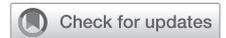


AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management



Catherine R. Weiler, MD, PhD,^{a*} K. Frank Austen, MD,^{b*} Cem Akin, MD, PhD,^{c*} Marla S. Barkoff, MD,^d Jonathan A. Bernstein, MD,^e Patrizia Bonadonna, MD,^f Joseph H. Butterfield, MD,^a Melody Carter, MD,^g Charity C. Fox, MD,^h Anne Maitland, MD, PhD,ⁱ Thanai Pongdee, MD,^a S. Shahzad Mustafa, MD,^j Anupama Ravi, MD,^k Mary C. Tobin, MD,^l Harissios Vliagoftis, MD,^m and Lawrence B. Schwartz, MD, PhD^{n*} *Rochester, Minn; Boston, Mass; Ann Arbor, Mich; Chicago, Ill; Cincinnati and Columbus, Ohio; Verona, Italy; Bethesda, Md; New York and Rochester, NY; Edmonton, Alberta, Canada; and Richmond, Va*

AAAAI Position Statements, Work Group Reports, and Systematic Reviews are not to be considered to reflect current AAAAI standards or policy after five years from the date of publication. The statement below is not to be construed as dictating an exclusive course of action nor is it intended to replace the medical judgment of healthcare professionals. The unique circumstances of individual patients and environments are to be taken into account in any diagnosis and treatment plan. The statement reflects clinical and scientific advances as of the date of publication and is subject to change.

For reference only.

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

From ^athe Department of Internal Medicine, Division of Allergy, and ^kthe Department of Pediatrics, Division of Pediatric Allergy and Immunology, Mayo Clinic, Rochester; ^bthe Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham & Women's Hospital, Boston; ^cthe Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor; ^dPrivate Practice, Endocrinology, Chicago; ^eInternal Medicine, Immunology and Allergy, University of Cincinnati College of Medicine and Partner of Bernstein Allergy Group, and Bernstein Clinical Research Center, Cincinnati; ^fthe Allergy Unit, Multidisciplinary Mastocytosis Clinic, Azienda Ospedaliera Universitaria Integrata of Verona, Verona; ^gthe National Institutes of Health Clinical Center, Bethesda; ^hthe Department of Otolaryngology, Division of Allergy and Immunology, Ohio State University Wexner Medical Center, Columbus; ⁱthe Department of Medicine, Icahn School of Medicine at Mount Sinai, New York; ^jAllergy and Clinical Immunology, Rochester Regional Health System, University of Rochester School of Medicine & Dentistry, Rochester; ^lthe Department of Internal Medicine, Allergy/Immunology Division, Rush University Medical Center, Chicago; ^mthe Department of Medicine, University of Alberta, Edmonton; and ⁿthe Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology, Virginia Commonwealth University, Richmond.

*These authors served as senior authors.

Disclosure of potential conflict of interest: C. Akin consults for Novartis and Blueprint Medicines Corporation for tyrosine kinase inhibitors in mastocytosis and receives

research support for a clinical trial in mastocytosis from Blueprint Medicines. A. Maitland is on the speakers' bureau for Sanofi/Regeneron and Genentech. S. S. Mustafa is on speakers' bureaus for Genentech, Teva, AstraZeneca, Regeneron and CSL Behring. L. B. Schwartz receives royalties for inventing the tryptase assay from Thermo Fisher; is a consultant for companies in the mastocytosis or anaphylaxis field, including Genentech, Deciphera Pharmaceuticals, Inc, Blueprint Medicines, and Allakos; receives research support for a multicenter Phase 1 mastocytosis clinical trial from Deciphera Pharmaceuticals, Waltham, Mass, USA (DCC-2618-01-001); and receives honoraria from UpToDate and Cecil Medicine for writing about anaphylaxis and tryptase. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 25, 2019; revised August 20, 2019; accepted for publication August 27, 2019.

Available online August 30, 2019.

Corresponding author: Lawrence B. Schwartz, MD, PhD, Virginia Commonwealth University, PO Box 980263, Richmond, VA 23298. E-mail: lawrence.schwartz@vcuhealth.org.

 The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2019.08.023>

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.)

Key words: Mast cell activation syndrome, tryptase, hereditary α -tryptasemia, mastocytosis, anaphylaxis, histamine, prostaglandin D₂, leukotriene C₄, c-kit

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/Fc ϵ RI but also by antigens through IgG/Fc γ RI/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) D₂, and leukotriene (LT) C₄, leading to increased levels in the blood or urine of secreted mediators or of their metabolites, including N-methylhistamine, 11 β -PGF_{2 α} and LTD₄/LTE₄. 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 PGD₂ or 5-lipoxygenase for LTC₄ 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 Fc ϵ RI and Fc γ RI/IIa

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

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.

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, PGD₂, and LTC₄, 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 _{2α}	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 MCAS²⁸⁻³⁰ 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 information³⁸ 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, dermatographism, 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 diagnose 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 agents⁶¹ 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 quintuplication⁴ 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

trypsinases, and acid hydrolases in all MCs, whereas chymase, carboxypeptidase A3, and cathepsin G are found in a subset (trypsinase 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 surfaces⁷² 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 PGD₂ 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 -trypsinases: *TPSB2*, expressing only β -trypsinase, and *TPSAB1*, expressing either α - or β -trypsinase.⁸¹⁻⁸⁴ Each is expressed as a 275-amino-acid pretrypsinase that is rapidly converted to a 257-amino-acid protrypsinase. One portion of these protrypsinases 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 -trypsinemia. However, another portion of the protrypsinase 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 -trypsinase are active proteases, whereas those of α -trypsinase do not exhibit a known proteolytic activity. A new form of trypsinase, α/β -trypsinase heterotetramers, forms naturally in MCs and has a distinct substrate repertoire from either homotetramer.⁸⁶ In healthy subjects α - and β -trypsinases 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 trypsinase assay (Thermo Fisher/Phadia Laboratory Systems, Uppsala, Sweden) measures both mature and pro forms of α - and β -trypsinases, sometimes referred to as total trypsinase.

Mature trypsinases released during episodes of systemic anaphylaxis triggered by insect stings result in increased levels of total trypsinase 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 trypsinase levels. In experimental insect sting-triggered anaphylaxis, peak levels of mature trypsinase 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 trypsinase 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 trypsinase level (sAT) to be considered clinically significant, the sAT should be greater than the serum (or plasma) baseline trypsinase 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 -trypsinemia 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 trypsinase itself increases this risk because it also serves as a surrogate for other underlying factors, such as GOF *KIT* mutations or increased *TPSAB1* α -trypsinase gene copy numbers, each of which increase the burden and activatability of MCs.

Hereditary α -trypsinemia, 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 -trypsinase gene encoded by *TPSAB1*, resulting in overexpression of α -trypsinase 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 PGD₂ and LTC₄, 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 PGD₂ production by inhibiting COX-1 and COX-2 and LTC₄ by inhibiting 5-lipoxygenase.

PGD₂ and its metabolites

PGD₂ is generated from arachidonic acid by the sequential actions first of either COX-1 or COX-2 to PGH₂ and then of either the hemopoietic or lipocalin type of PGD synthase to PGD₂. 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 lymphocytes¹¹⁰ but not by basophils.¹¹¹ Large amounts of PGD₂ can be rapidly synthesized and secreted by MCs activated when Fc ϵ RI 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 PGD₂ synthesis and secretion from other cell types is less obvious.

Once secreted, PGD₂ is metabolized by an aldo-keto reductase, principally AKR1C3, at the 11-ketone position to an 11 β -hydroxyl moiety or 9 α ,11 β -PGF₂ (also called 11 β -PGF_{2 α}). 11 β -PGF_{2 α} can then be metabolized by means of β -oxidation of its carboxyl

terminal, shortening the molecules by 2 carbons, called 2,3-dinor-11 β -PGF_{2 α} , 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 PGD₂ seems to persist longer than the parent and intermediate metabolites and in urine might be the predominant marker for PGD₂ production.¹¹³ In any assay these PGD₂-specific metabolites need to be distinguished from metabolites of either PGE₂ or PGH₂ catalyzed by AKR1B1 9 α ,11 α -PGF₂ (also called PGF_{2 α}) 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 PGD₂ production are urinary levels of dinor 11 β -PGF_{2 α} and PGD₂, with the metabolite being preferred because most of the PGD₂ is converted to its metabolite before being excreted. Measurement of serum PGD₂ levels is also available commercially but has not been validated as a diagnostic marker for MC disorders.

In 1980, increased PGD₂ production in 2 patients with SM was reported, and inhibiting PGD₂ 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 11 β -PGF_{2 α} levels were the most frequently increased MC mediator, and flushing and pruritus had the greatest correlation with increased baseline 11 β -PGF_{2 α} levels.¹⁰ Eight of 9 patients with MCAS who had increased 11 β -PGF_{2 α} levels at baseline underwent aspirin therapy.¹⁰ Follow-up urinary 11 β -PGF_{2 α} 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 11 β -PGF_{2 α} 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 11 β -PGF_{2 α} 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 11 β -PGF_{2 α} 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 PGD₂ or its metabolites as a validated biomarker for MC activation would better inform its positive and negative predictive values.

LTC₄ and its metabolites. LTC₄ is generated when arachidonic acid bound to 5-lipoxygenase activating protein is converted by 5-lipoxygenase to LTA₄, followed by LTC₄ synthase-conjugating LTA₄ with reduced glutathione to form bioactive LTC₄, which is then secreted through the ATP-binding cassette transporters 1 and 4. Secreted LTC₄ is rapidly metabolized to LTD₄ as γ -glutamyl transpeptidases remove glutamine and then to LTE₄, a more stable metabolite, as dehydropeptidase I removes glycine. LTC₄ is produced directly by activated MCs,^{116,117} basophils,¹¹⁸ eosinophils,¹¹⁹ monocytes and macrophages¹²⁰ and indirectly by transcellular metabolism when LTA₄ is transferred from a cell lacking LTC₄ synthase to one that has LTC₄ synthase, which includes platelets.¹²¹

LTE₄, the most stable cysteinyl leukotriene, is used to monitor this pathway in plasma or urine because its precursors, LTC₄ and especially LTD₄, are very transient. Urinary LTE₄ 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 LTC₄, LTD₄, and LTE₄, 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_{2α} levels in 8 of 9 patients.⁹⁶ One of the issues needing further study is whether LTC₄ 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 LTE₄ and 11β-PGF_{2α} 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_{2α} levels peaked in the 0- to 3-hour urine collection, whereas LTE₄ 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 levels¹³³⁻¹³⁵ 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 _{2α} 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.

(Continued)

TABLE IV. (Continued)

Intervention	Comments
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

LTC₄. 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}

PGD₂. Aspirin has been used to attenuate refractory flushing and hypotensive spells associated with PGD₂ 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.

Gluocorticosteroids. 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 anaphylaxis¹⁷¹⁻¹⁷³ 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 lectin 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

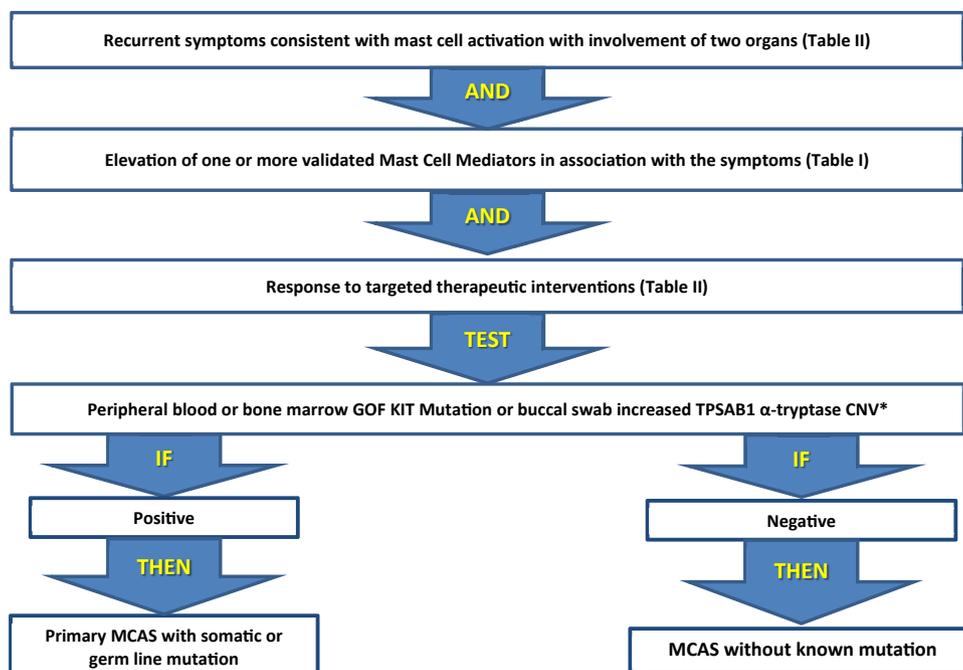


FIG 1. Algorithm for diagnosing MCAS. *Somatic *KIT* mutation assays have limited sensitivity.²¹⁹⁻²²⁴ The germline *TPSAB1* α -tryptase CNV test is available from Gene by Gene (Houston, Tex). If the peripheral blood allele-specific D816V *KIT* mutation is negative, perhaps because of a low allelic *KIT* mutation burden²²⁵ or a different GOF *KIT* mutation but positive REMA²²⁶ (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 cyto-reduction.

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 cohort¹⁰ 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 LTE₄ 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 tumors²⁰⁷⁻²¹⁰ 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

REFERENCES

- Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157:215-25.
- Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-25.
- Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. *Blood* 2007;110:2331-3.
- Sabato V, Chovanec J, Faber M, Milner JD, Ebo D, Lyons JJ. First identification of an inherited TPSAB1 quintuplication in a patient with clonal mast cell disease. *J Clin Immunol* 2018;38:457-9.
- Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. *Immunol Allergy Clin North Am* 2018;38:483-95.
- Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126:1099-104.
- Picard M, Giavina-Bianchi P, Mezzano V, Castells M. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndromes. *Clin Ther* 2013;35:548-62.
- Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. *J Allergy Clin Immunol* 2014;133:1471-4.
- Sabato V, Van De Vijver E, Hagedorens M, Vrelust I, Reyniers E, Franssen E, et al. Familial hypertryptasemia with associated mast cell activation syndrome. *J Allergy Clin Immunol* 2014;134:1448-50.e3.
- Ravi A, Butterfield J, Weiler CR. Mast cell activation syndrome: improved identification by combined determinations of serum tryptase and 24-hour urine 11 β -prostaglandin 2α . *J Allergy Clin Immunol Pract* 2014;2:775-9.
- Baretto RL, Beck S, Heselgrave J, Melchior C, Mohamed O, Ekbote A, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. *Allergy* 2017;72:2031-4.
- Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. *Prostaglandins Other Lipid Mediat* 2010;92:73-6.
- Lueke AJ, Meeusen JW, Donato LJ, Gray AV, Butterfield JH, Saenger AK. Analytical and clinical validation of an LC-MS/MS method for urine leukotriene E4: a marker of systemic mastocytosis. *Clin Biochem* 2016;49:979-82.
- Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Moller MB. Serum tryptase correlates with the KIT D816V mutation burden in adults with indolent systemic mastocytosis. *Eur J Haematol* 2013;91:106-11.
- Matito A, Morgado JM, Alvarez-Twose I, Sanchez-Munoz L, Pedreira CE, Jara-Acevedo M, et al. Serum tryptase monitoring in indolent systemic mastocytosis: association with disease features and patient outcome. *PLoS One* 2013;8:e76116.
- Quintas-Cardama A, Sever M, Cortes J, Kantarjian H, Verstovsek S. Bone marrow mast cell burden and serum tryptase level as markers of response in patients with systemic mastocytosis. *Leuk Lymphoma* 2013;54:1959-64.
- van Toorenbergen AW, Oranje AP. Comparison of serum tryptase and urine N-methylhistamine in patients with suspected mastocytosis. *Clin Chim Acta* 2005;359:72-7.
- Akin C, Metcalfe DD. Surrogate markers of disease in mastocytosis. *Int Arch Allergy Immunol* 2002;127:133-6.
- Butterfield JH, Ravi A, Pongdee T. Mast cell mediators of significance in clinical practice in mastocytosis. *Immunol Allergy Clin North Am* 2018;38:397-410.
- Oranje AP, Mulder PG, Heide R, Tank B, Riezebos P, van Toorenbergen AW. Urinary N-methylhistamine as an indicator of bone marrow involvement in mastocytosis. *Clin Exp Dermatol* 2002;27:502-6.
- van Doormaal JJ, van der Veer E, van Voorst Vader PC, Kluijn PM, Mulder AB, van der Heide S, et al. Tryptase and histamine metabolites as diagnostic indicators of indolent systemic mastocytosis without skin lesions. *Allergy* 2012;67:683-90.
- Morrow JD, Guzzo C, Lazarus G, Oates JA, Roberts LJ. Improved diagnosis of mastocytosis by measurement of the major urinary metabolite of prostaglandin D2. *J Invest Dermatol* 1995;104:937-40.
- Celejewska-Wojcik N, Mastalerz L, Wojcik K, Nieckarz R, Januszek R, Hartwich P, et al. Incidence of aspirin hypersensitivity in patients with chronic rhinosinusitis and diagnostic value of urinary leukotriene E4. *Pol Arch Med Wewn* 2012;122:422-7.
- Divekar R, Butterfield J. Urinary 11 β -PGF 2α and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. *Allergy* 2015;70:1230-8.
- Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, et al. KIT inhibition by imatinib in patients with severe refractory asthma. *N Engl J Med* 2017;376:1911-20.
- Lyons JJ, Stotz SC, Chovanec J, Liu Y, Lewis KL, Nelson C, et al. A common haplotype containing functional CACNA1H variants is frequently co-inherited with increased TPSAB1 copy number. *Genet Med* 2018;20:503-12.
- Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet* 2016;48:1564-9.
- Cardet JC, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Curr Allergy Asthma Rep* 2013;13:10-8.
- Hamilton MJ. Nonclonal mast cell activation syndrome: a growing body of evidence. *Immunol Allergy Clin North Am* 2018;38:469-81.
- Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;128:147-52.e2.
- Akin C. Mast cell activation syndromes. *J Allergy Clin Immunol* 2017;140:349-55.
- Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, Matito A, Esteban-Lopez MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 2010;125:1269-78.e2.
- Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. *Expert Opin Pharmacother* 2013;14:2033-45.
- Akin C. Mast cell activation disorders. *J Allergy Clin Immunol Pract* 2014;2:252-8.e1.
- Afrin LB, Butterfield JH, Raithel M, Molderings GJ. Often seen, rarely recognized: mast cell activation disease—a guide to diagnosis and therapeutic options. *Ann Med* 2016;48:190-201.
- Afrin LB, Self S, Menk J, Lazarchick J. Characterization of mast cell activation syndrome. *Am J Med Sci* 2017;353:207-15.
- Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. *Transl Res* 2016;174:33-59.
- Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J Hematol Oncol* 2011;4:10.
- Molderings GJ, Homann J, Raithel M, Frieling T. Interdisciplinary Multicenter Research Group on Systemic Mast Cell Activation Disease. Toward a global classification of mast cell activation diseases. *J Allergy Clin Immunol* 2011;127:1311, author reply 1312.
- Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. *J Allergy Clin Immunol Pract* 2014;2:70-6.
- Jennings SV, Slee VM, Zack RM, Verstovsek S, George TI, Shi H, et al. Patient perceptions in mast cell disorders. *Immunol Allergy Clin North Am* 2018;38:505-25.
- Afrin LB. A new era for an old cell: heightened appreciation of mast cell disease emerges. *Transl Res* 2016;174:1-4.
- Daens S, Grossin D, Hermanns-Le T, Peeters D, Manicourt D. [Severe mast cell activation syndrome in a 15-year-old patient with an hypermobile Ehlers-Danlos syndrome]. *Rev Med Liege* 2018;73:61-4.

45. Seneviratne SL, Maitland A, Afrin L. Mast cell disorders in Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet* 2017;175:226-36.
46. Bonamichi-Santos R, Yoshimi-Kanamori K, Giavina-Bianchi P, Aun MV. Association of postural tachycardia syndrome and Ehlers-Danlos syndrome with mast cell activation disorders. *Immunol Allergy Clin North Am* 2018;38:497-504.
47. Garland EM, Celedonio JE, Raj SR. Postural tachycardia syndrome: beyond orthostatic intolerance. *Curr Neurol Neurosci Rep* 2015;15:60.
48. Goodman BP. Evaluation of postural tachycardia syndrome (POTS). *Auton Neurosci* 2018;215:12-9.
49. Afrin LB. Sclerosing mediastinitis and mast cell activation syndrome. *Pathol Res Pract* 2012;208:181-5.
50. Afrin LB. Polycythemia from mast cell activation syndrome: lessons learned. *Am J Med Sci* 2011;342:44-9.
51. Afrin LB. Mast cell activation syndrome masquerading as agranulocytosis. *Mil Med* 2012;177:113-7.
52. Afrin LB. Mast cell activation syndrome as a significant comorbidity in sickle cell disease. *Am J Med Sci* 2014;348:460-4.
53. Seidel H, Molderings GJ, Oldenburg J, Meis K, Kolck UW, Homann J, et al. Bleeding diathesis in patients with mast cell activation disease. *Thromb Haemost* 2011;106:987-9.
54. Afrin LB. Burning mouth syndrome and mast cell activation disorder. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011;111:465-72.
55. Afrin LB, Pohlau D, Raitchel M, Haenisch B, Dumoulin FL, Homann J, et al. Mast cell activation disease: an underappreciated cause of neurologic and psychiatric symptoms and diseases. *Brain Behav Immun* 2015;50:314-21.
56. Angelidou A, Alysandros KD, Asadi S, Zhang B, Francis K, Vasiadi M, et al. Brief report: "allergic symptoms" in children with Autism Spectrum Disorders. More than meets the eye? *J Autism Dev Disord* 2011;41:1579-85.
57. Haenisch B, Molderings GJ. White matter abnormalities are also repeatedly present in patients with systemic mast cell activation syndrome. *Transl Psychiatry* 2018;8:95.
58. Afrin LB, Spruill LS, Schabel SI, Young-Pierce JL. Improved metastatic uterine papillary serous cancer outcome with treatment of mast cell activation syndrome. *Oncology* 2014;28:129-31, 34.
59. Molderings GJ, Knuchel-Clarke R, Hertfelder HJ, Kuhl C. Mast cell activation syndrome mimicking breast cancer: case report with pathophysiologic considerations. *Clin Breast Cancer* 2018;18:e271-6.
60. Molderings GJ, Zienkiewicz T, Homann J, Menzen M, Afrin LB. Risk of solid cancer in patients with mast cell activation syndrome: results from Germany and USA. *F1000Res* 2017;6:1889.
61. Afrin LB. Utility of hydroxyurea in mast cell activation syndrome. *Exp Hematol Oncol* 2013;2:28.
62. Afrin LB, Cichocki FM, Patel K, Molderings GJ. Successful treatment of mast cell activation syndrome with sunitinib. *Eur J Haematol* 2015;95:595-7.
63. Afrin LB, Fox RW, Zito SL, Choe L, Glover SC. Successful targeted treatment of mast cell activation syndrome with tofacitinib. *Eur J Haematol* 2017;99:190-3.
64. Irani AM, Schwartz LB. Human mast cell heterogeneity. *Allergy Proc* 1994;15:303-8.
65. Bencsath M, Paloczi K, Szalai C, Szenthe A, Szeberenyi J, Falus A. Histidine decarboxylase in peripheral lymphocytes of healthy individuals and chronic lymphoid leukemia patients. *Pathol Oncol Res* 1998;4:121-4.
66. Alcaniz L, Vega A, Chacon P, El Bekay R, Ventura I, Aroca R, et al. Histamine production by human neutrophils. *FASEB J* 2013;27:2902-10.
67. Liu YZ, Dvornyk V, Lu Y, Shen H, Lappe JM, Recker RR, et al. A novel pathophysiological mechanism for osteoporosis suggested by an in vivo gene expression study of circulating monocytes. *J Biol Chem* 2005;280:29011-6.
68. Sasaguri Y, Tanimoto A. Role of macrophage-derived histamine in atherosclerosis—chronic participation in the inflammatory response. *J Atheroscler Thromb* 2004;11:122-30.
69. Salem A, Rozov S, Al-Samadi A, Stegajev V, Listyarifah D, Kouri VP, et al. Histamine metabolism and transport are deranged in human keratinocytes in oral lichen planus. *Br J Dermatol* 2017;176:1213-23.
70. Jones BL, Kearns GL. Histamine: new thoughts about a familiar mediator. *Clin Pharmacol Ther* 2011;89:189-97.
71. O'Mahony L, Akdis M, Akdis CA. Regulation of the immune response and inflammation by histamine and histamine receptors. *J Allergy Clin Immunol* 2011;128:1153-62.
72. Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, et al. Histamine derived from probiotic *Lactobacillus reuteri* suppresses TNF via modulation of PKA and ERK signaling. *PLoS One* 2012;7:e31951.
73. Kounis NG, Patsouras N, Grapsas N, Hahalis G. Histamine induced coronary artery spasm, fish consumption and Kounis syndrome. *Int J Cardiol* 2015;193:39-41.
74. Feng C, Teuber S, Gershwin ME. Histamine (scombroid) fish poisoning: a comprehensive review. *Clin Rev Allergy Immunol* 2016;50:64-9.
75. De Gennaro L, Brunetti ND, Locuratolo N, Ruggiero M, Resta M, Diaferia G, et al. Kounis syndrome following canned tuna fish ingestion. *Acta Clin Belg* 2017;72:142-5.
76. Chomchai S, Chomchai C. Histamine poisoning from insect consumption: an outbreak investigation from Thailand. *Clin Toxicol (Phila)* 2018;56:126-31.
77. Ridolo E, Martignago I, Senna G, Ricci G. Scombroid syndrome: it seems to be fish allergy but... it isn't. *Curr Opin Allergy Clin Immunol* 2016;16:516-21.
78. Vysniauskaite M, Hertfelder HJ, Oldenburg J, Dressen P, Brettner S, Homann J, et al. Determination of plasma heparin level improves identification of systemic mast cell activation disease. *PLoS One* 2015;10:e0124912.
79. Pardanani A, Chen D, Abdelrahman RA, Reichard KK, Zblewski D, Wood AJ, et al. Clonal mast cell disease not meeting WHO criteria for diagnosis of mastocytosis: clinicopathologic features and comparison with indolent mastocytosis. *Leukemia* 2013;27:2091-4.
80. Butterfield JH, Weiler CR. Prevention of mast cell activation disorder-associated clinical sequelae of excessive prostaglandin D(2) production. *Int Arch Allergy Immunol* 2008;147:338-43.
81. Trivedi NN, Raymond WW, Caughey GH. Chimerism, point mutation, and truncation dramatically transformed mast cell delta-tryptases during primate evolution. *J Allergy Clin Immunol* 2008;121:1262-8.
82. Trivedi NN, Tamraz B, Chu C, Kwok PY, Caughey GH. Human subjects are protected from mast cell tryptase deficiency despite frequent inheritance of loss-of-function mutations. *J Allergy Clin Immunol* 2009;124:1099-105, e1-4.
83. Trivedi NN, Caughey GH. Mast cell peptidases: chameleons of innate immunity and host defense. *Am J Respir Cell Mol Biol* 2010;42:257-67.
84. Trivedi NN, Tong Q, Raman K, Bhagwandin VJ, Caughey GH. Mast cell alpha and beta tryptases changed rapidly during primate speciation and evolved from gamma-like transmembrane peptidases in ancestral vertebrates. *J Immunol* 2007;179:6072-9.
85. Schwartz LB, Min HK, Ren SL, Xia HZ, Hu J, Zhao W, et al. Tryptase precursors are preferentially and spontaneously released, whereas mature tryptase is retained by HMC-1 cells, mono-mac-6 cells, and human skin-derived mast cells. *J Immunol* 2003;170:5667-73.
86. Le QT, Lyons JJ, Naranjo AN, Olivera A, Lazarus RA, Metcalfe DD, et al. Impact of naturally forming human α/β -tryptase heterotetramers in the pathogenesis of hereditary α -tryptasemia. *J Exp Med* 2019 [Epub ahead of print].
87. Jogie-Brahim S, Min HK, Fukuoka Y, Xia HZ, Schwartz LB. Expression of alpha-tryptase and beta-tryptase by human basophils. *J Allergy Clin Immunol* 2004;113:1086-92.
88. Schwartz LB, Irani AM, Roller K, Castells MC, Schechter NM. Quantitation of histamine, tryptase, and chymase in dispersed human T and TC mast cells. *J Immunol* 1987;138:2611-5.
89. Van der Linden P-WG, Hack CE, Poortman J, Vивиé-Kipp YC, Struyvenberg A, Van der Zwan JK. Insect-sting challenge in 138 patients: relation between clinical severity of anaphylaxis and mast cell activation. *J Allergy Clin Immunol* 1992;90:110-8.
90. Schwartz LB, Atkins PC, Bradford TR, Fleekop P, Shalit M, Zweiman B. Release of tryptase together with histamine during the immediate cutaneous response to allergen. *J Allergy Clin Immunol* 1987;80:850-5.
91. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic-anaphylaxis and mastocytosis. *N Engl J Med* 1987;316:1622-6.
92. Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989;83:1551-5.
93. De Schryver S, Halbrich M, Clarke A, La Vieille S, Eisman H, Alizadehfar R, et al. Tryptase levels in children presenting with anaphylaxis: temporal trends and associated factors. *J Allergy Clin Immunol* 2016;137:1138-42.
94. Vitte J, Amadei L, Gouitaa M, Mezouar S, Zieleskiewicz L, Albanese J, et al. Paired acute-baseline serum tryptase levels in perioperative anaphylaxis: an observational study 97/100. *Allergy* 2019;74:1157-65.
95. Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract* 2019;7:1125-33.e1.
96. Nassiri M, Eckermann O, Babina M, Edenharter G, Worm M. Serum levels of $9\alpha,11\beta$ -PGF2 and cysteinyl leukotrienes are useful biomarkers of anaphylaxis. *J Allergy Clin Immunol* 2016;137:312-4.
97. Fellinger C, Hemmer W, Wohrl S, Sesztak-Greinecker G, Jarisch R, Wantke F. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. *Allergol Immunopathol (Madr)* 2014;42:544-52.

98. Sahiner UM, Yavuz ST, Buyukiryaki B, Cavkaytar O, Arik Yilmaz E, Tuncer A, et al. Serum basal tryptase levels in healthy children: correlation between age and gender. *Allergy Asthma Proc* 2014;35:404-8.
99. Aberer E, Savic S, Bretterklieber A, Reiter H, Berghold A, Aberer W. Disease spectrum in patients with elevated serum tryptase levels. *Australas J Dermatol* 2015;56:7-13.
100. Dugas-Breit S, Przybilla B, Dugas M, Arnold A, Pfundstein G, Kuchenhoff H, et al. Serum concentration of baseline mast cell tryptase: evidence for a decline during long-term immunotherapy for Hymenoptera venom allergy. *Clin Exp Allergy* 2010;40:643-9.
101. Vitte J, Bongrand P. Serum tryptase determination in patients with acute allergic reactions. *J Allergy Clin Immunol* 2013;131:1714.
102. Vitte J. Human mast cell tryptase in biology and medicine. *Mol Immunol* 2015; 63:18-24.
103. Urade Y, Hayaishi O. Biochemical, structural, genetic, physiological, and pathophysiological features of lipocalin-type prostaglandin D synthase. *Biochim Biophys Acta* 2000;1482:259-71.
104. Taba Y, Sasaguri T, Miyagi M, Abumiya T, Miwa Y, Ikeda T, et al. Fluid shear stress induces lipocalin-type prostaglandin D(2) synthase expression in vascular endothelial cells. *Circ Res* 2000;86:967-73.
105. Gallant MA, Samadfam R, Hackett JA, Antoniou J, Parent JL, de Brum-Fernandes AJ. Production of prostaglandin D(2) by human osteoblasts and modulation of osteoprotegerin, RANKL, and cellular migration by DP and CRTH2 receptors. *J Bone Miner Res* 2005;20:672-81.
106. Mahmud I, Ueda N, Yamaguchi H, Yamashita R, Yamamoto S, Kanaoka Y, et al. Prostaglandin D synthase in human megakaryoblastic cells. *J Biol Chem* 1997; 272:28263-6.
107. Mohri I, Kadoyama K, Kanekiyo T, Sato Y, Kagitani-Shimono K, Saito Y, et al. Hematopoietic prostaglandin D synthase and DP1 receptor are selectively upregulated in microglia and astrocytes within senile plaques from human patients and in a mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* 2007;66:469-80.
108. Shimura C, Satoh T, Igawa K, Aritake K, Urade Y, Nakamura M, et al. Dendritic cells express hematopoietic prostaglandin D synthase and function as a source of prostaglandin D2 in the skin. *Am J Pathol* 2010;176:227-37.
109. Luna-Gomes T, Magalhaes KG, Mesquita-Santos FP, Bakker-Abreu I, Samico RF, Molinaro R, et al. Eosinophils as a novel cell source of prostaglandin D2: autocrine role in allergic inflammation. *J Immunol* 2011;187:6518-26.
110. Tanaka K, Ogawa K, Sugamura K, Nakamura M, Takano S, Nagata K. Cutting edge: differential production of prostaglandin D-2 by human helper T cell subsets. *J Immunol* 2000;164:2277-80.
111. Van der Donk EMM, Blok W, Kok PTM, Bruijnzeel PLB. Leukotriene C₄ formation by enriched human basophil preparations from normal and asthmatic subjects. *Prostaglandins Leukot Essent Fatty Acids* 1991;44:11-7.
112. Benyon RC, Robinson C, Holgate ST, Church MK. Prostaglandin D2 release from human skin mast cells in response to ionophore A23187. *Br J Pharmacol* 1987;92: 635-8.
113. Roberts LJ, Sweetman BJ. Metabolic fate of endogenously synthesized prostaglandin D2 in a human female with mastocytosis. *Prostaglandins* 1985;30: 383-400.
114. Roberts LJ II, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D2 in patients with systemic mastocytosis. *N Engl J Med* 1980;303:1400-4.
115. Nittner-Marszalska M, Cichocka-Jaroszk E, Sanak M, Wujczyk M, Dor-Wojnarowska A, Lis G, et al. 9 α ,11 β -PGF₂, a prostaglandin D2 metabolite, as a marker of mast cell activation in bee venom-allergic patients. *Arch Immunol Ther Exp (Warsz)* 2015;63:317-25.
116. Robinson C, Benyon RC, Holgate ST, Church MK. The IgE- and calcium-dependent release of eicosanoids and histamine from human purified cutaneous mast cells. *J Invest Dermatol* 1989;93:397-404.
117. Benyon RC, Robinson C, Church MK. Differential release of histamine and eicosanoids from human skin mast cells activated by IgE-dependent and non-immunological stimuli. *Br J Pharmacol* 1989;97:898-904.
118. Eggleston PA, Kagey-Sobotka A, Proud D, Adkinson NF Jr, Lichtenstein LM. Disassociation of the release of histamine and arachidonic acid metabolites from osmotically activated basophils and human lung mast cells. *Am Rev Respir Dis* 1990;141:960-4.
119. Lam BK, Owen WF Jr, Austen KF, Soberman RJ. The identification of a distinct export step following the biosynthesis of leukotriene C4 by human eosinophils. *J Biol Chem* 1989;264:12885-9.
120. Penrose JF. LTC₄ synthase. *Enzymology, biochemistry, and molecular characterization*. *Clin Rev Allergy Immunol* 1999;17:133-52.
121. Rabinovitch N. Urinary leukotriene E4. *Immunol Allergy Clin North Am* 2007; 27:651-64, vii.
122. Tolar J, Tope WD, Neglia JP. Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004;350:735-6.
123. Turner PJ, Kemp AS, Rogers M, Mehr S. Refractory symptoms successfully treated with leukotriene inhibition in a child with systemic mastocytosis. *Pediatr Dermatol* 2012;29:222-3.
124. Laidlaw TM, Kidder MS, Bhattacharyya N, Xing W, Shen S, Milne GL, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood* 2012;119:3790-8.
125. Liu T, Kanaoka Y, Barrett NA, Feng C, Garofalo D, Lai J, et al. Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol* 2015;195:3537-45.
126. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *Clin Exp Allergy* 2002;32:1491-6.
127. Ono E, Taniguchi M, Mita H, Fukutomi Y, Higashi N, Miyazaki E, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. *Clin Exp Allergy* 2009;39:72-80.
128. Valent P, Sperr WR, Sotlar K, Reiter A, Akin C, Gotlib J, et al. The serum tryptase test: an emerging robust biomarker in clinical hematology. *Expert Rev Hematol* 2014;7:683-90.
129. Gonzalo-Garjio MA, Perez-Rangel I, Alvarado-Izquierdo MI, Perez-Calderon R, Sanchez-Vega S, Zambonino MA. Metrorrhagia as an uncommon symptom of anaphylaxis. *J Investig Allergol Clin Immunol* 2010;20:540-1.
130. Carvalhosa AB, Aouba A, Damaj G, Canioni D, Brouzes C, Gyan E, et al. A French National Survey on clotting disorders in mastocytosis. *Medicine (Baltimore)* 2015;94:e1414.
131. Marotta V, Zatelli MC, Sciammarella C, Ambrosio MR, Bondanelli M, Colao A, et al. Chromogranin A as circulating marker for diagnosis and management of neuroendocrine neoplasms: more flaws than fame. *Endocr Relat Cancer* 2018; 25:R11-29.
132. Hanjra P, Lee CR, Maric I, Carter M, Olivera A, Metcalfe DD, et al. Chromogranin A is not a biomarker of mastocytosis. *J Allergy Clin Immunol Pract* 2018;6:687-9.e4.
133. Ind PW, Brown MJ, Lhoste FJ, Macquin I, Dollery CT. Concentration effect relationships of infused histamine in normal volunteers. *Agents Actions* 1982;12: 12-6.
134. Poli C, Laurichesse M, Rostan O, Rossille D, Jeannin P, Drouet M, et al. Comparison of two enzymatic immunoassays, high resolution mass spectrometry method and radioimmunoassay for the quantification of human plasma histamine. *J Pharm Biomed Anal* 2016;118:307-14.
135. Keyzer JJ, Wolthers BG, Muskiet FA, Breukelman H, Kauffman HF, de Vries K. Measurement of plasma histamine by stable isotope dilution gas chromatography-mass spectrometry: methodology and normal values. *Anal Biochem* 1984;139: 474-81.
136. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging* 1999;15:15-28.
137. Boustani M, Hall KS, Lane KA, Aljadhey H, Gao S, Unverzagt F, et al. The association between cognition and histamine-2 receptor antagonists in African Americans. *J Am Geriatr Soc* 2007;55:1248-53.
138. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015;175:401-7.
139. Wu YH, Wang CJ, Hung CH, Chen LY, Lin MH, Wang PN, et al. Association between using medications with anticholinergic properties and short-term cognitive decline among older men: a retrospective cohort study in Taiwan. *Geriatr Gerontol Int* 2017;17(suppl 1):57-64.
140. Richardson K, Fox C, Maidment I, Steel N, Loke YK, Arthur A, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315.
141. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A systematic review of amnesic and non-amnesic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging* 2012; 29:639-58.
142. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-32.
143. Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis—a single-centre experience. *Clin Exp Allergy* 2014;44:121-9.
144. Bonadonna P, Bonifacio M, Lombardo C, Zanotti R. Hymenoptera anaphylaxis and C-kit mutations: an unexpected association. *Curr Allergy Asthma Rep* 2015;15:49.
145. Rajan JP, Simon RA, Bosso JV. Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014;2:168-71.

146. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: practical recommendations. *Am J Clin Dermatol* 2011;12:259-70.
147. Gulen T, Akin C. Pharmacotherapy of mast cell disorders. *Curr Opin Allergy Clin Immunol* 2017;17:295-303.
148. Triggiani M, Montagni M, Parente R, Ridolo E. Anaphylaxis and cardiovascular diseases: a dangerous liaison. *Curr Opin Allergy Clin Immunol* 2014;14:309-15.
149. Ting S. Ketotifen and systemic mastocytosis. *J Allergy Clin Immunol* 1990;85:818.
150. Siebenhaar F, Fortsch A, Krause K, Weller K, Metz M, Magerl M, et al. Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial. *Allergy* 2013;68:949-52.
151. Nurmatov UB, Rhatigan E, Simons FE, Sheikh A. H1-antihistamines for primary mast cell activation syndromes: a systematic review. *Allergy* 2015;70:1052-61.
152. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. *Ann Intern Med* 1979;90:769-71.
153. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. *J Allergy Clin Immunol* 1981;68:365-71.
154. Ko K, Kim HJ, Ho PS, Lee SO, Lee JE, Min CR, et al. Discovery of a novel highly selective histamine H4 receptor antagonist for the treatment of atopic dermatitis. *J Med Chem* 2018;61:2949-61.
155. Roberts LJ, Turk JW, Oates JA. Shock syndrome associated with mastocytosis: pharmacologic reversal of the acute episode and therapeutic prevention of recurrent attacks. *Adv Shock Res* 1982;8:145-52.
156. Lorcerie B, Arveux I, Chaffert B, Dalac S, Lambert D, Martin F. Aspirin and systemic mastocytosis. *Lancet* 1989;2:1155.
157. Butterfield JH, Kao PC, Klee GC, Yocum MW. Aspirin idiosyncrasy in systemic mast cell disease: a new look at mediator release during aspirin desensitization. *Mayo Clin Proc* 1995;70:481-7.
158. Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol* 1990;85:852-5.
159. Soter NA, Austen KF, Wasserman SI. Oral disodium cromoglycate in the treatment of systemic mastocytosis. *N Engl J Med* 1979;301:465-9.
160. Welch EA, Alper JC, Bogaars H, Farrell DS. Treatment of bullous mastocytosis with disodium cromoglycate. *J Am Acad Dermatol* 1983;9:349-53.
161. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117:134-40.
162. Castells MC, Hornick JL, Akin C. Anaphylaxis after hymenoptera sting: is it venom allergy, a clonal disorder, or both? *J Allergy Clin Immunol Pract* 2015;3:350-5.
163. da Silva EN, Randall KL. Omalizumab mitigates anaphylaxis during ultrarush honey bee venom immunotherapy in monoclonal mast cell activation syndrome. *J Allergy Clin Immunol Pract* 2013;1:687-8.
164. Klunker S, Saggart LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR, et al. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007;120:688-95.
165. Kontou-Fili K. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis. *Allergy* 2008;63:376-8.
166. Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. *Ann Allergy Asthma Immunol* 2012;108:383-4.
167. Broesby-Olsen S, Vestergaard H, Mortz CG, Jensen B, Havelund T, Hermann AP, et al. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. *Allergy* 2018;73:230-8.
168. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. *J Allergy Clin Immunol* 2007;119:1550-1.
169. Douglass JA, Carroll K, Voskamp A, Bourke P, Wei A, O'Hehir RE. Omalizumab is effective in treating systemic mastocytosis in a nonatopic patient. *Allergy* 2010;65:926-7.
170. Kluin-Nelemans HC, Jansen JH, Breukelman H, Wolthers BG, Kluin PM, Kroon HM, et al. Response to interferon alfa-2b in a patient with systemic mastocytosis. *N Engl J Med* 1992;326:619-23.
171. Tefferi A, Li CY, Butterfield JH, Hoagland HC. Treatment of systemic mast-cell disease with cladribine. *N Engl J Med* 2001;344:307-9.
172. Kluin-Nelemans HC, Oldhoff JM, van Doormaall JJ, 't Wout JW, Verhoef G, Gerits WB, et al. Cladribine therapy for systemic mastocytosis. *Blood* 2003;102:4270-6.
173. Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood* 2015;126:1009-16, quiz 50.
174. Peter B, Winter GE, Blatt K, Bennett KL, Stefanzi G, Rix U, et al. Target interaction profiling of midostaurin and its metabolites in neoplastic mast cells predicts distinct effects on activation and growth. *Leukemia* 2016;30:464-72.
175. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med* 2016;374:2530-41.
176. Jawhar M, Schwaab J, Naumann N, Horny HP, Sotlar K, Haferlach T, et al. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. *Blood* 2017;130:137-45.
177. Valent P, Akin C, Hartmann K, George TI, Sotlar K, Peter B, et al. Midostaurin: a magic bullet that blocks mast cell expansion and activation. *Ann Oncol* 2017;28:2367-76.
178. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia* 2018;32:470-8.
179. van Anrooij B, Oude Elberink JNG, Span LFR, de Monchy JGR, Rosati S, Mulder AB, et al. Midostaurin in patients with indolent systemic mastocytosis: an open-label phase 2 trial. *J Allergy Clin Immunol* 2018;142:1006-8.e7.
180. Kasamon YL, Ko CW, Subramaniam S, Ma L, Yang Y, Nie L, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. *Oncologist* 2018;23:1511-9.
181. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol* 2019;94:363-77.
182. Lortholary O, Chandesris MO, Bulai Livideanu C, Paul C, Guillet G, Jassem E, et al. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study. *Lancet* 2017;389:612-20.
183. Akin C, Metcalfe DD. The biology of Kit in disease and the application of pharmacogenetics. *J Allergy Clin Immunol* 2004;114:13-9.
184. Regan JA, Cao Y, Dispenza MC, Ma S, Gordon LI, Petrich AM, et al. Ibrutinib, a Bruton's tyrosine kinase inhibitor used for treatment of lymphoproliferative disorders, eliminates both aeroallergen skin test and basophil activation test reactivity. *J Allergy Clin Immunol* 2017;140:875-9.e1.
185. Baird JH, Gotlib J. Clinical validation of KIT inhibition in advanced systemic mastocytosis. *Curr Hematol Malig Rep* 2018;13:407-16.
186. Fletcher L, Borate U. Novel approaches for systemic mastocytosis. *Curr Opin Hematol* 2019;26:112-8.
187. Legrand F, Cao Y, Wechsler JB, Zhu X, Zimmermann N, Rampertaap S, et al. Sialic acid-binding immunoglobulin-like lectin (Siglec) 8 in patients with eosinophilic disorders: receptor expression and targeting using chimeric antibodies. *J Allergy Clin Immunol* 2019;143:2227-37.e10.
188. Youngblood BA, Brock EC, Leung J, Falahati R, Bryce PJ, Bright J, et al. AK002, a humanized sialic acid-binding immunoglobulin-like lectin-8 antibody that induces antibody-dependent cell-mediated cytotoxicity against human eosinophils and inhibits mast cell-mediated anaphylaxis in mice. *Int Arch Allergy Immunol* 2019 [Epub ahead of print].
189. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am* 2014;34:283-95.
190. Escribano L, Alvarez-Twose I, Sanchez-Munoz L, Garcia-Montero A, Nunez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. *J Allergy Clin Immunol* 2009;124:514-21.
191. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol* 2009;84:790-4.
192. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-36.
193. Pardanani A, Tefferi A. Systemic mastocytosis in adults: a review on prognosis and treatment based on 342 Mayo Clinic patients and current literature. *Curr Opin Hematol* 2010;17:125-32.
194. Pardanani A, Tefferi A. A critical reappraisal of treatment response criteria in systemic mastocytosis and a proposal for revisions. *Eur J Haematol* 2010;84:371-8.
195. Hannah-Shmouni F, Stratakis CA, Koch CA. Flushing in (neuro)endocrinology. *Rev Endocr Metab Disord* 2016;17:373-80.
196. Izikson L, English JC 3rd, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. *J Am Acad Dermatol* 2006;55:193-208.
197. Sadeghian A, Rouhana H, Oswald-Stumpf B, Boh E. Etiologies and management of cutaneous flushing: malignant causes. *J Am Acad Dermatol* 2017;77:405-14.
198. adegghian A, Rouhana H, Oswald-Stumpf B, Boh E. Etiologies and management of cutaneous flushing: nonmalignant causes. *J Am Acad Dermatol* 2017;77:391-402.
199. Wilkin JK. Flushing reactions: consequences and mechanisms. *Ann Intern Med* 1981;95:468-76.

200. Mooney E. The flushing patient. *Int J Dermatol* 1985;24:549-54.
201. Ikizoglu G. Red face revisited: flushing. *Clin Dermatol* 2014;32:800-8.
202. Welsh O, Vera-Cabrera L. Red face and fungi infection. *Clin Dermatol* 2014;32:734-8.
203. Huguet I, Grossman A. Management of endocrine disease: flushing: current concepts. *Eur J Endocrinol* 2017;177:R219-29.
204. Smith JA Jr. Management of hot flushes due to endocrine therapy for prostate carcinoma. *Oncology* 1996;10:1319-22, discussion 24.
205. Graham-Brown R. Dermatologic problems of the menopause. *Clin Dermatol* 1997;15:143-5.
206. Hedlund PO. Side effects of endocrine treatment and their mechanisms: castration, antiandrogens, and estrogens. *Prostate Suppl* 2000;10:32-7.
207. Solcia E, Fiocca R, Rindi G, Villani L, Cornaggia M, Capella C. The pathology of the gastrointestinal endocrine system. *Endocrinol Metab Clin North Am* 1993;22:795-821.
208. Solcia E, Fiocca R, Rindi G, Villani L, Luinetti O, Burrell M, et al. Endocrine tumors of the small and large intestine. *Pathol Res Pract* 1995;191:366-72.
209. Tiensuu Janson EM, Oberg KE. Carcinoid tumours. *Baillieres Clin Gastroenterol* 1996;10:589-601.
210. Boushey RP, Dackiw AP. Carcinoid tumors. *Curr Treat Options Oncol* 2002;3:319-26.
211. Heymann WR. Flushing, pheochromocytoma, and the dermatologist. *J Am Acad Dermatol* 2006;55:1075-7.
212. Boutzios G, Kaltsas G. Clinical syndromes related to gastrointestinal neuroendocrine neoplasms. *Front Horm Res* 2015;44:40-57.
213. Knapp TR, Middleton RK. Adverse effects of sustained-release niacin. *DICP* 1991;25:253-4.
214. Evans JD, Hill SR. A comparison of the available phosphodiesterase-5 inhibitors in the treatment of erectile dysfunction: a focus on avanafil. *Patient Prefer Adherence* 2015;9:1159-64.
215. Bosron WF, Lumeng L, Li TK. Genetic polymorphism of enzymes of alcohol metabolism and susceptibility to alcoholic liver disease. *Mol Aspects Med* 1988;10:147-58.
216. Quak SH, Prabhakaran K, Kwok R, O'Reilly AP. Vasoactive intestinal peptide secreting tumours in children: a case report with literature review. *Aust Paediatr J* 1988;24:55-8.
217. Colachis SC 3rd. Autonomic hyperreflexia with spinal cord injury. *J Am Paraplegia Soc* 1992;15:171-86.
218. Tascilar N, Tekin NS, Erdem Z, Alpaya A, Emre U. Unnoticed dysautonomic syndrome of the face: Harlequin syndrome. *Auton Neurosci* 2007;137:1-9.
219. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia* 2015;29:1223-32.
220. Corless CL, Harrell P, Lacouture M, Bainbridge T, Le C, Gatter K, et al. Allele-specific polymerase chain reaction for the imatinib-resistant KIT D816V and D816F mutations in mastocytosis and acute myelogenous leukemia. *J Mol Diagn* 2006;8:604-12.
221. Kristensen T, Vestergaard H, Bindslev-Jensen C, Moller MB, Broesby-Olsen S. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol* 2014;89:493-8.
222. Kristensen T, Vestergaard H, Moller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. *J Mol Diagn* 2011;13:180-8.
223. Schumacher JA, Elenitoba-Johnson KS, Lim MS. Detection of the c-kit D816V mutation in systemic mastocytosis by allele-specific PCR. *J Clin Pathol* 2008;61:109-14.
224. Van den Poel B, Kochuyt AM, Del Biondo E, Dewaele B, Lierman E, Tousseyn T, et al. Highly sensitive assays are mandatory for the differential diagnosis of patients presenting with symptoms of mast cell activation: diagnostic work-up of 38 patients. *Acta Clin Belg* 2017;72:123-9.
225. Carter MC, Bai Y, Ruiz-Estevés KN, Scott LM, Cantave D, Bolan H, et al. Detection of KIT D816V in peripheral blood of children with manifestations of cutaneous mastocytosis suggests systemic disease. *Br J Haematol* 2018;183:775-82.
226. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012;157:275-80.
227. Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 2018;141:180-8.e3.