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MAST CELL DISORDERS: OVERVIEW, CLINICAL PEARLS AND PERSPECTIVES

It has been almost 145 years since the discovery of mast cells (MC) and we continue to learn about their function and the consequences of their dysregulation. The focus of this article is to provide an overview on the current, yet evolving, classification of mast cell disorders (MCD) and provide clinical pearls and perspectives for their management for the allergist/immunologist (A/I).

THE SENTINELS OF THE IMMUNE SYSTEM

MC, first identified in 1878 by Paul Ehrlich, have mainly been viewed as effectors of allergic processes.[1] In recent decades research has revealed many other processes where these cells play essential roles, particularly as sentinels of the immune system and in the maintenance and restoration of homeostasis.[2]

MC are predominantly present at the interface between the host and the external environment, not in circulation, and, in contrast with other hematopoietic cells, they do not mature in the bone marrow but rather in the tissues where they are extensively distributed. These include the skin, conjunctiva, respiratory mucosa, gastrointestinal tract, genitourinary tract, myocardium, connective tissue surrounding blood vessels, lymphatics, nerves, smooth muscle cells, mucus glands, and hair follicles.[3] Of note, they are also present in the brain (choroid plexus, thalamus, hypothalamus, basal ganglia, vascular bed of the meninges) where they appear to act as sensors of environmental and psychological stress and first responders at sites of injury.[4]

As innate immune cells, MC can rapidly sense invading microorganisms, antigens, and toxins (venoms); recruit eosinophils, neutrophils and others to sites of inflammation; amplify complement activation; phagocyte bacteria or immobilize them by ejecting extracellular DNA traps or mast cell extracellular traps (MCETs).[2,5,6] For the adaptive immunity, MC act as antigen-presenting cells, help in the defense against parasitic infections, and lead to the activation of Th2 responses. They are also immunomodulatory by limiting the duration and magnitude of immune responses and contributing to tissue repair and angiogenesis.[1] Their role in IgE-mediated allergic/anaphylactic reactions is the most widely known and studied.[7]

Knowing the MC mediators (close to 100 biologically active mediators described to date[8])and their physiological targets and effects is key to understanding the varied symptomatology of MCD. For the purposes of this article, **Table 1** provides a non-exhaustive overview of the most relevant mediators, their physiological effects, associated signs and symptoms, and the therapies currently used to target them.[1,6,9,10,11,12]

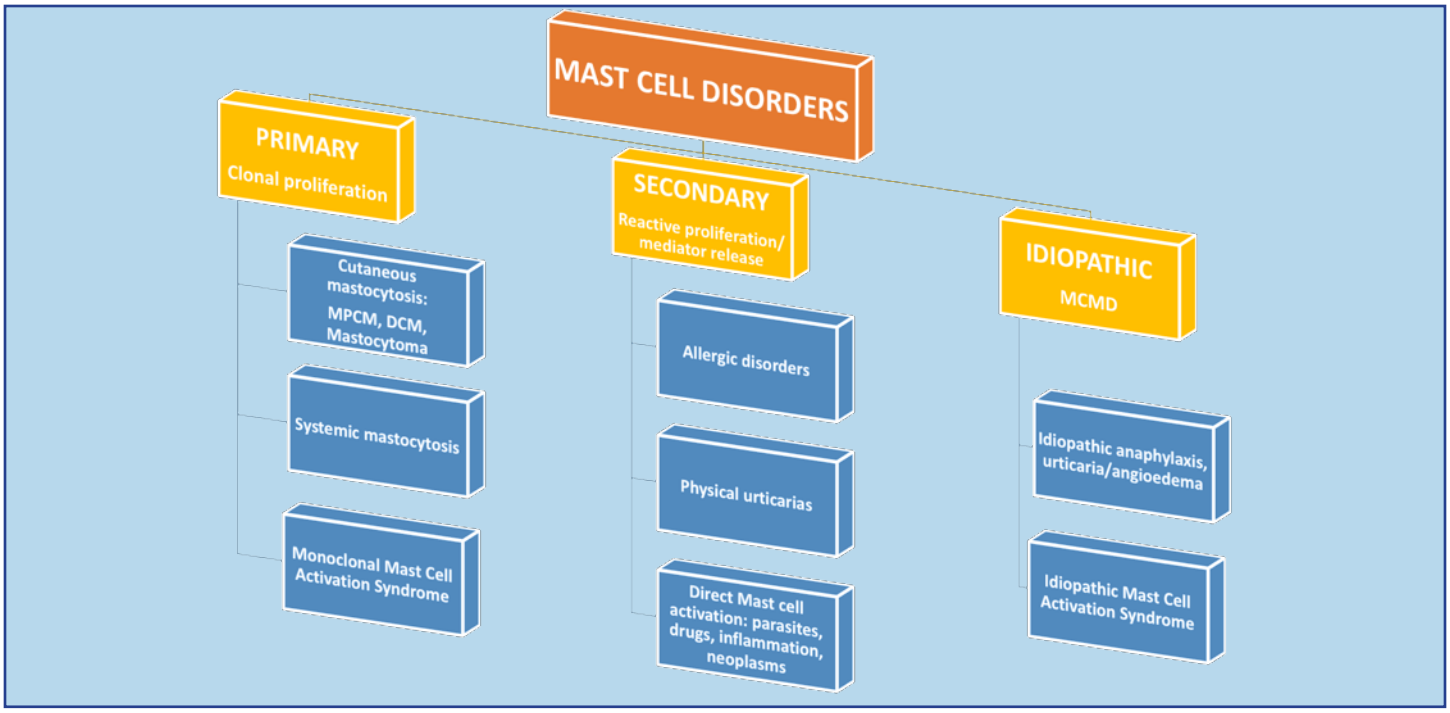

Figure 1. Classification of Mast Cell Disorders; (Adapted from Theoharides TC et al. 2019[9], Valent P et al. 2012[13], and Valent P et al. 2013[14])
Abbreviations. MPCM: maculopapular cutaneous mastocytosis, DCM: diffuse cutaneous mastocytosis, MCMD: mast cell mediator disorders.

MC are stimulated by an array of triggers including allergens, physical conditions (cold, heat, pressure, vibration); microorganisms, foods, drugs, heavy metals, neuropeptides, antibodies, and cytokines. Exercise and psychological stress are also well-recognized triggers, that often act as co-factors in amplification of histamine release. Some of these triggers cause degranulation but, contrary to the classical notion, others do not and instead cause the selective release of mediators.[9]

MAST CELL DISORDERS

Classification of MCD commonly causes confusion and it continues to evolve as the understanding of these conditions deepens. **Figure 1** shows the current proposed classification of MCD into primary, secondary, and idiopathic conditions. Primary disorders are those with abnormal clonal proliferation of MC, secondary disorders cause reactive MC proliferation and/or mediator release, and idiopathic or MC mediator disorders (MCMD) are those in which there is no evidence of proliferation yet mediator release from unknown trigger leads to the clinical picture.[9,13,14]

PRIMARY MAST CELL DISORDERS

Also referred simply as "Mastocytosis", these disorders are characterized by the clonal expansion and activation of MCs primarily in the skin (cutaneous) or the bone marrow and other tissues (systemic), mostly caused by gain-of-function mutations in the *KIT* gene.

Cutaneous mastocytosis (CM)

CM is the abnormal clonal proliferation of MC in the skin and most commonly seen in children; however, adult patients with systemic mastocytosis (SM) also frequently have cutaneous manifestations of the disease. It presents in 3 forms: 1) maculopapular cutaneous mastocytosis (MPCM) or urticaria pigmentosa ("UP") as shown in **Figure 2**, with two variants (monomorphic and polymorphic), 2) diffuse cutaneous mastocytosis (DCM), and 3) mastocytoma of the skin. The lesions can be highly heterogeneous (macular, nodular, plaques, and sometimes blistering) and also differ between children (polymorphic) and adults (monomorphic).[15] The term often described for mastocytoma is "peau d'orange" or skin that looks like the "peel of an orange".

The diagnosis of CM is mainly clinical, but it may be helpful to have histological confirmation of MC infiltration and, in 35% (children) to 80% (adult) of patients, the finding of an

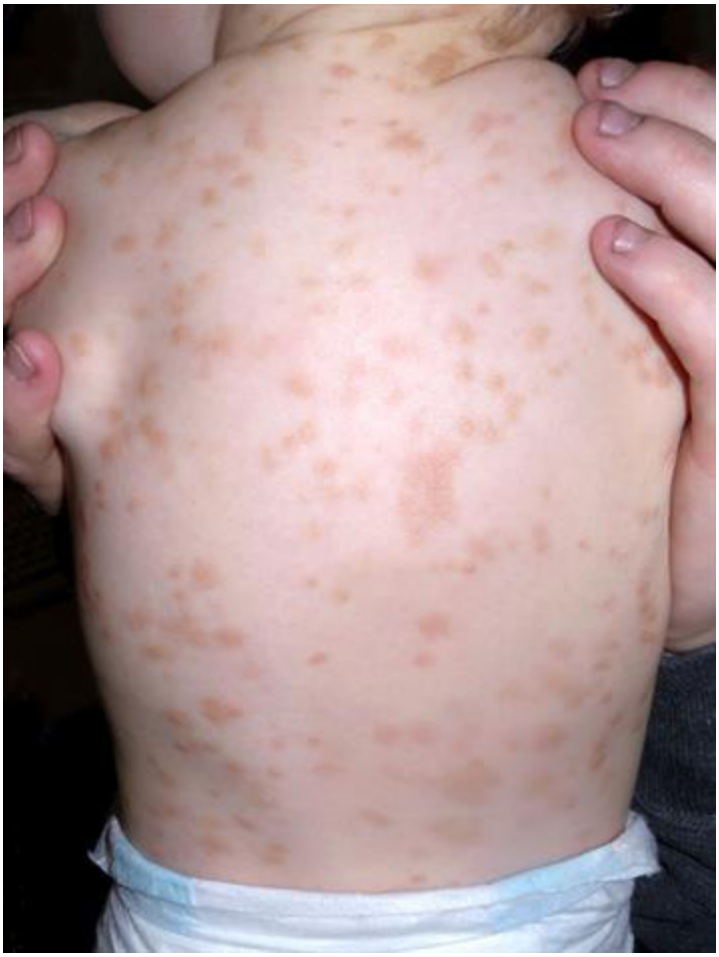

Figure 2. Urticaria pigmentosa in a pediatric patient; from aboutkidshealth.ca

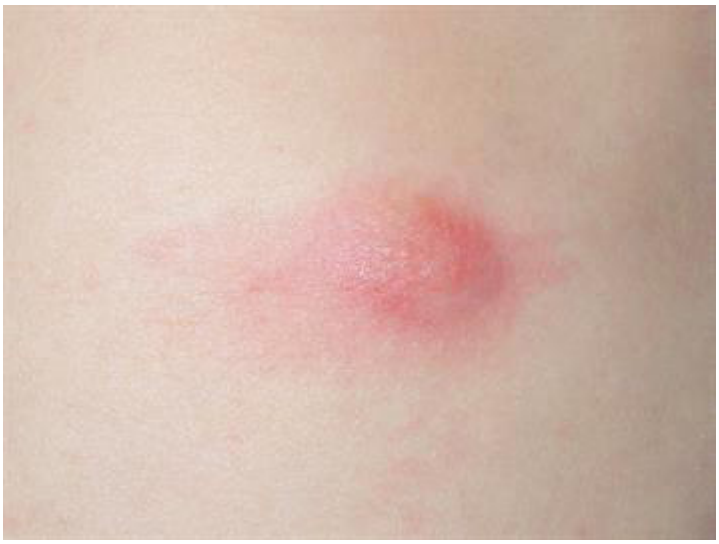

Figure 3. Positive Darier's sign; from aboutkidshealth.ca

activating *KIT* mutation (D816V in adults and others in children) is present.[15,16] A highly specific diagnostic clinical tool is Darier's sign (**Figure 3**), which manifests as wheals and erythema of the lesions after rubbing them.[17]

Even when the abnormal accumulation of MC is limited to the skin, DCM and MPCM can be associated with systemic symptoms from the release of MC mediators into the bloodstream (see **Box 1**). It is very important not to confuse this with SM, which is extraordinarily rare in the pediatric population, with only two case reports cited in the literature.[18]

Children with CM usually have spontaneous resolution by puberty and, in contrast to adults, less than 10% experience anaphylaxis, therefore the prescription of an adrenaline auto-injector in children is left to individual clinician preference rather than being a requirement.[15,16,18] (See **Box 2**)

Systemic mastocytosis (SM)

SM refers to the oligoclonal and neoplastic extra-cutaneous proliferation of MC.[19] The diagnosis of SM requires the fulfillment of one major and one minor criterion, or three minor criteria, as established by the World Health Organization's classification of myeloid neoplasms and acute leukemia . The one major criterion is the finding of multifocal, dense infiltrates of MC (≥15 cells and in aggregates) in bone marrow and/or other organs. The minor criteria are: 1) finding by biopsy of bone marrow and/or other organs of > 25% of MC to be spindle shaped or with other atypical morphology; or when > 25% of MC in a bone marrow aspirate smear are shown to be immature or atypical, 2) finding of *KIT* D816V mutation in bone marrow, blood, or other extracutaneous organ, 3) CD2 and/or CD25 expression in MC in the bone marrow, blood or other extracutaneous organ, and 4) persistently elevated baseline serum total tryptase of >20 ng/ml.[20]

The classification and risk stratification of SM is based on the correlation between clinical and laboratory evaluations. It includes indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis

- **Skin**: pruritus, urticaria, angioedema, flushing, dermatographism
- **Cardiovascular**: hypotension, tachycardia, syncope
- **Respiratory**: cough, wheezing, stridor, hoarseness, nasal congestion, rhinorrhea
- **Gastrointestinal**: nausea/vomiting, abdominal pain/cramping, bloating, diarrhea
- **Musculoskeletal**: bone/muscle pain, osteoporosis/osteopenia
- **Neurologic**: headache, memory and concentration difficulties ("brain fog"), irritability
- **Systemic**: fatigue, malaise

Box 1. Systemic symptoms associated with mast cell mediator release

-associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), and mast cell sarcoma (MCS).[19,20] Details of each are beyond the scope of this review.

The treatment of SM is highly individualized and involves the use of kinase inhibitors (imatinib for SM without D816V, and midostaurin and avapritinib for those with the mutation) and symptom-directed treatment for other causes of mast cell mediator release.[19] (See **Box 1, Box 2, and Table 1**)

Collaboration with hematologists who specialize in MCD is essential in the proper investigation and treatment of patients with SM. For systemic mastocytosis, all adult medicine tertiary centers with a Hematology service will generally see these patients. For cutaneous mastocytosis, there is great variability in regard to diagnosis and treatment of these patients. Some are seen exclusively by dermatologists, some by community allergists, and some (usually the ones with diffuse cutaneous mastocytosis) are seen by immunologists in tertiary centers.

Monoclonal mast cell activation syndrome (MMCAS)

MMCAS is characterized by intermittent episodes of the release of MC mediators without an identified trigger. Patients with MMCAS are usually identified through systemic reactions to Hymenoptera stings or unexplained episodes of anaphylaxis.[18,21] Patients, mostly adults, do not have cutaneous lesions nor MC aggregates in the bone marrow and they manifest clinically with the signs and symptoms of MC mediator release.[22] (see **Box 1**)

- **Non-sedating, second generation anti-H1 antihistamines**: cetirizine, rupatadine, bilastine, fexofenadine, desloratadine
- **Anti-H1 antihistamine with anti-PAF and anti-eosinophil actions**: rupatadine, ketotifen
- **Anti-H1 antihistamine with anti-serotonin action**: cyproheptadine
- **Anti-H1 antihistamine with tricyclic antidepressant action**: doxepin
- **Anti-H2 antihistamines**: famotidine, cimetidine, ranitidine
- **Mast cell stabilizers**: ketotifen, cromolyn sodium (sodium cromoglycate), rupatadine, flavonoids (quercetin, luteolin)
- **Leukotriene antagonist**: montelukast
- **Antispasmodics (overactive bladder)**: oxybutynin, fesoterodine

Box 2. Symptomatic treatment agents for mast cell mediator release

MAST CELL MEDIATOR	PHYSIOLOGIC EFFECT	SIGNS/SYMPTOMS	THERAPY
Histamine	**H1 receptors** Blood vessels and sensory nerves of: • Skin: increased vascular permeability • Bronchial, intestinal, and cardiac smooth muscle: contraction Brain: cerebral cortex and infralimbic structures in regions concerned with neuroendocrine, behavioral, and nutritional state control.	• Urticaria, flushing, pruritus • Cough, wheezing • Diarrhea • Increased heart rate and cardiac output • Headaches, memory and attention deficit ("brain fog"), fatigue, malaise, weight loss	• Non-sedating, second generation anti-H1 antihistamines: cetirizine, bilastine, fexofenadine, loratadine, desloratadine • Anti-H1 with anti-platelet-activating factor effect: rupatadine • Anti-H1 mast stabilizing antihistamine: ketotifen • Anti-H1 tricyclic antidepressant: doxepin
	H2 receptors • Gastric mucosa: increased acid secretion • Airway mucous glands: increased production • Brain: basal ganglia, hippocampus, amygdala • Chondrocytes	• Gastritis, gastric or duodenal ulcers, abdominal pain • Congestion • Potentiation of synapsis excitation	For gastric effects*: Famotidine, cimetidine, ranitidine
	H3 receptors • Brain (cortex, thalamus, basal ganglia, hypothalamus): regulates serotonergic, noradrenergic, cholinergic, and dopaminergic release • Presynaptic nerves in the peripheral sympathetic adrenergic system: suppression of norepinephrine release	• Sleep disturbances • "brain fog": memory, concentration, and attention deficits • Fatigue/lethargy • Sleep disturbances	None available for this clinical use* (Pitolisant is the first available anti-H3 but only authorized for narcolepsy in adults in U.S.A)
	H4 receptors • Eosinophils, mast cells, basophils, neutrophils, and dendritic cells: potent chemotaxis and cytokine release	• Inflammatory responses	None available for clinical use

MAST CELL MEDIATOR	PHYSIOLOGIC EFFECT	SIGNS/SYMPTOMS	THERAPY
Tryptase	• Bronchial smooth muscle contraction • Proliferation of fibroblasts and degradation of collagen • Chemotaxis for eosinophils • anticoagulation	• Cough, wheezing • fibrosis and tissue remodeling • osteopenia/ osteoporosis • Bleeding	None available for clinical use*
Serotonin	• Gastrointestinal tract: regulates intestinal movements • CNS: regulation of mood, appetite, and sleep	• Diarrhea • Flushing • Sleep and appetite disturbances	Cyproheptadine
Prostaglandins (D2 and E2)	• Vasodilation and increased vasopermeability • Airway smooth muscle bronchoconstriction • Nerve cell activation	• Angioedema, flushing • Cough, wheezing, mucus secretion • Sleep-inducing	None available for this clinical use. NSAIDs are known triggers of mediator release and should be avoided, if possible.
Leukotrienes (B4 and C4)	• Increased microvascular permeability • Smooth muscle constriction	• Angioedema, flushing • Long lasting wheal-flare responses • bronchoconstriction	Montelukast
Platelet-activating factor (PAF)	• Vasopermeability • Bronchoconstriction • Neutrophil attachment and transmigration	• Pruritus • Urticaria • bronchoconstriction	Rupatadine Ketotifen
Heparin	• Anticoagulation • Others not well defined	• Bleeding (reported in severe SM)	Protamine
Th1 (IL-6, TNFα) and Th2 cytokines (IL-4, IL-5, IL-9, IL-31), chemokines	• Multiple cellular targets and functions	• Allergic and non-allergic inflammation • IL-31: particularly pruritogenic	Specific anti-cytokine treatments have only seldomly been used for mast cell disorders

Table 1. Mast cell mediators, physiologic effects, signs and symptoms, and targeted therapy.[1,6,9,10,11,12]

Abbreviations. PAF: platelet-activating factor, CNS: central nervous system, NSAID: non-steroidal anti-inflammatory drugs, SM: systemic mastocytosis.

** Complementary agents include: mast cell stabilizers preventing the release of most mediators; topical cromolyn sodium preparations for skin manifestations; oral cromolyn sodium for gastrointestinal symptoms; flavonoids for CNS and gastrointestinal symptoms; calcium and vitamin D supplementation for osteopenia/osteoporosis; antispasmodics for overactive bladder.*

To be considered MMCAS, the *KIT* D816V mutation and the abnormal expression of CD25 and CD2 should be present in at least a few clonal MC in the bone marrow.[21,22] If these features are not found, then idiopathic mast cell activation syndrome (IMCAS) may be considered. In MMCAS patients, baseline serum tryptase is typically not elevated but may occur during acute exacerbations between 30 minutes to 2 hours after symptom onset. In order to establish clinical significance and support the diagnosis of MMCAS, **the tryptase elevation from baseline should be ≥ 1.2 times plus 2 ng/ml.**[22] Ordering a c-kit D816V test can be done through one of two methods.

1. In bone marrow aspirate/biopsy in the setting of systemic mastocytosis: it is requested directly by hematology through the hemopathology department assessing the sample.
2. In peripheral blood for all mast cell disorders, when indicated: it is ordered, with prior approval by the local Genetic Resource Center, through any of the genetic testing companies as a single gene test.

SECONDARY (REACTIVE) MAST CELL DISORDERS

These are disorders in which external stimuli cause the reactive polyclonal proliferation, hyperplasia, and/or mediator release of MC. Included among these secondary mast cell disorders are the classic IgE-mediated hypersensitivity reactions induced by allergens (foods, drugs, insect venoms, and other environmental factors); physical urticarias (heat, cold, vibration, stress); and direct MC activation from infections (parasites, tuberculosis, syphilis), drugs (vancomycin, opioids, NSAIDs, muscle relaxants, contrast media), inflammation (psoriasis, rheumatoid arthritis), and neoplasms (melanoma, gastrointestinal neoplasms).[1,16]

IDIOPATHIC MAST CELL MEDIATOR DISORDERS (MCMD)

In these disorders, the cause of abnormal MC activation is unknown. Importantly, the mediator release is thought to happen without proliferation or even degranulation of MC. One way of describing MC status is as "unstable" and exhibiting aberrant stimulation.[9] Included in this group are idiopathic anaphylaxis (not explained by MMCAS), idiopathic urticaria/angioedema, and IMCAS (see next section).

Idiopathic mast cell activation syndrome (IMCAS)

The diagnostic criteria for IMCAS (requires all three) are: 1) episodic, objective signs and symptoms of MC activation in at least two organ systems. Clinicians should note that subjective symptoms (e.g., fatigue, brain fog) in the absence of the signs and symptoms in two other organs systems **do not count**, 2) evidence of systemic MC mediator release corresponding temporally to the presence of symptoms, and 3) clinical response to medications that inhibit MC mediators.[14]

Other conditions that can be frequently reported by patients with IMCAS include postural orthostatic tachycardia syndrome and other dysautonomia[23], hypermobile Ehlers-Danlos syndrome and other hypermobility conditions[23,24], psoriasis[25], fibromyalgia and chronic fatigue syndromes[23], interstitial cystitis/overactive bladder syndrome[26], irritable bowel syndrome[27], post-traumatic stress disorder, and neuropsychiatric disorders[4,28], to name the most relevant. More studies are needed to clarify these associations and the specific role of MC. Given the type of symptoms and, very often, the lack of objective evidence of systemic MC mediator release, the diagnosis of IMCAS is prone to be misused by parents/patients (online self-diagnosing and other motives), physicians (in the presence of a challenging diagnosis and often challenging patients/families), and more concerningly by non-physicians who profit from the often long journey that many of these patients endure and that greatly affects their quality of life.[29]

Clinical pearls and perspectives

- Knowledge about the effects of MC mediators is key in understanding the clinical presentation of patients with MCD and in tailoring their therapy.
- The classification, nomenclature, and diagnostic criteria of MCD causes confusion. It is relevant for the A/I to stay informed on this topic.
- The distinction between SM and CM with systemic symptoms is very important; often the cause of referral to an A/I.
- Patients with CM, especially DCM, can sometimes have tryptase levels >20 ng/ml at presentation. In children, and in the absence of cytopenia and/or other infiltrative features such as lymphadenopathy, hepatomegaly, or abnormal liver function, a referral to hematology for a bone marrow aspirate/biopsy is **not required**. Follow up of these levels with age and adequate symptomatic treatment usually reveals normalization.
- SM is extremely rare in children. As per above, the same rules would apply for referral to hematology.
- MMCAS and IMCAS are diagnoses of exclusion, after ruling out other serious diagnoses such as SM, carcinoid, pheochromocytoma, vipoma, gastrinoma, and medullary carcinoma of the thyroid, when applicable
- The most objective, yet challenging way to assess for MCD is the proper measurement of mediators in blood and urine.
- Currently, there are no drugs that solely and selectively target MC.
- It is important, for both the patient and treating clinician to accept that limiting triggers and targeting the patient's specific symptoms of mediator release are currently the best available therapeutic approaches
- The recommended therapy is a combined approach of at least anti-H1 + H2 antihistamine(s) + mast cell stabilizer(s), with the addition of other agents based on specific symptoms. Doses should be maximized as indicated/tolerated aiming for full symptomatic control to then progressively taper to lower doses that are able to achieve symptom control.
- More targeted therapies are needed (e.g. anti-H3 and -H4 antihistamines, anti-tryptase agents, non-NSAID prostaglandins inhibitors, anti-IL-31), and more effective MC stabilizers
- Prophylactic precautions may be warranted for some patients before and during surgical procedures.
- The ideal care for patients with/suspicion of a MCD may include and involve A/I, dermatology, hematology and, clinical psychology and social work.
- When assessing for MCD especially MMCAS and IMCAS, explore alternative or concomitant mental health conditions.

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