Position Paper: Diagnosis and Investigation of Mast Cell Activation Disorders and Syndrome

This document has been developed by ASCIA, the peak professional body of clinical immunology/allergy specialists in Australia and New Zealand. ASCIA information is based on published literature and expert review, is not influenced by commercial organisations and is not intended to replace medical advice. Patient/carer support organisations are listed at www.allergy.org.au/patients/patient-support-organisations .

Key points

- Mast cell activation syndrome (MCAS) can be defined as a heterogenous group of disorders presenting with episodic symptoms involving multiple systems that are attributable to mast cell mediator release (e.g. flushing, pruritus, wheeze, gastrointestinal symptoms).
- The definition and criteria for MCAS have evolved over time, and there are established diagnostic criteria for MCAS.
- Many patients may have symptoms seen in MCAS but do not meet criteria for MCAS.
- Diagnosis of MCAS based on consensus criteria requires clinical assessment in conjunction with laboratory assessments, of which tryptase is the most accessible and validated test within Australia. Other laboratory tests are inferior in sensitivity and specificity, are without clinically validated cut-offs established for diagnosis in MCAS and are generally not offered within Australia due to their poor clinical utility.
- When a diagnosis of MCAS is being considered it is important to ensure differential diagnoses with overlapping clinical features have been investigated. If a patient meets criteria for anaphylaxis this should be managed as per usual standard of care.

1. Background - mast cells

Mast cells are long-living innate immune cells of myeloid lineage that reside within the connective tissues.[1] Although most well recognised for their key role in IgE-mediated immediate allergic responses, mast cells are also involved in tissue inflammation and repair, vascular homeostasis and host defence against various pathogens including parasites and bacteria.[1] They originate from haematopoietic stem cells of the bone marrow, and mature into mast cells under influence of c-kit ligand and stem cell factor.[1]

Mast cells contain various mediators within cytoplasmic granules that are released upon activation. Mediators include tryptase, histamine, heparin, prostaglandins, proteases and various cytokines, which have varied effects on different organs.[1, 2] Release of mediators results in typical effects well recognised in IgE-mediated immediate allergic reactions such increased vascular permeability, pruritus, increased mucous production leading to airway constriction and congestion, cutaneous urticaria and angioedema, and gastrointestinal upset.[1, 3, 4]

Mast cells can be activated by both IgE-mediated and non-IgE mediated mechanisms. The classic mechanism is via antigen that crosslinks IgE antibodies bound to high-affinity FcεRI receptors on mast cells. Once crosslinking occurs, downstream signalling occurs that ultimately results in degranulation.[1, 3] Mast cells are also activated via non-IgE mediated mechanisms including via IgG, complement, microbial components, drugs, toxins, hormones, physical and emotional stimuli, hormones and cytokines.[2, 5]

Pathologic activation of mast cells can occur in two key settings: (1) Increased numbers or increased function in the absence of usual triggers; or (2) activation and release of mediators out of proportion to a stimulus e.g. infections, venom, allergens.[3] Anaphylaxis is included in this latter example.[3]

2. Mast cell activation disorders

The terminology and nomenclature regarding mast cell activation disorders can lead to confusion.

- **Mast cell activation (MCA*)*** – release of mediators from mast cells due to activation; whereby activation can be local (e.g. urticaria, allergic rhinitis, asthma) or systemic (e.g. anaphylaxis) with varying severity.[5] Markers of activation such as mast cell tryptase (tryptase) increase in level during an activation event.[5]
- **Mast cell activation disorders (MCAD**) – an umbrella term describing a group of disorders where mast cell activation occurs, which includes mast cell activation syndrome.
- **Mast cell activation syndrome (MCAS)** – a syndrome defined by specific criteria, where there is a history of systemic severe and recurrent mast cell activation with evidence of mast cell mediator release and response to medications directed at mast cell mediators and their effects.[5]

Mast cell activation disorders can be classified as primary, secondary, or idiopathic in aetiology (see Table 1).

Primary mast cell activation disorders are a heterogenous group of disorders due to defective mast cell progenitors, resulting in clonally increased numbers or increased function of mast cells.[3, 6] Symptoms in patients with primary MCAD relate to effects of the mediators and include flushing, hypotension, gastrointestinal cramping, vomiting, diarrhoea and tachycardia.[3] Contrasting with secondary MCAD, chronic urticaria and angioedema are <u>not</u> common in primary MCAD (including systemic mastocytosis)[3].

Secondary mast cell activation disorder patients have normal mast cell progenitors, and usually mast cell numbers are normal.[3] However they are activated by micro-environmental triggers,[6] or in other words, the population of mast cells is “hyperresponsive”.[2] In these diseases mast cells are recruited through a non-mast cell dependent, extrinsic mechanism.[2] Examples of secondary mast cell activation disorders include allergic disorders (e.g. IgE or non-IgE mediated), physical urticarias and chronic spontaneous urticaria.[2] Symptoms may be sporadic or chronic.[2]

Idiopathic mast cell activation disorder occurs where there is no identifiable cause.[6] This can manifest as anaphylaxis, angioedema, urticaria or mast cell activation syndrome. This diagnosis should be considered when there is recurrent anaphylaxis with no identifiable clonal or mast cell aetiology.[2]

Table 1 – Classification of mast cell disorders [4, 7]

Primary mast cell disorders (increased numbers of identical mast cells [clones], or increased internal signalling of mast cells)	• Cutaneous mastocytosis
	  ○ More common in children, with more than 90% of cases resolving by adolescence.[3]
	• Systemic mastocytosis
	  ○ Associated with gain-of-function mutations in proto-oncogene c-*KIT*, which has a role in proliferation and differentiation of mast cells.[3] KIT D816V is detected in >90% of all cases,[8] but other mutations may be implicated
	• Mastocytoma
	• Mast cell leukaemia
	• Monoclonal mast cell activation syndromes (MMAS)
	  ○ Present with symptoms of mast cell activation and lack cutaneous findings. Have either the KIT D816V mutation or CD25+ mast cells in their bone marrow.[3]
	  ○ Meet one or two minor diagnostic criteria for mastocytosis, but do not meet full criteria.[9]

Secondary mast cell disorders
(normal mast cells and normal numbers, but "hyper-responsive" to external stimuli; have a condition that can induce mast cell activation)
	• IgE-mediated hypersensitivity reactions
	  ○ e.g. food, venom, drug-induced
	• IgE-independent reactions (other receptors/pathways involved)
	  ○ e.g. vancomycin, opioids
	• Mast cell hyperplasia
	  ○ associated with neoplasia, autoimmune conditions, chronic infections

Idiopathic (no identifiable clonal or underlying mast cell pathology)	• Includes idiopathic anaphylaxis • Includes mast cell activation syndrome (a syndrome defined by specific criteria)

3. Mast cell activation syndrome (MCAS)

Mast cell activation syndrome (MCAS) has been defined as a heterogenous group of disorders of varied causes that present with episodic symptoms involving multiple systems that are attributable to mast cell mediator release.[3] There is no single symptom that is considered specific for mast cell activation syndrome.[3]

An internationally endorsed position paper including definitions for MCAS was published in 2012 (see below).[4] It is agreed that MCAS should be considered a diagnosis of exclusion.[6, 7, 10] Therefore for a diagnosis of MCAS, the diagnostic criteria for primary, secondary, and other well-defined idiopathic mast cell activation disorders (MCAD) must be ruled out first, and in addition the criteria for MCAS must be met.[5, 7]

A common clinical scenario is that patients with varied chronic rather than episodic symptoms involving multiple organ systems with no clear unifying cause are referred on for investigation of MCAS.

Symptoms of concern may include flushing, unexplained hypotension and fluctuations in blood pressure, itching, chronic fatigue, fibromyalgia-like pain, headache, various types of rashes, intolerances to foods, medications, environmental triggers, and neuropsychiatric features.[2, 3, 10, 11]

In recent years patients presenting with such symptoms with no other clear cause identified after extensive review have increasingly been labelled with so called “MCAS”,[2] without meeting the consensus criteria for MCAS which will be discussed below. Incorrectly diagnosed patients may then receive unnecessary treatments or inappropriate treatment, or may not receive treatment for other medical conditions that may present with similar clinical features.[11]

Additionally, patients with some forms of Ehlers-Danlos syndrome and postural orthostatic tachycardia syndrome (POTS), may describe features that overlap with those of mast cell activation (e.g. flushing and gastrointestinal symptoms).[3, 6, 11] There is currently no scientific evidence that these conditions are associated with dysregulated mast cells and chronic mast cell mediator release, and these conditions should not be used as part of the criteria to diagnose MCAS.[3, 11, 12]

Differential diagnoses for MCAS

Of importance, there is considerable overlap between symptoms occurring in MCAS and various other clinical entities. For example flushing can occur in various neuroendocrine or neoplastic conditions such as carcinoid syndrome, medullary thyroid cancer, renal cell carcinoma and phaeocromocytoma.[10] Other conditions with similar symptoms to those in MCAS include testosterone or estrogen deficiency, inflammatory bowel disease and allergic reactions.[2]

It is therefore essential that tailored workup based on clinical assessment has been appropriately performed to rule out these other differentials. Some examples are provided below in Table 2, but additional discussion is beyond the scope of this paper. Further detail can be obtained from an excellent review by Picard, et al. (2013).[7]

Table 2 – Examples of differentials and investigations for mast cell activation disorders (adapted from Picard, et al.)[7, 13]

Differential	Relevant signs and symptoms	Tests
Carcinoid syndrome	Flushing, diarrhoea, wheeze	• Plasma 5-hydroxyindoleatic acid (HIAA) • 24-hour urinary HIAA
Phaeochromocytoma	Flushing, hypertension, tachycardia	• Plasma metanephrines • 24 hr Urinary metanephrines and catecholamines
Menopause	Flushing	• FSH, LH, oestrogen
Medullary carcinoma of thyroid	Flushing	• Serum calcitonin
Cardiac arrhythmias	Tachycardia, presyncope/syncope, hypotension	• ECG
Postural tachycardia syndrome	Tachycardia, presyncope/syncope, hypotension	• Tilt table test
Asthma	Wheeze	• Pulmonary function tests
Vocal cord dysfunction	Wheeze, stridor	• Laryngoscopy, spirometry
Hereditary angioedema	Angioedema, throat tightness	• C4 +/- C1 inhibitor levels and/or function
Primary bowel disease (e.g. irritable bowel syndrome, inflammatory bowel disease)	Diarrhoea	• Endoscopy with biopsy
Neuroendocrine tumours	May include flushing	• Serum vasoactive intestinal peptide
Hereditary alpha tryptasemia (HAT) – can co-exist with MCAS	Flushing, urticaria, pruritus, hypotension, tachycardia, syncope/presyncope, gastrointestinal symptoms	• Baseline mast cell tryptase • Increased *TPSAB1* gene copy number (not currenty available in Australia)

MCAS and hereditary α tryptasemia

A proportion of patients diagnosed with MCAS may have a co-existing recently described genetic trait hereditary alpha tryptasemia (HAT)[3]. Patient with HAT have an increased copy number of the gene *TPSAB1* on a single allele – the gene encoding alpha-tryptase.[14] Confirmation of HAT is performed by genetic testing generally requested via tertiary centres. The clinical phenotype for HAT is still being elucidated, though common features include systemic reactions to stinging insects, respiratory wheeze, atopy, skin flushing and itching, symptoms of autonomic dysfunction, and inflammatory bowel syndrome-like abdominal symptoms.[5, 14, 15] HAT patients typically have a basal serum tryptase > 8 ng/ml,[16] which notably is below the common cutoff of 11.4 ng/ml used in labs within Australia.

Although the exact interplay between HAT and MCAS is uncertain, it has been hypothesised that HAT may be a risk factor for MCAS, though the clinical phenotype for HAT appears broader than that described for MCAS.[13] It has been suggested that those with MCAS should be investigated for HAT,[13] and HAT has been linked to elevated risk to develop anaphylaxis and MCAS.[5] More research is needed in this area. Testing for TPSAB1 gene copy number is currently not available in Australia and the results of the test do not affect management of patients with a constitutively elevated baseline mast cell tryptase.

4. Diagnosis of MCAS

Diagnostic criteria

The definitions and criteria for diagnosis of mast cell activation disorders and mast cell activation syndrome have evolved over time. The key considerations to make a diagnosis of MCAS include severe, recurrent symptoms of mast cell activation (typically anaphylaxis), along with confirmation of mast cell lineage involvement via detection of mast cell mediators.[5]

In an attempt to provide a consensus on the diagnosis criteria for MCAS, an international consensus group (Valent et. al 2012) proposed the following criteria, where all three criteria should be fulfilled for MCAS to be diagnosed.[17] The criteria have since been validated in various studies.[5]

- Typical signs and symptoms of mast cell mediator release (affecting at least 2 organ systems)
    - Skin: flushing, pruritus, urticaria, angioedema
    - Cardiovascular: hypotension
    - Respiratory: wheezing, objective upper-airway involvement (e.g. stridor, laryngeal oedema)
    - GI: diarrhea
    - Naso-ocular: pruritus
- Objective evidence of mediator release
    - Elevated serum tryptase: 20% + 2 ng/mL above baseline
- Elevated 24-hour urinary histamine metabolites (N-methylhistamine)*
    - Elevated 24-hour urinary prostaglandins (prostaglandin D2; 11β platelet-derived growth factor 2α) **
- Response to therapy that blocks mast cell mediator activity
    - H1-receptor with or without H2-blockers, ketotifen, sodium cromoglicate, aspirin, and leukotriene receptor antagonists

*Although 24-hour urinary N-methylhistamine is available in Australia and is useful in investigation of systemic mastocytosis, it has demonstrated little clinical utility in investigation of MCAS,

perhaps because mast cell metabolites released immediately after mast cell activation are not collected.

** Plasma and serum assays for these prostaglandins and their metabolites are not offered by Australian laboratories, since these assays have not been clinically validated for diagnosis of MCAS and appropriate cut-offs have not been established.

The role of laboratory testing in MCAS

As previously mentioned, various mediators are produced and released by mast cells when activated. Various mediators can be detected in serum or urine and thus used as biomarkers for mast cell activation.[5] Such markers vary in sensitivity and specificity for mast cell activation.[5] Unfortunately, non-validated laboratory tests have been used in some cases to make a diagnosis of MCAS which can cause confusion for both patients and clinicians.[11]

Mast cell tryptase (trypase) remains the marker of choice for laboratory investigation of MCAS as per international consensus.[4] This is due to issues with sensitivity, specificity and established reference ranges for other markers of mast cell activation such as urinary metabolites of histamine, blood prostaglandin D_2, metabolite 11-β-prostaglandin $F_{2}\alpha$, and urinary leukotriene E4.[4]

Markers of mast cell activation are discussed in further detail in Table 3 below.

Importantly, reference ranges for mediators other than tryptase have not been established for mast cell activation,[3] and other laboratory tests not mentioned in Table 3 have not been validated nor recommended for diagnosis of MCAS.

A rise in tryptase level occurs following mast cell activation, peaking within 4 hours and returning to normal levels by 24 hours. Therefore ideally, tryptase should be measured:

- between 30 mins and 2 hours after an event but can still be useful if elevated above the baseline up to 6 hours after the event.
- A baseline measurement for comparison is required and should be collected either before an event or at least 24 hours after the resolution of all symptoms and signs related to the event, to ensure a subsequent fall to baseline levels.[7]
- Criteria of an elevation in tryptase least 20% + 2ng/mL over baseline is considered indicative of mast cell activation as per the aforementioned consensus guidelines.[4]

Unfortunately, the majority of patients describing symptoms relating to potential MCAS have either slight elevations in tryptase not considered a significant change from baseline, or no increase from their baseline - hence not meeting criteria for MCAS.[5] Therefore, in such cases a diagnosis of MCAS cannot be made.[5]

To summarise, the majority of laboratory markers of mast cell activation that have been described in the literature are either not recommended, or not readily available for assessment in clinical laboratories within Australia, because reference intervals for normal individuals and those with MCAS have not been established and because errors associated with specimen collection and handling can significantly alter results.

Table 3: Markers of mast cell activation

Marker	
Serum mast cell tryptase (tryptase)	• Marker of choice as per international consensus[4] • Specific marker of mast cell activation and/or mast cell burden[3] • Levels more than 11.4ug/L are considered increased. • Criteria of at least 20% + 2ng/mL over baseline is considered indicative of mast cell activation.[4] • Can also be increased due to other reasons e.g. renal failure, hereditary α tryptasemia and clonal mast cell disorders e.g. systemic mastocytosis, all of which lead to elevated baseline tryptase levels.
Urinary metabolites of histamine (e.g. N-methyl histamine and 1-methyl-4-imidazole acetic acid)	• 24-hour collection recommended • Relatively specific for mast cell activation[3] • Reference intervals and cut-offs for diagnosis of MCAS not established • Although 24-hour urinary N-methylhistamine is available in Australia and is useful in investigation of systemic mastocytosis, it has demonstrated little clinical utility in investigation of MCAS, perhaps because mast cell metabolites released immediately after mast cell activation are not collected.
Blood histamine levels	• Histamine lacks sensitivity and specificity[4] and is unstable, with a short half-life (1-2 minutes) • May be derived from basophils at baseline rather than mast cells[3, 4] • Can have spuriously elevated results relating to storage and collection[3] • Reference intervals and cut-offs for MCAS are not established • Of no value in investigation of mast-cell disorders
Urinary histamine levels	• Histamine lacks sensitivity and specificity[4] and is unstable, with a short half-life (1-2 minutes) • Can be affected by microbial contamination; as well as diet and sample collection, transport & storage[3] • Reference intervals and cut-offs for MCAS are not established • Of no value in assessment of mast-cell disorders
Blood prostaglandin D_2 and metabolite 11-β-prostaglandin $F_2\alpha$	• PGD2 lacks sensitivity but is not produced by basophils[4] • Marker of mast cell activation but not specific; also produced by eosinophils and non-immune cells • Reference intervals and cut-offs for MCAS are not established • Plasma and serum assays for prostaglandins and their metabolites are not offered by Australian laboratories since these assays have not been clinically validated for diagnosis of MCAS and appropriate cut-offs have not been established.
Urinary leukotriene E4 (metabolite of leukotriene C4, lipid mediator)	• Not well correlated with mast cell activation symptoms • Cutoffs for MCAS not established • Plasma and serum assays for leukotrienes and their metabolites are not offered by Australian laboratories since these assays have not been clinically validated for diagnosis of MCAS and appropriate cut-offs have not been established.
Chromogranin A	• Resides in neuroendocrine cells, not derived from mast cells[11] • Of no value in investigation of mast cell disorders.
Heparin	• Not validated as serum marker of mast cell activation[11] • Of no value in investigation of mast cell disorders.

5. Management of MCAS

Management of MCAS varies depending on the underlying cause. For suspected primary MCAS, referral to Clinical Immunologists and Haematologists may be required for additional investigations such as a bone marrow biopsy to confirm or rule out a clonal disorder.

A detailed discussion of management of MCAS is beyond the scope of this paper, but in general the approach to management will include:

- **Identification and avoidance of triggers (e.g. allergens, physical)**
    - This can be facilitated by Immunological assessment to confirm history and to facilitate further investigations if indicated (e.g. skin prick testing, specific IgE testing if IgE-mediated reaction suspected).
    - This includes appropriate management of anaphylaxis with adrenaline autoinjector training and Anaphylaxis Action Plan if indicated.
- **Pharmacological management targeting mast cell mediators**
    - Pharmacological management is an important part of management of MCAS and patients with this syndrome should be able to demonstrate improvement and response to medications targeting mast cell mediators.3
    - This is usually trialled in a stepwise fashion under specialist guidance, and some medications can be targeted to the particular systems involved.
    - Medications that can be utilised include3, 7:
    - H1 histamine receptor antagonists (e.g. cetirizine, desloratadine, fexofenadine – non-sedating second generation agents preferred)
    - H2 histamine receptor antagonists (e.g. nizatidine, famotidine)
    - Anti-leukotriene medications (e.g. Montelukast)
    - Mast cell stabilisers (e.g. sodium cromoglicate, ketotifen)
    - There are no evidence-based dietary modifications recommended for patients with MCAS.[18]

Current consensus guidelines do not suggest any dietary modifications for MCAS.

It is not uncommon for patients to have trialled a low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) diet or a low histamine diet.[18] Such diets are commonly encouraged via social media platforms or lay literature online,[18] but there are no sufficiently well designed clinical trials or biomarkers available to assess the efficacy of such diets in MCAS. It is important to ensure patient diets are well-balanced and not excessively nutritionally restrictive, and in the setting of dietary modifications seeking input from a dietician experienced in food intolerances is recommended.

Content developed April 2024

For more information go to www.allergy.org.au/anaphylaxis

To support allergy and immunology research go to www.allergyimmunology.org.au/donate

References

1 Krystel-Whittemore M, Dileepan KN, Wood JG. Mast cell: a multi-functional master cell. *Frontiers in immunology*. 2016: 620.

2 Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. *The Journal of allergy and clinical immunology*. 2010; **126**: 1099-104.e4.

3 Akin C. Mast cell activation syndromes. *Journal of Allergy and Clinical Immunology*. 2017; **140**: 349-55.

4 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. *International archives of allergy and immunology*. 2012; **157**: 215-25.

5 Valent P, Hartmann K, Bonadonna P, Niedoszytko M, Triggiani M, Arock M*, et al.* Mast cell activation syndromes: Collegium Internationale Allergologicum update 2022. *International Archives of Allergy and Immunology*. 2022; **183**: 693-705.

6 Frieri M. Mast Cell Activation Syndrome. *Clin Rev Allergy Immunol*. 2018; **54**: 353-65.

7 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.

8 Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. *British journal of haematology*. 2018; **180**: 11-23.

9 Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K*, et al.* Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest*. 2007; **37**: 435-53.

10 Lafont E, Sokol H, Sarre-Annweiler M-E, Lecornet-Sokol E, Barete S, Hermine O*, et al.* Étiologies et orientation diagnostique devant un flush. *La Revue de médecine interne*. 2014; **35**: 303-09.

11 Weiler CR, Austen KF, Akin C, Barkoff MS, Bernstein JA, Bonadonna P*, et al.* AAAAI Mast Cell Disorders Committee Work Group Report: mast cell activation syndrome (MCAS) diagnosis and management. *Journal of Allergy and Clinical Immunology*. 2019; **144**: 883-96.

12 Jackson CW, Pratt CM, Rupprecht CP, Pattanaik D, Krishnaswamy G. Mastocytosis and mast cell activation disorders: clearing the air. *International Journal of Molecular Sciences*. 2021; **22**: 11270.

13 Kranyak A, Shuler M, Lee LW. Cutaneous Manifestations in Hereditary Alpha Tryptasemia. *Cutis*. 2023; **111**: 49-52.

14 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. *Nature genetics*. 2016; **48**: 1564-69.

15 Robey RC, Wilcock A, Bonin H, Beaman G, Myers B, Grattan C*, et al.* Hereditary alpha-tryptasemia: UK prevalence and variability in disease expression. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020; **8**: 3549-56.

16 Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. *Immunology and Allergy Clinics*. 2018; **38**: 483-95.

17 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.

18 Hamilton MJ, Scarlata K. Mast Cell Activation Syndrome-What it Is and Isn't. *Pract Gastroenterol*. 2020; **44**: 26-32.