGD_2 production.[113] In any assay these PGD_2-specific metabolites need to be distinguished from metabolites of either PGE_2 or PGH_2 catalyzed by AKR1B1 9α,11α-PGF_2 (also called $PGF_{2\alpha}$) and its dinor β-oxidation and tetranor ω-oxidation metabolites, which is accomplished by using liquid chromatography–tandem mass spectrometry. Increased levels of these metabolites in 24-hour urine collections normalized to the creatinine level or in plasma can provide biochemical evidence for MC activation, as recommended by the European Competence Network on Mastocytosis consensus conference.[1] Levels considered to be increased are determined by each diagnostic laboratory. The currently available commercial clinical tests for PGD_2 production are urinary levels of dinor 11β-$PGF_{2\alpha}$ and 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 MC 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 H1R resulted in symptomatic improvement and decreased hospitalizations for hypotensive episodes.[114] In a retrospective study of 25 patients with MCAS, baseline 24-hour urine 11β-$PGF_{2\alpha}$ levels were the most frequently increased MC mediator, and flushing and pruritus had the greatest correlation with increased baseline 11β-$PGF_{2\alpha}$ levels.[10] Eight of 9 patients with MCAS who had increased 11β-$PGF_{2\alpha}$ levels at baseline underwent aspirin therapy.[10] Follow-up urinary 11β-$PGF_{2\alpha}$ levels normalized for patients receiving 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 to be increased in patients with systemic allergic reactions to venom in a small number of patients and seem to have promise as a marker of MC activation.[115] 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 LT levels in serum.[96] 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 increased 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 MC 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 through 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 MCs,[116,117] basophils,[118] eosinophils,[119] monocytes and macrophages[120] 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.[121]

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 increased at baseline in patients with SM, and clinical improvement can occur with montelukast.[12,13,122,123]

By 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 with an immunoassay that detects LTC_4, LTD_4, and LTE_4, revealing that acute levels of cysteinyl leukotrienes were increased to greater than baseline values in 6 of 8 patients, tryptase levels in 6 of 9 patients (by the algorithm), and 11β-$PGF_{2\alpha}$ levels in 8 of 9 patients.[96] One of the issues needing further study is whether LTC_4 is released into the serum during blood clotting by cells, such as eosinophils, basophils, or monocytes, or by platelets through transcytosis versus by tissue MCs before the blood draw. In addition to SM, there are several studies showing the utility of measuring urinary LT levels in patients with aspirin-exacerbated respiratory disease[124,125] and the benefit from LT-modifier drugs.[126] A study of urinary LTE_4 and 11β-$PGF_{2\alpha}$ levels after anaphylaxis measured by using immunoassays and normalized to creatinine levels found that they correlated with one another and with anaphylactic severity.[127] Furthermore, 11β-$PGF_{2\alpha}$ levels peaked in the 0- to 3-hour urine collection, whereas LTE_4 levels were comparable in the 0- to 3- and 3- to 6-hour collections.

In summary, increases in 1 or a combination of the above mediators is observed in patients with a variety of MC activation disorders, including allergen-triggered systemic anaphylaxis, as well as systemic anaphylaxis occurring in association with SM, MCAS, aspirin-exacerbated respiratory disease, and hereditary α-tryptasemia (Table I). For MCAS, measuring levels of secreted MC 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 with baseline levels is optimal for tryptase and likely to be the case for histamine, another preformed mediator, but this needs more research. Having a baseline level to compare with the acute level might not be as critical for newly generated lipid mediators or their metabolites, although additional research should help clarify this point.

Bone marrow biopsy/aspirate

A bone marrow biopsy and aspirate are needed to precisely diagnose and stage SM, which, if present, would increase the possibility of an associated clonal MCAS. Also, the procedure can identify clonal MCs with a GOF mutation in *KIT* in the absence of other criteria for diagnosing SM, 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 an antimediator, 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 MC activation. Also, a buccal swab rather than a bone marrow biopsy is needed to diagnose hereditary α-tryptasemia, another condition associated with MCAS.

TESTS THAT ARE NOT RECOMMENDED FOR THE DIAGNOSIS OF MCAS

For more information on tests that are not recommended for the diagnosis of MCAS, see this article's Online Repository.

Biomarkers for MC activation events, as discussed above, should include substances secreted by activated MCs and for which assays are available with sufficient sensitivity and specificity to clearly distinguish levels during MC activation versus basal levels and to distinguish MC activation events from other acute conditions. Putative biomarkers of MC activation that are problematic include heparin,[53,78,128-130] which has not been validated as a marker of MC activation in blood, and chromogranin A,[78,131,132] which resides in neuroendocrine cells but not in MCs. Also, for reasons discussed above, neither plasma nor urine histamine levels[133-135] are recommended over histamine metabolites.

MANAGEMENT AND THERAPEUTIC OPTIONS FOR PATIENTS WITH MC DISORDERS

MCAS presents with a constellation of symptoms related to mediators secreted by activated MCs.[1] Treatment of patients with MCAS is highly individualized and targeted to bothersome symptoms and the underlying pathology (Table IV).[136-141] Other coexisting medical conditions need to be treated by an appropriate specialist.

Acute management of an MC activation attack corresponds to acute management of systemic anaphylaxis. Hypotensive episodes should be managed by patients assuming the supine position, followed by administration of intramuscular epinephrine. Laryngeal angioedema requires intramuscular epinephrine; bronchospasm also can be treated with intramuscular epinephrine 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 patients with SM, 20% to 50% experience systemic anaphylaxis,[142,143] typically with hypotension and 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 department by ambulance while remaining in the supine position.

Prevention of future MC activation events first involves identification and avoidance of the trigger or triggers, such as insect venoms, temperature extremes, mechanical irritation, alcohol, or medications (eg, aspirin, radiocontrast agents, and certain anesthetic agents). The second step is to attenuate the clinical response to MC activation by reducing MC mediator production or by blocking the action of MC mediators with appropriate medical therapy. The third step might involve reducing the ability of MCs to respond to activation triggers or, possibly, to reduce MC numbers. A patient with SM 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.[144]

Eliminating additives in drugs used to treat or prevent anaphylaxis by compounding them is not recommended. Although additives have not been evaluated for patients with MCAS, for 100 patients with chronic urticaria, 43 of whom complained of additive allergies, single- or double-blind challenges were used to rule this out in all of these patients.[145]

TABLE IV. Treatment interventions for MCAS

Intervention	Comments
Prevention	
Avoidance of known triggers	
Pharmacologic agents for prevention	
H1R antihistamines*	Nonsedating H1 histamines are generally preferred and can be increased to 2 to 4 times the standard dose; sedating H1 antihistamines might acutely cause drowsiness and impair driving ability and chronically lead to cognitive decline, particularly in the elderly.
H2R antihistamines	H2R antihistamines can be used as first-line therapy for gastrointestinal symptoms and might help H1R antihistamines attenuate cardiovascular symptoms.
Cromolyn sodium (oral formulation)	Cromolyn sodium can reduce abdominal bloating, diarrhea, and cramps. Benefit might extend to neuropsychiatric manifestations. Divided dosing and weekly upward titration to reach the desired target dose might improve tolerance and adherence.
Doxepin*	Doxepin, a potent H1 + H2 antihistamine with tricyclic antidepressant activity, might reduce central nervous system manifestations in patients with MCAS or SM but also might cause drowsiness and cognitive decline, particularly in the elderly, and might increase suicidal tendencies in children and young adults with depression.
Aspirin	Aspirin might reduce flushing and hypotension in some patients, particularly those with increased urinary 11β-$PGF_{2\alpha}$ levels, but is contraindicated in those with allergic or adverse reactions to nonsteroidal anti-inflammatory drugs. Clinical improvement might require a dosing increase up to 650 mg twice daily, as tolerated. Use with caution.
Steroid taper/steroid burst	Steroid taper/steroid burst might be useful for refractory signs or symptoms at an initial oral dosage of 0.5 mg/kg/d, followed by a slow taper over 1 to 3 months. It might be helpful to give 50 mg of prednisone 13 hours, 7 hours, and 1 hour before radiologic or invasive procedures when MC activation has been problematic. Steroid side effects dampen enthusiasm for long-term use.
Omalizumab	Cases indicate prevention of anaphylactic episodes in some patients with MCAS or SM or in those who cannot otherwise tolerate needed insect venom immunotherapy.
Cysteinyl leukotriene inhibitor (eg, montelukast) or 5-lipoxygenase inhibitor (zileuton)	These agents might reduce bronchospasm or gastrointestinal symptoms in patients with MCAS or SM, particularly if urinary LTE_4 levels are increased, but they are not well studied.
Cyproheptadine	Cyproheptadine is a sedating H1 antihistamine with extended anticholinergic and antiserotonergic activities and might help gastrointestinal symptoms.
Ketotifen	This sedating H1R antagonist is approved in the United States for allergic eye disease but can be compounded as tablets. Whether it is beneficial beyond other antihistamines, such as diphenhydramine, is unproved.
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 by using a bedpan for diarrhea and an emesis basin after rolling on to the side or abdomen.
Bronchodilator (albuterol)	A bronchodilator (albuterol) can be inhaled by using a nebulizer or metered-dose inhaler 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.[136-141]

Mediator and mast cell targets

Histamine. *H1R and H2R antagonists.* Recommendations for antihistamine therapy for MC activation disorders are based on expert opinion. The objective is to relieve symptoms caused by secreted histamine.[34,146,147] H1R and H2R antihistamine 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 that histamine to its receptors. H1R blockers in patients with MCAS reduce dermatologic manifestations, such as flushing and pruritus, along with tachycardia and abdominal discomfort. These medications, particularly later-generation nonsedating H1R antihistamines, such as fexofenadine and cetirizine, are often used at 2 to 4 times US Food and Drug Administration–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 about their use in patients with MCAS who are prone to cardiovascular events.[148] 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 a sedating agent, is now available as a compounded medication in the United States and is used to treat dermatologic, gastrointestinal, and neuropsychiatric symptoms.[149]

Rupatadine, an H1R blocker that also blocks platelet-activating factor binding to its receptor, is approved for use in many countries but not in the United States. In patients with mastocytosis,[150] 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.[151]

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 are limited to case reports and case series.[152] However, H2R antihistamines prevent histamine-mediated acid secretion from parietal cells and blunt the vasoactive effects of intravenously infused histamine if combined with an H1R antagonist.[153] Importantly, H1R and H2R blocking agents, especially those with anticholinergic effects, can be associated with cognitive decline that is worse in elderly populations.[136-140]

H3 and H4 receptor antagonists. Therapeutic antagonists for these receptors are in development and beyond the scope of this current communication but might have novel clinical value, particularly H4 receptor antagonists, which reduce pruritus and inflammation occurring in patients with atopic dermatitis.[154]

LTC_4. Other therapies for MCAS include cysteinyl leukotriene receptor blocking agents, such as montelukast and zafirlukast, or the 5-lipoxygenase inhibitor zileuton. These medications might work best in conjunction with H1R antihistamines, being most efficacious for dermatologic symptoms.[122,123]

PGD_2. Aspirin has been used to attenuate refractory flushing and hypotensive spells associated with PGD_2 secretion by inhibiting its synthesis.[80,155,156] Aspirin should be introduced in a controlled clinical setting because of the risk of triggering MC degranulation.[80,157]

Cromolyn. Oral cromolyn is used predominately for gastrointestinal symptoms, although its mechanism of action is not known.[158,159] Cromolyn taken orally or applied topically also might reduce pruritus.[160] Patients should be counseled that the onset of action can be delayed and should be taken for at least 1 month before deciding whether it is helping. It should be introduced at the lowest dose, with the dose gradually increased to 200 mg 4 times a day given before each meal and at bedtime.

Glucocorticosteroids. Systemic steroids might help some patients, as indicated in case reports, but should be tapered as quickly as possible to limit their numerous adverse effects.

Anti-IgE therapy. Omalizumab binds free IgE, preventing its binding to FcεRI, and has been approved for treating poorly controlled moderate-to-severe atopic asthma and antihistamine-resistant chronic urticaria. The mechanism of action of omalizumab remains incomplete but might affect the activation threshold of MCs when surface levels of FcεRI are reduced by blocking IgE binding. For example, omalizumab reduces the severity and frequency of allergic reactions during aeroallergen rush immunotherapy and insect venom immunotherapy in patients with mastocytosis.[161-165] Omalizumab also prevents spontaneous episodes of anaphylaxis in case reports and case series.[166-169] Omalizumab is an expensive therapeutic option, although case reports support its benefit in the prevention of anaphylaxis, emergency department visits, and lost time from work. Therefore it should be considered in cases of MCAS resistant to mediator-targeted therapies.

Cytoreductive therapies. For patients with clonal MCAS in advanced SM (aggressive SM, MC leukemia or sarcoma, SM associated with a non-MC hematologic clonal disorder, and in some cases smoldering SM) with signs and symptoms refractory to antimediator therapy, cytoreductive therapy should be considered. Two of the most commonly used agents have been IFN-α and cladribine. Commonly observed adverse events of IFN-α include flu-like symptoms, depression, hypothyroidism, and a variety of autoimmune disorders.[170] Cladribine can be efficacious in patients with advanced SM with severe life-threatening or disabling anaphylaxis[171-173] but is associated with an increased risk of infection.

Signal transduction inhibitors have been considered for MCAS symptoms that cannot be adequately controlled with safer interventions. Based on laboratory studies, inhibitors of Kit tyrosine kinase decrease MC activatability and survival and thus might be helpful in patients with MCAS.[174] Midostaurin is a multikinase inhibitor (Tyr and Ser/Thr kinases) with activity against wild-type and D816V Kit and has been approved for treating advanced SM.[175-181] Although nausea, vomiting, and cytopenias are relatively common, for most patients, nausea can be controlled by taking ondansetron 30 to 60 minutes before midostaurin, and cytopenias can be managed by adjusting the dose of midostaurin. This agent can replace IFN-α and cladribine in the treatment paradigm for clonal MC disorders.

Masitinib is a tyrosine kinase inhibitor with activity against wild-type Kit and Lyn tyrosine kinases and has been used to treat mediator-related symptoms in patients with MCAS, but asthenia is a common side effect.[182] 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.[183] Ibrutinib (used to treat mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom macroglobulinemia) decreases IgE-mediated reactivity but not non–IgE-mediated MC activation.[184] Patients with advanced SM, including those with MC 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.[181,185] Another inhibitor of D816V Kit, DCC2618, is in a phase 1 trial for smoldering and advanced SM.[186]

Current studies using an mAb targeting sialic acid–binding immunoglobulin-like lection 8 reported that in humanized mice eosinophil numbers in the circulation and MC activation tested by passive cutaneous anaphylaxis were both reduced,[187,188] but data in human subjects have not yet been published.

Whether such newer therapies targeting signaling pathways will have a favorable long-term benefit/toxicity ratio for treating MCAS remains to be determined but might depend in part on

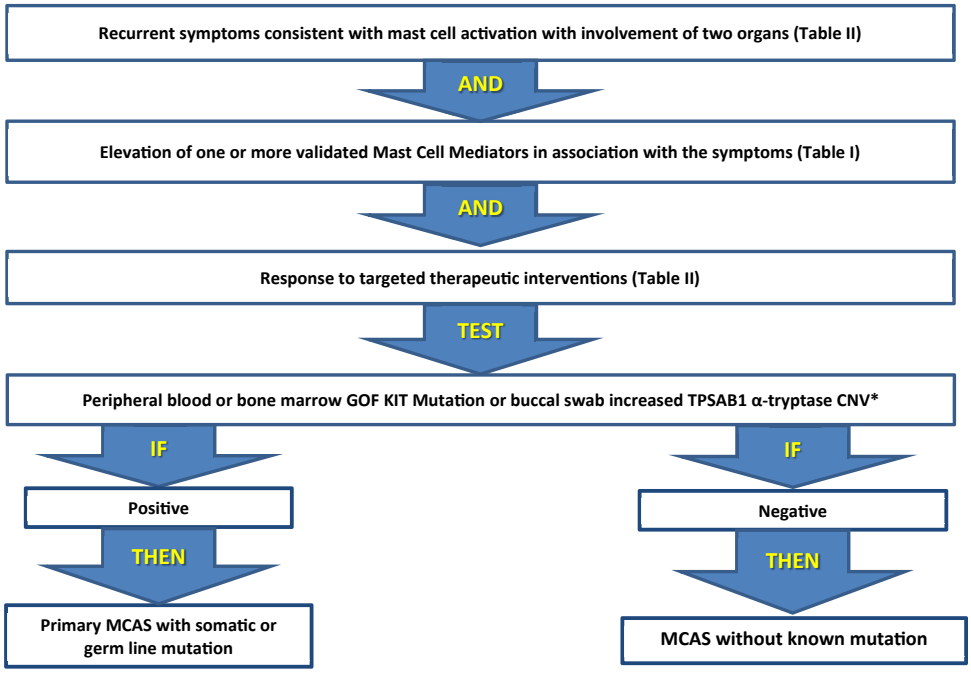

FIG 1. Algorithm for diagnosing MCAS. *Somatic *KIT* mutation assays have limited sensitivity.[219-224] The germline *TPSAB1* α-tryptase CNV test is available from Gene by Gene (Houston, Tex). If the peripheral blood allele-specific D816V *KIT* mutation is negative, perhaps because of a low allelic *KIT* mutation burden[225] or a different GOF *KIT* mutation but positive REMA[226] (sex; sBT; pruritus, hives, or angioedema; and presyncope or syncope)[226] or NIH (similar to REMA plus allele-specific D816V *Kit* PCR on peripheral blood)[227] scores, then a bone marrow study for a GOF *KIT* mutation should be considered.

whether such drugs inhibit MC 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 patients with clonal MCAS can progress to SM, most likely indolent SM. None of the patients in the Mayo Clinic cohort[10] followed for more than 15 years had mastocytosis. However, data regarding patients with indolent SM demonstrate a normal life expectancy.[10,189-194] We propose treatment based on symptoms and increased levels of MC mediators. For example, if a patient with MCAS has increased urinary LTE_4 levels, then LT antagonists are recommended; if urinary PG metabolite levels were increased, then treatment with aspirin might help. Therefore the therapeutic intervention should be adjusted to fit each patient.

DIFFERENTIAL DIAGNOSIS

Clinical presentations of patients with MCAS are discussed in Diagnosis of MCAS: Clinical signs and symptoms and outlined in Table II. It should be noted that there is a wide differential diagnosis. For example, flushing is not limited to MC disorders but is a hallmark of other conditions as well.[195-198] These include benign flushing,[199-202] familial flushing, and endocrine disorders,[203] such as hyperthyroidism and hormone withdrawal.[204-206] Neuroendocrine tumors, such as carcinoid tumors[207-210] and pheochromocytomas,[211,212] cause spells and flushing as well. Dermatologic conditions, such as rosacea,[202] medications,[213,214] reduced alcohol metabolism,[215] and other less common conditions,[216-218] are also associated with flushing. It is beyond the scope of this communication to discuss the diagnostic workup and treatment of all conditions that might clinically mimic certain signs or symptoms of MCAS.

CURRENT CLASSIFICATION AND UNMET NEEDS

Our current recommendations for diagnosing MCAS make use of the latest studies and consensus guidelines for clinically diagnosing systemic anaphylaxis in real time, regardless of whether allergen was triggered through the IgE pathway or through other pathways; our current understanding of the mediators secreted by activated MCs that best discriminate this disorder from other conditions; and the drugs that might selectively affect those mediators or MCs themselves. Whether precise measurement of additional mediators will provide complementary and clinically useful insight, such as platelet-activating factor, heparin, chymase, or carboxypeptidase A3, requires further research. Also, our recommendations do not address the occurrence of local MC activation. An increase in MC numbers in the gastrointestinal tract or elsewhere by itself does not provide a diagnosis of MC activation or indicate that MC activatability is affected. Whether the plasticity of human MCs, governed largely by their local tissue or inflammatory environment, might affect their activation in a clinically significant manner needs to be better understood. Detection of an activating *KIT* mutation, such as one causing D816V, in peripheral blood or tissue demonstrates clonality; surface expression of CD25 on MCs is a surrogate marker for clonality; and the presence of dense aggregates of spindle-shaped MCs suggests underlying mastocytosis. Finding familial or

somatic mutations of other genes that identify hyperactivatable MCs 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 MCASs described herein will provide clinicians with practical criteria of sufficient sensitivity and specificity to diagnose most cases, without overdiagnosing 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.[219-227]

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