

Review

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Progress in mast cell activation syndrome: the global consensus-2 diagnostic criteria at six years

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Abstract: Since establishment in 2020 of the global consensus-2 diagnostic criteria for mast cell activation syndrome (MCAS), recognition of this prevalent disease, existing alongside rare cutaneous or systemic mastocytosis, has grown significantly. Despite this progress, some have continued using more restrictive criteria, significantly underdiagnosing this complex but treatable disorder. Consensus-2 has brought diagnosis and effective treatment in many MCAS patients previously labeled with unexplained (mostly inflammatory) syndromes or misdiagnosed as somatization or other primary

psychiatric disorders. Fears that consensus-2 diagnostic criteria might bring overdiagnosis have not been realized. Appropriate therapy for MCAS can dramatically improve quality of life, sometimes after decades of morbidity and disability despite extensive past unhelpful workups and treatment. Appreciating the breadth and heterogeneity of MCAS, and achieving good management outcomes, requires understanding the complexity of mast cell biology and pathophysiology as well as the range of comorbidities the disease can drive and which can aggravate the disease. The spectrum of diseases thought possibly rooted in variants of MCAS (or to which MCAS is significantly contributing) continues expanding, calling for more research. New therapeutic options have emerged, and clinicians have gained better appreciation for use of existing treatments and mitigation of impediments to treatment. MCAS research remains in early stages, hampered by many factors including limited awareness of the disease and challenges in objective assessment of treatment response. This review examines developments in awareness, education, clinical care, and research since consensus-2 emerged, while discussing challenges and opportunities for accelerating progress.

Keywords: mast cell activation syndrome (MCAS); mast cell activation disease; mast cell disease; chronic illness; misdiagnosis; medical controversies

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Introduction

Dominantly at environmental interfaces and abutting all vessels and neurons, mast cells (MCs) contribute to innate and adaptive immunity and homeostasis [1–4]. With such sitings and responses magnitudes faster than other leukocytes, MCs are first-line sentinels against bodily assaults [5]. Long before emergence of other leukocytes, MCs comprised the entirety of the eukaryotic immune system [6], developing wide-ranging abilities to recognize and respond to threats. Though other leukocytes emerged to better handle specific threats and now

dominate modern immunity, MCs have persisted and still express hundreds of mediators and receptors, conferring remarkable capacities to recognize, and to facilitate resistance to and recovery from, vast arrays of insults [7, 8]. However, aberrancies in MC mediator expression [a.k.a. MC “activation” (MCA)] can leverage this diversity to compromise health in many ways. Emerging research is increasingly suggesting most MC disorders are rooted in (usually somatic) variants in assortments of MC regulatory genes [9, 10], always bringing some extent of aberrant MCA [i.e., one (yet undistinguished) type or another of “MC activation syndrome” (MCAS)]. Occasionally, KIT codon 816 variants are also present, usually conferring substantial MC neoplasia (“mastocytosis”, common in some animals [11, 12] but rare in humans [13–17]) in addition to symptoms from the other variants (i.e., making MCAS “part and parcel” of mastocytosis). However, most MCAS patients do not meet diagnostic criteria for systemic or cutaneous mastocytosis and suffer symptoms stemming directly and/or indirectly from aberrant MC mediator expression, impacting cells, tissues, organs, and systems throughout the body with dominantly inflammatory, allergic, and dystrophic effects but sometimes also coagulation and endocrine disruptions and other issues [7].

Cutaneous and systemic mastocytosis have been recognized for approximately 150 and 100 years, respectively. In the 1980s, MCAS was first hypothesized to exist based on reasoning that if mastocytosis involves both substantial MC proliferation and chronic inappropriate MCA, then diseases of inappropriate MCA without substantial MC neoplasia likely also occur [18–21]. Two decades have passed since the first case reports of MCAS [22, 23].

Two schools of thought have emerged regarding the scope of MCAS, appropriate diagnostic criteria, and reasonable treatment approaches [24, 25]. One perspective, “consensus-1” [26–46], emerging from an earlier proposal [47] and labeled by its authors as “the consensus” or “the global consensus”, has persistently expressed the sense that MCAS is rare (similar to mastocytosis) and usually idiopathic. Additionally, consensus-1 characterizes MCAS as typically involving recurrent anaphylaxis and rises in serum tryptase concentrations of at least 20% above baseline asymptomatic levels, plus an additional 2 ng/mL (rises so subtle that the higher level often is still within the normal range), and which must be found to occur within 4 h of symptom onset. Tryptase is a multifunction protease which MCs constitutively express and represents approximately 25 % of total MC protein content [48, 49]. Recent updates to consensus-1 criteria now allow alternative biomarkers for MCA when tryptase testing cannot be used or

yields “unclear” results (though what is meant by “unclear” is unclear). Accepted alternatives are limited – urinary *N*-methylhistamine and 2,3-dinor-11 β -prostaglandin-F₂ α (metabolites of histamine and prostaglandin D₂ (PGD₂), respectively) at least twice their baseline levels [36–39] – challenging criteria given significant hurdles in accurately determining their levels, especially at a truly asymptomatic baseline or so quickly (within 4h) soon after symptom onset.

An alternative perspective, now called “consensus-2” [25, 50] (Table 1), emerged almost simultaneously but regards MCAS as prevalent (approximately 17–20 % of the Western population) [15, 51] and commonly presenting with diverse manifestations stemming from diverse profiles of aberrant release of MC mediators with very diverse effects [52, 53]. Consensus-2 recognizes MCAS usually shows no significant tryptase elevation and uncommonly manifests anaphylaxis [53, 54]. Consensus-2 encourages measurement of other MC-specific mediators (see Table 1). Furthermore, consensus-1 advocates maintain no specific MC count in tissues can be considered abnormal unless the unique MC histomorphologic anomalies in mastocytosis are present [55–57], while consensus-2 considers MC counts exceeding 20 per high-power (400 $\times$) field in gastrointestinal and genitourinary tissues to be abnormal, even with histomorphologically normal MC appearance (as is typical in MCAS) [25, 58–60].

Analyses of these perspectives have been published [24, 25]. Though assertions of validity and superiority of consensus-1 have been published by its advocates [28, 39, 61, 62], actual evidence has been limited to select anaphylactic scenarios in small cohorts and have provided little data to support a restricted view of MCAS [63–69].

Consensus-2 has been criticized, too [27, 28, 39–42, 62]. One study claimed consensus-2 has low sensitivity for detecting MCAS, though it used diagnostic tests not typically employed by either consensus (KIT-D816V mutation analysis, flow cytometry, and marrow examination) [70]. Another study utilized artificial intelligence systems – some known for generating erroneous or fabricated findings – to conclude consensus-2 diagnoses were “more variable” and “less precise” than consensus-1 diagnoses [71], perhaps unsurprising when comparing restrictive vs. broader diagnostic criteria.

Meanwhile, evidence supporting consensus-2 has been growing [4, 51, 59, 60, 72–96]. This review details recent developments regarding diseases likely intersecting with MCAS, diagnostic and therapeutic issues in MCAS, and research issues in MCAS. Summaries of these developments are provided here; additional details are provided in the Supplementary Material, Appendix.

Table 1: Consensus-2 Diagnostic Criteria for mast cell activation syndrome.**Major criterion**

1. Constellation of clinical complaints in two or more systems attributable to pathologically increased MC activity (MC mediator release syndrome)

Minor criteria

1. Multifocal or disseminated infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract; >19 MCs/high power field)

2. Abnormal spindle-shaped morphology in >25 % of MCs in marrow or other extracutaneous organ(s)

3. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)

4. MC genetic changes (e.g., activating KIT codon 419, 509 or 560 mutations) shown to increase MC activity

5. Evidence [typically from body fluids such as whole blood, serum, plasma, and/or urine (random and/or 24-h)] of above-normal levels of MC mediators including:

- Tryptase
- Histamine or its metabolites (e.g., N-methylhistamine)
- Heparin
- Chromogranin A (note potential confounders of cardiac or renal failure, neuroendocrine tumors, or recent proton pump inhibitor use)
- Other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D₂, its metabolite 11-β-PGF_{2α}, or leukotriene E₄)

6. Symptomatic response to inhibitors of MC activation or MC mediator production or action

Diagnosis established upon demonstration of the major criterion combined with at least one minor criterion (and in the unstated but inferred absence of any other disease better accounting for the patient’s problems).

Diseases likely intersecting with MCAS

Given the diversity in mediator expression and distribution of MCs, a limited presentation scope for MCAS would be surprising. Instead, the overarching theme of MCAS’s clinical presentation (chronic multisystem polymorbidity of generally inflammatory, allergic-type, and dystrophic issues) follows from the dominant effects of the mediators. With few symptoms being highly specific to MCA, it instead is the totality of “MCAS-consistent” presentation/behavior (and absence of better unifying diagnosis), preferably together with laboratory evidence, which allows confident diagnosis of MCAS. Beyond mere awareness of the existence of MCAS, this marked heterogeneity in MCAS’s superficial clinical presentation challenges clinicians, impeding initial recognition that MCAS belongs in the differential diagnosis.

Such heterogeneity brings potential for MCAS to “be involved in” (including potentially being the root cause of) a wide range of “idiopathic” clinical phenomena/disorders/diseases. For example, there is growing evidence that MCAS often is involved in various inflammatory disorders and unusually severe acute and chronic courses of some infections, such as Covid-19 [84, 97, 98] or certain vector-borne infections [99]. MCs manifest innate and acquired/learned immunity, but the ability of dysfunctional MCs to learn which novel exposures are harmful may be impaired, and their responses may be exaggerated, to various chemical compounds of the modern era (including many medication product excipients (fillers, preservatives, dyes, etc.) and

implanted foreign materials [80–82, 100–104]) for which innate tolerance has not yet evolved.

Neuronal abutment by MCs [105, 106] suggests mast cell involvement likely underlies (or significantly contributes to) many cases of a broad swath of idiopathic manifestations of central and peripheral nervous system disorders, including many categorized as “neurologic” (e.g., paresthesia, headache, tics, tremor), “cognitive” (e.g., autism, attention deficit and hyperactivity disorders, disorders of memory and word-finding often colloquially labeled as “brain fog”), “psychiatric” (especially anxiety and mood disorders), and “autonomic” (including dysregulation of temperature, heart and respiratory rates, blood pressure, gastrointestinal motility, sweating, sleep, etc.). [4, 74, 107]. Reactive anxiety and/or depression can develop from ineffective evaluation and treatment (or misattribution of symptoms to psychosomatism), and chronic neuroinflammation can cause significant neurologic dysfunction. However, much of the neurologic manifestations often seen in MCAS could be due to normal nerve fibers reacting to constant aberrant expression of heterogeneous potpourris of potent mediators from some (likely mutated, i.e., primarily dysfunctional) subpopulation of MCs.

The expansive repertoire of MC cell-surface receptors includes receptors for the major sex hormones [108]. Ligand binding to some (e.g., progesterone, testosterone) may inhibit MCA in some patients, while others (e.g., estrogen) almost always increase MCA (and further activate aberrant MCs in aberrant ways), leading to involvement of MCAS in many menstrual, fertility, and pregnancy disorders [91, 92]. MC expression of receptors and mediators relevant to other endocrine systems brings common involvement in other endocrinologic disorders, too.

Many MC mediators help guide growth/development in many tissues, creating potential for involvement of MCAS in many benign and malignant dystrophisms, potentially at any site. Features of MCA are commonly seen [109] in patients with some connective tissue disorders [e.g., hypermobile Ehlers-Danlos Syndrome (hEDS)] for which no causative germline mutation has yet been found, increasing suspicion that some connective tissue disorders may often be rooted in certain forms of (again, mostly somatically mutated) MCAS (or at least that MCAS is significantly contributing to the development of those disorders) [93, 110]. Recognition in some patients of certain recurrent patterns of comorbidities associated with (and perhaps rooted in) MCAS – such as a “pentad” including the chronic multisystem inflammation of MCAS plus connective tissue disorders, dysautonomia, gastrointestinal dysmotility, and autoimmunity – has been slowly increasing, too [77, 78, 111–113]. In addition to MCAS’s involvement in some vasospastic incidents (Kounis syndrome), MCAS may sometimes drive the dystrophisms underlying some vascular compression syndromes such as median arcuate ligament syndrome (MALS), nutcracker syndrome, and pelvic vein congestion syndrome [114–118].

More details regarding data and perspectives recently emerging regarding the wide array of long-idiopathic disorders in which MCAS of one variant or another might have a pivotal role (e.g., long-Covid syndrome, multiple chemical sensitivity (or, as more recently termed, toxicant-induced loss of tolerance (TILT)), dysautonomia, etc.) can be found in Section 1 of the Supplementary Material, Appendix.

Diagnostic issues in MCAS

In addition to differences between consensus-1 and consensus-2 regarding MCAS scope and diagnostic criteria, other diagnostic challenges have become evident.

The marked thermolability of most of the clinically measurable MC mediators fairly specific to the MC makes accurate testing challenging [24, 25]. Attention to detail (e.g., continuous chilling of relevant specimens) is necessary. Recent discovery of hereditary alpha-tryptasemia (HaT (and elsewhere)), a common inheritance of one or more extra copies of the TPSAB1 gene for alpha-tryptase resulting in typically modest, stable elevations in serum tryptase, now requires genetic testing for HAT in MCAS patients with modestly elevated serum tryptase to determine whether such elevations come from MCA (when HAT is not found) or merely reflect germline-programmed slight overexpression of tryptase [not yet proven to be pathogenic, but associated with an increased incidence of MCAS, hEDS, and postural orthostatic tachycardia syndrome (POTS)].

Interpretation of tissue MC counts has remained controversial. Though definitive study is still needed, additional data in recent years suggest consensus-2’s regard of such counts as significant remains reasonable [58, 60, 82, 85, 96]. Some recent studies [56, 57, 119] found no utility of biopsies in diagnosing MCAS (and thus have been asserted to refute consensus-2) but suffered methodologic flaws (e.g., “healthy control” populations not screened to exclude MCAS). Consensus-1 advocates have asserted that, except in mastocytosis, no number of MCs in a biopsy would ever be considered abnormal, a notion which certainly would not apply to other cells and thus likely does not apply to MCs.

Appreciation has increased regarding immune system impacts of MCAS. Insufficiently cautious interpretations of antibody-probing tests in MCAS patients can result in incorrect diagnoses with adverse therapeutic consequences [120].

Even though MCAS can directly drive many symptoms, distinctly recognizable comorbidities both consequent to and independent of MCAS also can be present. The rare inborn autoinflammatory and primary immunodeficiency syndromes can mimic symptoms of MCAS. Patients whose histories suggest such issues warrant genetic testing regardless of whether MCAS is found. Although treatment of MCAS is often successful, expectations with MCAS treatment must remain tempered if other issues remain afoot. When proven MCAS appears “treatment-resistant”, clinicians must consider presence/persistence of MCA triggers and/or comorbidities.

Accurate identification of triggers remains challenging, as is monitoring of treatment response. Triggers may spark MCA flaring via IgE-mediated, IgG-mediated, or other pathways. Triggering of dysfunctional MCs by various exposures may be modulated by dynamic factors (e.g., hormonal fluctuating with menses), leading to startling variances in results from serial iterations of some allergy tests. The accuracy of present clinical laboratory testing for reactivity to medication product excipients and implanted foreign materials remains unclear, requiring cautious clinical usage and interpretation. Such testing nevertheless sometimes can be helpful. Efforts to correlate therapeutic improvements with reductions in mediators tested for diagnosing MCAS generally have been unsuccessful, probably because most symptoms in MCAS stem from aberrant expression of mediators not clinically measurable or not specific to MCs. Advances in objective assessment of MCAS treatment response are needed; response assessment likely will remain dominantly clinical for some time to come.

More details regarding recent diagnostic issues in MCAS (e.g., specifics regarding specimen handling, interpretation of tissue biopsies and antibody tests, overlap with auto-inflammatory syndromes, etc.) can be found in Section 2 of the Supplementary Material, Appendix.

Therapeutic issues in MCAS

The complexity of MC biology and heterogeneity of MCAS provide many therapeutic opportunities. Many treatments have proven helpful for various patients. Comprehensive treatment compendia have been published [121, 122]; for reader convenience, an update of one scheme [124] is provided in Figure 1. It seems almost certain that many MCAS variants exist and could be defined through mutational profiling of isolated MCs, but such profiling is not yet clinically available. As such, most MCAS cases continue to be “lumped together” as the single entity of MCAS. Since MCAS variants cannot yet be defined, no evidence-based guidance yet exists for personalizing treatment. However, when physician and patient exhibit patience, persistence, and a methodical approach, the goal of significant sustained improvement is usually reached by assembly of a (usually

fairly small, but patient-unique) regimen of MCAS-targeting treatments. Recent therapeutic advances have included new pathobiology-appropriate treatments and increased recognition of issues hampering treatment.

Many chemical and other “foreign material” exposures long thought “inactive” and inconsequential are significant triggers, even at low levels, in some patients in whom treatment successes are limited while trigger exposure continues. Although desensitization therapies may be successful in some cases, elimination of exposure – at least until the MCAS has come to be considerably better controlled – often is the more expedient and effective approach.

Treatment sometimes is hampered by cessation of helpful MCAS-targeting medications due to misinterpretation of recent studies showing increased risk for various morbidities in patients using medications helpful in MCAS (e.g., the reported risk of increased dementia in long-term

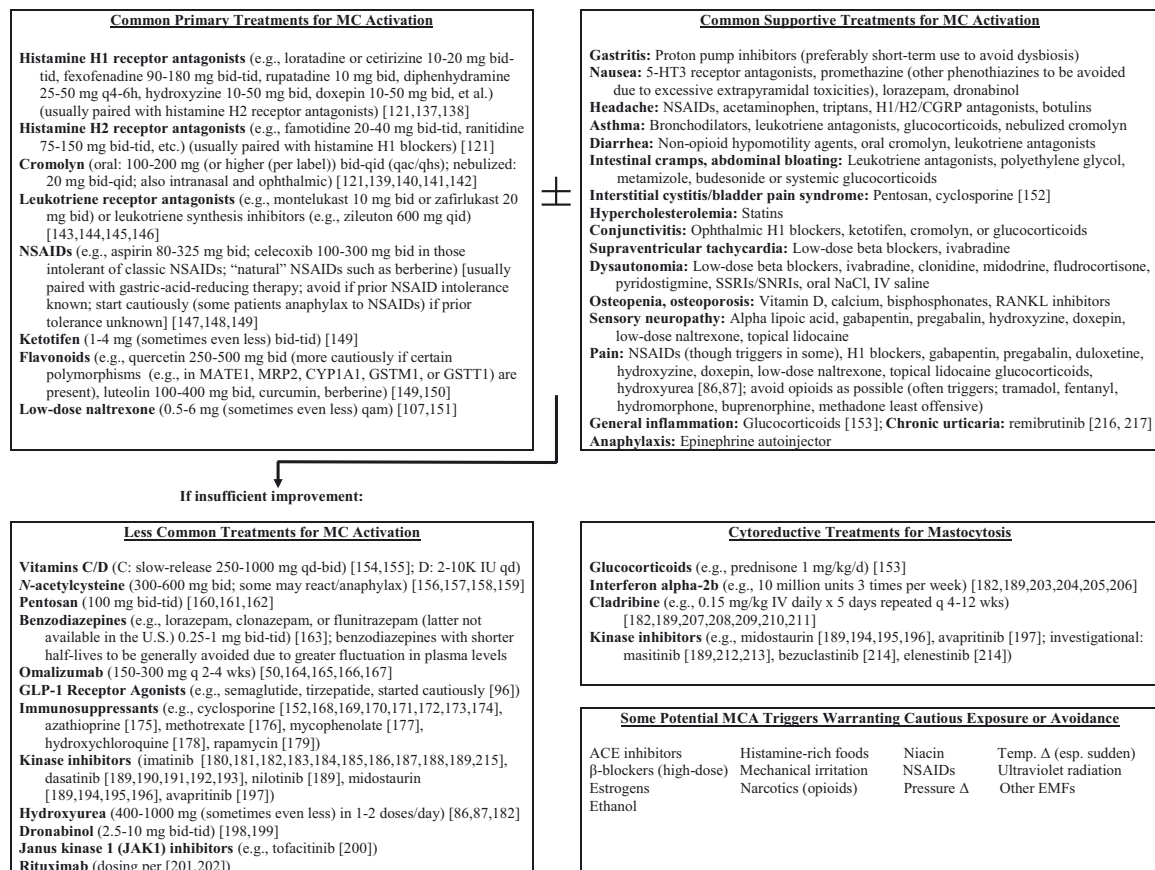


Figure 1: An algorithm for approaching treatment of mast cell activation syndrome (MCAS). Example dosages are for adults. Consider potential interactions of polypharmacy (e.g., curcumin vis-à-vis aspirin, warfarin, clopidogrel, histamine H₂ receptor antagonists, proton pump inhibitors, etc.) do not assume all acute symptoms are due to MCAS; assess acute symptoms in standard fashions. Treatment of MCAS remains largely “trial and error,” guided mostly by assessment of the individual patient and the clinician’s judgment as influenced by experience. Not every drug listed here will be effective in, or even appropriate to be tried in, every MCAS patient. ACE=angiotensin converting enzyme. CGRP=calcitonin gene-related peptide. EMFs=electromagnetic frequencies. IV=intravenous. MCA=mast cell activation. NSAIDs = non-steroidal anti-inflammatory drugs. RANKL=receptor activator of nuclear factor kappa-B ligand. SNRI=serotonin-norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

users of histamine H1 or H2 receptor antagonists) [123–126]. Risk, however, is not a guarantee, and association does not imply causation; we are unaware of any literature showing H1 receptor antagonists (or other commonly used MCAS-targeting drugs examined in these studies) directly cause dementia. Instead, it is possible that hyperactive mast cells may play a role in the pathogenesis of cognitive impairment, raising questions not whether chronic use of MCAS-helpful medications might be associated with increased risk for developing such diseases but rather (1) whether partial control of MCAS with such medications might *decrease* such risk, and (2) whether *earlier recognition and better control* of MCAS might further decrease such risk. Further studies are needed to investigate this hypothesis.

MCAS often causes various dietary intolerances, and MCAS increasingly is being recognized in patients with various eating disorders [127–129]. Furthermore, though MCAS can lead, via a variety of mechanisms, to assorted micronutrient deficiencies, some such deficiencies (e.g., vitamins C and D) can exacerbate MCAS. Increased recognition of these issues may yield clinical fruit.

As more techniques and tools emerge for identifying triggers, new (sometimes even non-pharmacologic) approaches for trigger mitigation are emerging. For example, some MCAS patients learn cyclic migration to avoid seasonal allergens, and avoidance of mycotoxin exposure [130, 131], can be helpful.

Increased recognition of potential for some coagulation disorders (bleeding and/or thromboembolic) [53, 132] and some chronic inflammatory disorders to be rooted in MCAS [53, 133] (or that MCAS is significantly contributing to such disorders) is beginning to lead to consideration of MCAS (diagnostically and therapeutically) in some such patients.

Many new treatments – pharmacologic and non-pharmacologic – with at least anecdotal evidence for being able to improve MCAS have been emerging, too. Increasingly recognized for their anti-inflammatory activities, glucagon-like-peptide-1 (GLP-1) receptor agonists have been reported, anecdotally, as helpful in some MCAS patients [96]. As another example, given that remibrutinib (inhibiting the Bruton tyrosine kinase pathway known to be relevant in MCA) was recently approved for chronic spontaneous urticaria (a disease likely often rooted in MCAS), it becomes possible that remibrutinib might be helpful in MCAS, possibly even for symptoms beyond urticaria. Research is needed to identify such treatments’ roles in MCAS, a disease of much broader spectrum than the approved indications.

More details regarding recent therapeutic issues in MCAS (e.g., alleged toxicities of chronic MCAS-targeting treatments, micronutrient deficiencies, newly emerging

treatments, etc.) can be found in Section 3 of the Supplementary Material, Appendix.

Research issues in MCAS

Largely due to unawareness of this prevalent disease, little research in MCAS has been done or is underway. Hopefully, research will increase as awareness increases. Although the pharmaceutical industry is motivated to develop better treatments for a prevalent disease which presently has no specifically approved medications, the human and financial costs of MCAS to society and to all public and private health insurers make it even more appropriate for these interests, too, to fund MCAS research.

As noted previously, lack of methods to objectively monitor treatment response is a barrier to therapeutic research, but patient-reported outcomes may be sufficient while more objective assessments remain unavailable [134, 135]. No validated patient-reported symptom assessment tool for comprehensive assessment of an MCAS patient’s symptoms has yet emerged, but the authors are aware of one such tool being developed.

Although genetic research begun nearly 20 years ago at one laboratory quickly identified that most MCAS patients have somatic variants in KIT and other MC-regulating genes [9, 10] such findings have not yet been independently confirmed, not because such efforts have been pursued and failed but rather because such efforts have not been pursued (or were not completed [136]). There is ample potential for exploring intersections of MCAS with many associated disorders, investigating the proportion of the population with the associated disease which meets diagnostic criteria for MCAS and whether such populations harbor specific somatic mutational profiles in their MCs, helping direct research in disease mechanisms and treatments. MCAS-oriented directions for further research in such diverse areas as chronic fatigue syndrome, postural orthostatic tachycardia syndrome, hEDS, long-Covid syndrome, and other chronic multisystem inflammatory diseases could emerge from MCAS-exploring pilot studies of 20–30 patients with each of these diseases/disorders.

Hopefully, genetic dissection of MCAS will enable identification of specific variants, a feat which patient histories, physical exams, and available laboratory tests have not yet permitted. Variant information at the mutational level not only might obviate challenging mediator testing but also seems likely to foster personalized therapy.

Still to be defined are the mechanisms by which somatic genetic variants emerge in MCAS. Preliminary research suggests heritable epigenetic variants (creating a fundamental

genomic fragility rendering the genome more susceptible to sustaining somatic variants induced by various insults, such as stressor-driven cytokine storms) may be one root mechanism, but more research is needed.

Discussion

Time affords perspective. Since consensus-2 emerged six years ago, it has become clear that many patients who do not meet consensus-1 criteria but do meet consensus-2 criteria are significantly helped by MCAS-targeting treatments inaccessible without a diagnosis of MCAS. Multiple articles have contended that overdiagnosis of MCAS by broader criteria will bring erroneous and excessive treatment [27, 28, 39–42, 62]. One article [62] assessing MCAS diagnostic criteria even purported to discuss problems from overdiagnosis and from underdiagnosis but then only discussed potential harms of overdiagnosis (i.e., did not address underdiagnosis at all) and further asserted that increased demand for health care from feared (but not yet observed) overdiagnosis justifies restrictive diagnostic criteria. No study, or even case report, demonstrating overdiagnosis (let alone harms from such) has been published. Despite such objections to consensus-2, our experience is that consensus-2 has been used by many practitioners of many specialties around the world to help thousands of patients, most of whom would not meet other diagnostic schemas for MCAS despite their MCAS-consistent presentations and their consensus-2-satisfying laboratory testing. We have seen no overdiagnosis or increased demand for health care from such. If anything, and perhaps unsurprisingly, in our experience accurate diagnosis and effective therapy seems to decrease our MCAS patients’ consumption of health care. We feel underdiagnosis – principally due to ongoing physician unawareness of MCAS but also somewhat to use of restrictive criteria for diagnosing it – remains substantial, not only impeding patients from accessing disease-appropriate treatments but also driving clinicians to waste resources trying to treat symptoms without recognizing, let alone treating, the underlying condition.

We have observed, too, it is common that physicians do not follow consensus-1 criteria by asking the patient to pursue repeat tryptase testing during an attack. Instead, the patient often has a single tryptase level determined at (always symptomatic) baseline, and when it (usually) is found to be normal, the patient often is informed this result excludes MCAS. There are a few small studies which document “20 % + 2” rise in serum tryptase during certain types of symptom flares [63–65]. In some of these studies, it is unclear if the higher level was determined in a blood sample drawn within the 4 h limit, after onset of the symptoms, as required

by consensus-1, and in none of these studies is there any clarity as to whether baseline serum tryptase was determined at the “asymptomatic” point required by consensus-1. Across our thousands of MCAS patients, we have never seen one who is truly asymptomatic at any point. Instead, they often are at their “baseline” or “usual” level of health (i.e., their personal “normal”), but that baseline is always symptomatic in multiple fashions to various degrees. The complexity of MC biology and heterogeneity of MCAS pathobiology makes it illogical to exclude the diagnosis based on absence of one particular issue (anaphylaxis) or one particular mediator elevation (tryptase) [53], particularly when other clinical and laboratory evidence supports MCAS as the best diagnosis accounting for the largest extent of the patient’s course.

We feel that when (1) MCAS can be reasonably included in the differential diagnosis for the patient at hand, (2) MCAS is the differential diagnosis which better accounts than any of the other differential diagnoses for the largest range of findings in the patient’s history and physical exam, and (3) the patient can be shown to meet any peer-reviewed published proposed diagnostic schema for MCAS, then it is reasonable to diagnose MCAS and to attempt to treat it. If another diagnosis later becomes apparent which even better accounts for all the findings in the patient (including demonstrable MCA), then the new diagnosis should become the primary diagnosis and treatment should pivot accordingly. However, until discovery of a better diagnosis, persistence at efforts to treat MCAS in a patient who has met any published diagnostic schema for MCAS seems reasonable, with the understanding that the aforementioned great heterogeneity in pathobiology ensures there will be great heterogeneity in treatments found efficacious – thus necessitating persistence by physician and patient in trying sensible options. Responses to most MCAS-targeting drugs are seen quickly, allowing timely elimination of ineffective treatments and retention only of significantly helpful treatments to craft the patient’s optimal regimen. Advancing science and testing eventually will permit identifying specific MCAS variants, leading to more efficient and effective treatment. Until then, it remains better to establish a sensible diagnosis and find effective treatment for a disease which may be endured for the rest of the patient’s life. Lack of diagnosis facilitates harmful dismissal and gaslighting.

All clinicians (and trainees) and laboratory, pharmaceutical, and health insurance industries, governmental health care agencies, and health care research organizations need to learn about MCAS. Many patients continue reporting their local practitioners lack awareness of MCAS or deny it exists (or confuse it with mastocytosis or assert the patient “cannot have it because it is rare”). Although allergy/

immunology training programs have begun providing trainees some education about MCAS, most training programs remain unaware of the disease. The first teaching about MCAS provided to undergraduates (freshman medical students) was delivered at the University of California at Irvine in May 2025, providing a model for other schools. Time will tell how these trainees’ recognition of possible MCAS in their patients is received by their supervisors who have not yet come to know MCAS. Ultimately, awareness of MCAS will broaden, and students will become teachers, leading to widespread acceptance and recognition of MCAS just as with many other significant developments in the history of medicine.

Improvement of education and research will benefit from organized approaches leveraging expertise in MCAS in the form of clinicians who never received formal training about MCAS but have nevertheless acquired extensive experience. Although some organizations conducting research in the MCAS arena [e.g., the European Competence Network in Mastocytosis (ECNM, <https://innere-med-1.meduniwien.ac.at/unsere-klinischen-abteilungen/haematologie-und-haemostaseologie/projekte/ecnm-registry-european-competence-network-mastocytosis/>) and the American Initiative in Mast Cell Disorders (AIM, <https://aimcd.net/>)] have helped define, and have adopted, a consensus-1-based approach to MCAS, another such organization, the International Society for Mast Cell Activation Syndromes (ISMicas, <https://ismicas.org/>), has more recently emerged and embraced a consensus-2-based approach to the disease. Also, as awareness of MCAS has been increasing in the patient community, mast cell disease patient support organizations have been increasing their presence and activities, including The Mast Cell Disease Society (<https://tmsforacure.org/>) and Super T’s Mast Cell Foundation (<https://supertmastcell.org/>) in the U.S. as well as similar organizations in many other countries around the world (a comprehensive list is available at <https://mastocytosis-mcas.org/support/>).

Conclusions

A consensus-2-based approach to diagnosing MCAS continues to enable diagnosis and successful treatment in many patients not meeting other diagnostic schemas. Consensus-2-enabled overdiagnosis has not been observed, but underdiagnosis remains a frequent, significant problem. Most MCAS patients find treatment which gains them better quality of life for the remainder of a normal life span, so establishing diagnosis (to gain access to treatment) remains a major barrier. Until more research allows clarification of optimal diagnostic criteria, prioritization of patients’ interests compels physicians to use

consensus-2 diagnostic criteria for MCAS to establish diagnosis in any patient with presentation inviting consideration of MCAS.

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Use of Large Language Models, AI and Machine Learning

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References

1. Akin C, Metcalfe DD. The biology of kit in disease and the application of pharmacogenetics. *J Allergy Clin Immunol* 2004;114:13–19.
2. Kalesnikoff J, Galli SJ. New developments in mast cell biology. *Nat Immunol* 2008;9:1215–23.
3. Theoharides TC. Mast cells: the immune gate to the brain. *Life Sci* 1990;46:607–17.
4. Afrin LB, Pöhlau D, Raithel 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.
5. Galli SJ, Maurer M, Lantz CS. Mast cells as sentinels of innate immunity. *Curr Opin Immunol* 1999;11:53–9.
6. Crivellato E, Ribatti D. The mast cell: an evolutionary perspective. *Biol Rev Camb Phil Soc* 2010;85:347–60.
7. Molderings GJ, Afrin LB. A survey of the currently known mast cell mediators with potential relevance for therapy of mast cell-induced symptoms. *Naunyn-Schmied Arch Pharmacol* 2023;396:2881–91.
8. Ibelgauf H. Mast cells. In: COPE: cytokines and cells online pathfinder encyclopaedia; 2025. <http://www.cells-talk.com/index.php/page/copelibrary?key=mast%20cells> [Accessed 19 Jan 2026].
9. Molderings GJ, Kolck UW, Scheurlen C, Brüss M, Homann J, Von Kügelgen I. Multiple novel alterations in kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand J Gastroenterol* 2007;42:1045–53.
10. Molderings GJ, Meis K, Kolck UW, Homann J, Frieling T. Comparative analysis of mutation of tyrosine kinase kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 2010;62:721–7.
11. Takahashi T, Kadosawa T, Nagase M, Matsunaga S, Mochizuki M, Nishimura R, et al. Visceral mast cell tumors in dogs: 10 cases (1982–1997). *J Am Vet Med Assoc* 2000;216:222–6.
12. Govier SM. Principles of treatment for mast cell tumors. *Clin Tech Small Anim Pract* 2003;18:103–6.

13. Amon U, Hartmann K, Horny HP, Nowak A. Mastocytosis – an update. *J Dtsch Dermatol Ges* 2010;8:695–711.
14. Haenisch B, Nöthen MM, Molderings GJ. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. *Immunology* 2012;137:197–205.
15. Molderings GJ, Haenisch B, Bogdanow M, Fimmers R, Nöthen MM. Familial occurrence of systemic mast cell activation disease. *PLoS One* 2013;8:e76241.
16. Cohen SS, Skovbo S, Vestergaard H, Kristensen T, Møller M, Bindslev-Jensen C, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol* 2014;166:521–8.
17. van Doormaal JJ, Arends S, Bruneekreeft KL, van der Wal VB, Sietsma J, van Voorst Vader PC, et al. Prevalence of indolent systemic mastocytosis in a Dutch region. *J Allergy Clin Immunol* 2013;131:1429–31.e1.
18. Soter NA, Wasserman SI. Physical urticaria/angioedema: an experimental model of mast cell activation in humans. *J Allergy Clin Immunol* 1980;66:358–65.
19. Roberts LJ2nd. Recurrent syncope due to systemic mastocytosis. *Hypertension* 1984;6:285–94.
20. Roberts LJ, 2nd. Carcinoid syndrome and disorders of systemic mast-cell activation including systemic mastocytosis. *Endocrinol Metab Clin N Am* 1988;17:415–36.
21. Roberts LJ2nd, Oates JA. Biochemical diagnosis of systemic mast cell disorders. *J Invest Dermatol* 1991;96:195–245; discussion 245–255; 605–655.
22. Sonneck K, Florian S, Müllauer L, Wimazal F, Födinger M, Sperr WR, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol* 2007;142:158–64.
23. 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.
24. Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol* 2014;3:1–17.
25. Afrin LB, Ackerley MB, Bluestein LS, Brewer JH, Brook JB, Buchanan AD, et al. Diagnosis of mast cell activation syndrome: a global “consensus-2”. *Diagnosis (Berl)* 2020;8:137–52.
26. 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.
27. Valent P, Akin C, Bonadonna P, Hartmann K, Broesby-Olsen S, Brockow K, et al. Mast cell activation syndrome: importance of consensus criteria and call for research. *J Allergy Clin Immunol* 2018;142:1008–10.
28. Valent P, Akin C. Doctor, I think I am suffering from MCAS: differential diagnosis and separating facts from fiction. *J Allergy Clin Immunol Pract* 2019;7:1109–14.
29. 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.
30. 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. *J Allergy Clin Immunol* 2019;144:883–96.
31. Passia E, Jandus P. Using baseline and peak serum tryptase levels to diagnose anaphylaxis: a review. *Clin Rev Allergy Immunol* 2020;58:366–76.
32. Valent P, Akin C, Nedoszytko B, Bonadonna P, Hartmann K, Niedoszytko M, et al. Diagnosis, classification and management of mast cell activation syndromes (MCAS) in the era of personalized medicine. *Int J Mol Sci* 2020;21:9030.
33. Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. *HemaSphere* 2021;5:e646.
34. Romantowski J, Górka A, Lange M, Nedoszytko B, Gruchala-Niedoszytko M, Niedoszytko M. How to diagnose mast cell activation syndrome: practical considerations. *Pol Arch Intern Med* 2020;130:317–23.
35. Sabato V, Michel M, Blank U, Ebo DG, Vitte J. Mast cell activation syndrome: is anaphylaxis part of the phenotype? A systematic review. *Curr Opin Allergy Clin Immunol* 2021;21:426–34.
36. Valent P, Hartmann K, Bonadonna P, Niedoszytko M, Triggiani M, Arock M, et al. Mast cell activation syndromes: collegium Internationale Allergologicum Update 2022. *Int Arch Allergy Immunol* 2022;183:693–705.
37. Valent P, Hartmann K, Bonadonna P, Gülen T, Brockow K, Alvarez-Twose I, et al. Global classification of mast cell activation disorders: an ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. *J Allergy Clin Immunol Pract* 2022;10:1941–50.
38. Akin C. How to evaluate the patient with a suspected mast cell disorder and how/when to manage symptoms. *Hematol Am Soc Hematol Educ Program* 2022;2022:55–63.
39. Gülen T. Using the right criteria for MCAS. *Curr Allergy Asthma Rep* 2024;24:39–51.
40. Mikryukova NV, Kalinina NM. Mast cell activation syndrome: a new outlook. *Med Immunol (Russia)* 2023;25:1289–98.
41. Mikryukova NV, Kalinina NM. Mast cell activation syndrome: the overdiagnosis problem. *Med Immunol (Russia)* 2025;27:651–6.
42. Akin C. Dilemma of mast cell activation syndrome: overdiagnosed or underdiagnosed? *J Allergy Clin Immunol Pract* 2024;12:762–3.
43. Lee E, Picard M. Diagnosis and management of mast cell activation syndrome (MCAS) in Canada: a practical approach. *Allergy Asthma Clin Immunol* 2025;21:49.
44. Valent P, Carter M. Diagnosis, prognostication, and management of patients with mastocytosis: status 2026. *J Allergy Clin Immunol Pract* 2026;14:53–5.
45. Carter MC, Lange M, Alvarez-Twose I, Renke J, Morales-Cabeza C, Caligaris H, et al. Management of mastocytosis and mast cell activation in children. *J Allergy Clin Immunol Pract* 2026;14:30–42.
46. Akin C, Gülen T, Castells MC, Elberink HO, Valent P. Diagnosis and management of patients with mast cell activation syndromes: status 2026. *J Allergy Clin Immunol Pract* 2026;14:19–28.
47. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010;126:1099–104.e4.
48. Sakai K, Ren S, Schwartz LB. A novel heparin-dependent processing pathway for human tryptase. Autocatalysis followed by activation with dipeptidyl peptidase I. *J Clin Invest* 1996;97:988–95.
49. Zhang MQ, Timmerman H. Mast cell tryptase and asthma. *Mediat Inflamm* 1997;6:311–17.
50. 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.

51. Maitland A, Brock I, Reed W. Immune dysfunction, both mast cell activation disorders and primary immune deficiency, is common among patients with hypermobile spectrum disorder (HSD) or hypermobile type Ehlers Danlos Syndrome (hEDS). In: Proceedings of the EDS ECHO summit; 2020. Session 12, poster number 001. <https://www.ehlers-danlos.com/wp-content/uploads/2020/09/Poster-001-FINAL-A-Maitland-et-al-EDS-ECHO-SUMMIT-Oct-2020.pdf> [Accessed 3 August 2025].
52. Jennings SV, Slee VM, Finnerty CC, Hempstead JB, Bowman AS. Symptoms of mast cell activation: the patient perspective. *Ann Allergy Asthma Immunol* 2021;127:407–9.
53. Afrin LB, Self S, Menk J, Lazarchick J. Characterization of mast cell activation syndrome. *Am J Med Sci* 2017;353:207–15.
54. Zenker N, Afrin LB. Utilities of various mast cell mediators in diagnosing mast cell activation syndrome. *Blood* 2015;126:5174.
55. Doyle LA, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL. A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients. *Am J Surg Pathol* 2014;38:832–43.
56. Panarelli NC, Hornick JL, Yantiss RK. What is the value of counting mast cells in gastrointestinal mucosal biopsies? *Mod Pathol* 2023;36:100005.
57. Panarelli NC. Mast cell disorders of the gastrointestinal tract: clarity out of chaos. *Surg Pathol Clin* 2023;16:755–64.
58. Weinstock LB, Pace LA, Rezaie A, Afrin LB, Molderings GJ. Mast cell activation syndrome: a primer for the gastroenterologist. *Dig Dis Sci* 2021;66:965–82.
59. Weinstock LB. Mast cell activation syndrome and the triad of MCAS, POTS, and hypermobile EDS. *Am J Gastroenterol* 2024;120:1429–33.
60. Weinstock LB, Walters AS, Brook JB, Kaleem Z, Afrin LB, Molderings GJ. Restless legs syndrome is associated with mast cell activation syndrome. *J Clin Sleep Med* 2020;16:401–8.
61. Valent P, Bonadonna P, Hartmann K, Broesby-Olsen S, Brockow K, Butterfield JH, et al. Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe systemic mast cell activation and mast cell activation syndrome. *Int Arch Allergy Immunol* 2019;180:44–51.
62. Gülen T, Akin C, Bonadonna P, Siebenhaar F, Broesby-Olsen S, Brockow K, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: a critical review. *J Allergy Clin Immunol Pract* 2021;9:3918–28.
63. De Schryver S, Halbrich M, Clarke A, La Vielle 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.
64. Baretto RL, Beck S, Heslegrave 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.
65. Egner W, Cook TM, Garcez T, Marinho S, Kemp H, Lucas DN, et al. Specialist perioperative allergy clinic services in the UK 2018: results from the Royal College of Anaesthetists Sixth National Audit Project (NAP6) investigation of perioperative anaphylaxis. *Clin Exp Allergy* 2018;48:846–61.
66. 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. *Allergy* 2019;74:1157–65.
67. Dua S, Dowey J, Foley L, Islam S, King Y, Ewan P, et al. Diagnostic value of tryptase in food allergic reactions: a prospective study of 160 adult peanut challenges. *J Allergy Clin Immunol Pract* 2018;6:1692–8.e1.
68. Butterfield JH. Survey of mast cell mediator levels from patients presenting with symptoms of mast cell activation. *Int Arch Allergy Immunol* 2020;181:43–50.
69. Butterfield JH. Increased excretion of mast cell mediator metabolites during mast cell activation syndrome. *J Allergy Clin Immunol Pract* 2023;11:2542–6.
70. Zaghmout T, Maclachlan L, Bedi N, Gülen T. Low prevalence of idiopathic mast cell activation syndrome among 703 patients with suspected mast cell disorders. *J Allergy Clin Immunol Pract* 2024;12:753–61.
71. Solomon BD, Khatri P. Clustering of clinical symptoms using large language models reveals low diagnostic specificity of proposed alternatives to consensus mast cell activation syndrome criteria. *J Allergy Clin Immunol* 2025;155:213–18.e4.
72. Quigley EMM, Noble O, Ansari U. The suggested relationships between common GI symptoms and joint hypermobility, POTS, and MCAS. *Gastroenterol Hepatol* 2024;20:479–89.
73. Blitshteyn S. Dysautonomia, hypermobility spectrum disorders and mast cell activation syndrome as migraine comorbidities. *Curr Neurol Neurosci Rep* 2023;23:769–76.
74. Weinstock LB, Nelson RM, Blitshteyn S. Neuropsychiatric manifestations of mast cell activation syndrome and response to mast-cell-directed treatment: a case series. *J Pers Med* 2023;13:1562.
75. Wang E, Ganti T, Vaou E, Hohler A. The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome. *Allergy Asthma Proc* 2021;42:243–6.
76. Yao L, Subramaniam K, Raja KM, Arunachalam A, Tran A, Pandey T, et al. Association of postural orthostatic tachycardia syndrome, hypermobility spectrum disorders, and mast cell activation syndrome in young patients; prevalence, overlap and response to therapy depends on the definition. *Front Neurol* 2025;16:1513199.
77. Schofield JR. Persistent antiphospholipid antibodies, mast cell activation syndrome, postural orthostatic tachycardia syndrome and post-COVID syndrome: 1 year on. *Eur J Case Rep Intern Med* 2021;8:002378.
78. Hashemizad A, Dela Cruz J, Narayan A, Maxwell AJ. Hyperventilation during rest and exercise in orthostatic intolerance and spiky-leaky syndrome. *Front Neurol* 2025;16:1512671.
79. Afrin LB, Dempsey TT, Weinstock LB. Post-HPV-vaccination mast cell activation syndrome: possible vaccine-triggered escalation of undiagnosed pre-existing mast cell disease? *Vaccines (Basel)* 2022;10:127.
80. Miller CS, Palmer RF, Dempsey TT, Ashford NA, Afrin LB. Mast cell activation may explain many cases of chemical intolerance. *Environ Sci Eur* 2021;33:129.
81. Palmer RF, Dempsey TT, Afrin LB. Chemical intolerance and mast cell activation: a suspicious synchronicity. *J Xenobiot* 2023;13:704–18.
82. Nagy ÉS, Westaway M, Danieletto S, Afrin LB. Breast implant illness may be rooted in mast cell activation: a case-controlled retrospective analysis. *Ann Surg Open* 2024;5:e398.
83. Afrin LB. Mast cell activation syndrome as a significant comorbidity in sickle cell disease. *Am J Med Sci* 2014;348:460–4.
84. Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in long-COVID. *Int J Infect Dis* 2021;112:217–26.
85. Weinstock LB, Brook JB, Blasingame KE, Kaleem Z, Afrin LB, Molderings GJ. Tinnitus in mast cell activation syndrome: a prospective survey of 114 patients. *J Otolaryngol Neurotol Res* 2021;4:92–6. Available from: <https://www.gidocnet.net/wp-content/uploads/2024/11/1291738.pdf>.

86. Afrin LB. Utility of hydroxyurea in mast cell activation syndrome. *Exp Hematol Oncol* 2013;2:28.
87. Weinstock LB, Brook JB, Molderings GJ. Efficacy and toxicity of hydroxyurea in mast cell activation syndrome patients refractory to standard medical therapy: retrospective case series. *Naunyn-Schmied Arch Pharmacol* 2022;395:1441–7.
88. Häder T, Molderings GJ, Klawonn F, Conrad R, Mücke M, Sellin J. Cluster-analytic identification of clinically meaningful subtypes in MCAS: the relevance of heat and cold. *Dig Dis Sci* 2023;68:3400–12.
89. Hamilton MJ. Mast cell activation syndrome and gut dysfunction: diagnosis and management. *Curr Gastroenterol Rep* 2024;26:107–14.
90. Wilder-Smith CH, Drewes AM, Materna A, Olesen SS. Symptoms of mast cell activation syndrome in functional gastrointestinal disorders. *Scand J Gastroenterol* 2019;54:1322–5.
91. Afrin LB, Dempsey TT, Rosenthal LS, Dorff SR. Successful mast-cell-targeted treatment of chronic dyspareunia, vaginitis, and dysfunctional uterine bleeding. *J Obstet Gynaecol* 2019;39:664–9.
92. Dorff SR, Afrin LB. Mast cell activation syndrome in pregnancy, delivery, postpartum and lactation: a narrative review. *J Obstet Gynaecol* 2020;40:889–901.
93. 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.
94. Pearce G, Bell L, Pezaro S, Reinhold E. Childbearing with hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders: a large international survey of outcomes and complications. *Int J Environ Res Publ Health* 2023;20:6957.
95. 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.
96. Afrin LB, Weinstock LB, Dempsey TT, Aschenbrenner K, Blitshteyn S, Schofield JR. Utility of glucagon-like-peptide-1-receptor agonists in mast cell activation syndrome. *Am J Med Sci* 2025;15:S0002–9629 01106–1.
97. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis* 2020;100:327–32.
98. Theoharides TC, Conti P. COVID-19 and multisystem inflammatory syndrome, or is it mast cell activation syndrome? *J Biol Regul Homeost Agents* 2020;34:1633–6.
99. Talkington J, Nickell SP. *Borrelia burgdorferi* spirochetes induce mast cell activation and cytokine release. *Infect Immun* 1999;67:1107–15.
100. Schofield JR, Afrin LB. Recognition and management of medication excipient reactivity in patients with mast cell activation syndrome. *Am J Med Sci* 2019;357:507–11.
101. Taylor CR, Anderson RR, Gange RW, Michaud NA, Flotte TJ. Light and electron microscopic analysis of tattoos treated by Q-switched ruby laser. *J Invest Dermatol* 1991;97:131–6.
102. Kröger M, Schleusener J, Lademann J, Meinke MC, Jung S, Darvin ME. Tattoo pigments are localized intracellularly in the epidermis and dermis of fresh and old tattoos: in vivo study using two-photon excited fluorescence lifetime imaging. *Dermatology* 2023;239:478–93.
103. Vera-Sirera B, Riusueño-Mata P, Ricart-Vayá JM, Baquero Ruiz de la Hermosa C, Vera-Sempere F. Clinicopathological and immunohistochemical study of oral amalgam pigmentation. *Acta Otorrinolaringol Esp* 2012;63:376–81.
104. Patipa M, Jakobiec FA, Krebs W. Light and electron microscopic findings with permanent eyeliner. *Ophthalmology* 1986;93:1361–5.
105. Rozniecki JJ, Dimitriadou V, Lambracht-Hall M, Pang X, Theoharides TC. Morphological and functional demonstration of rat dura mater mast cell-neuron interactions in vitro and in vivo. *Brain Res* 1999;849:1–15.
106. Kovacs M, Alamón C, Maciel C, Varela V, Ibarburu S, Tarragó L, et al. The pathogenic role of c-Kit+ mast cells in the spinal motor neuron-vascular niche in ALS. *Acta Neuropathol Commun* 2021;9:136.
107. Weinstock LB, Afrin LB, Reiersen AM, Brook J, Blitshteyn S, Ehrlich G, et al. Prevalence and treatment response of neuropsychiatric disorders in mast cell activation syndrome. *Brain Behav Immun Health* 2025;48:101048.
108. Theoharides TC, Stewart JM. Genitourinary mast cells and survival. *Transl Androl Urol* 2015;4:579–86.
109. Daylor V, Griggs M, Weintraub A, Byrd R, Petrucci T, Huff M, et al. Defining the chronic complexities of hEDS and HSD: a global survey of diagnostic challenges, life-long comorbidities, and unmet needs. *J Clin Med* 2025;14:5636.
110. Afrin LB. Some cases of hypermobile Ehlers-Danlos syndrome may be rooted in mast cell activation syndrome. *Am J Med Genet C Semin Med Genet* 2021;187:466–72.
111. Maxwell AJ, Wardly D. The complex path to intracranial hypertension and CSF leak in those with hypermobility and dysautonomia; the theory of spiky-leaky syndrome. *J Mar Pediatr* 2024;5:2–86. Available from: https://www.medicalandresearch.com/current_issue/1962.
112. Maxwell AJ. Dysautonomia. In: Jovin D, editor. *Disjointed: navigating the diagnosis and management of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders*, 1st ed. San Francisco: Hidden Stripes Publications; 2020:135–215 pp. Available from: <https://www.amazon.com/Disjointed-Navigating-hypermobile-Ehlers-Danlos-Hypermobility/dp/1734794909>.
113. Volberding PA, Bascom R, Bitterman AD, Bulbena-Villarrasa A, Chopra P, Dietz HC, et al. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Selected Heritable Disorders of Connective Tissue and Disability. In: Wedge RA, Cartaxo T, Spicer CM, Volberding PA, editors. *Selected heritable disorders of connective tissue and disability*. Washington (DC): National Academies Press (US); 2022. 4. Ehlers-Danlos syndromes and hypermobility spectrum disorders. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK584966/>.
114. Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *Int J Cardiol* 2017; 232:1–4.
115. Chen M, Kim A, Zuraw B, Doherty TA, Christiansen S. Mast cell disorders: protean manifestations and treatment responses. *Ann Allergy Asthma Immunol* 2018;121:128–30.
116. DeCicco J, Johnson J, Wilson R. Conditions associated with median arcuate ligament syndrome: POTS, MCAS, EDS. In: Shouhed D, Ghanem OM, El-Hayek K, editors. *Median arcuate ligament syndrome: state of the art management*. Cham, Switzerland: Springer; 2025:39–57 pp.
117. Chao N, Dunlap E, Plant J, Nagarsheth KH. Vascular compressions and syndromes associated with median arcuate ligament syndrome: May-Thurner, nutcracker, and pelvic congestion syndrome. In: Shouhed D, Ghanem OM, El-Hayek K, editors. *Median arcuate ligament syndrome: state of the art management*. Cham, Switzerland: Springer; 2025:59–80 pp.

118. Smith SJ, Smith BH, Sichlau MJ, Chen B, Knight D, Rowe PC. Nonpelvic comorbid symptoms of 45 patients with pain of pelvic venous origin, before and after treatment. *Phlebology* 2025;40:66–79.
119. Odin R, Zhang S, Zimmermann N, Bernstein JA. Utility of quantifying mast cells in gastrointestinal biopsies in patients with suspected mast cell activation disorder. *Ann Allergy Asthma Immunol* 2025;20: S1081–1206 01351-1.
120. Afrin LB, Dempsey TT, Molderings GJ. Learned cautions regarding antibody testing in mast cell activation syndrome. *Diagnosis (Berl)* 2023;10:424–31.
121. Molderings GJ, Haenisch B, Brettner S, Homann J, Menzen M, Dumoulin FL, et al. Pharmacological treatment options for mast cell activation disease. *Naunyn-Schmied Arch Pharmacol* 2016;389: 671–94.
122. 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.
123. Kan J, Chen Y, Gu Q, Hu N, Qiao Y, Chen Y, et al. Analysis of the relationship between histamine H1 receptor antagonists and broad dementia events using the FAERS, JADER, and CVAR databases. *Expert Opin Drug Saf* 2025;1–12. <https://doi.org/10.1080/14740338.2025.2517232>.
124. Su CH, Huang KH, Yang Y, Gau S-Y, Chung N-J, Wu P-T, et al. Cumulative dose effects of H1 antihistamine use on the risk of dementia in patients with allergic rhinitis. *J Allergy Clin Immunol Pract* 2024;12:2155–65.
125. Yang CC, Chien WC, Chung CH, Lai CY, Tzeng NS. The usage of histamine type 1 receptor antagonist and risk of dementia in the elderly: a nationwide cohort study. *Front Aging Neurosci* 2022;14: 811494.
126. Hwang IC, Chang J, Park SM. A nationwide population-based cohort study of dementia risk among acid suppressant users. *Am J Geriatr Psychiatry* 2018;26:1175–83.
127. Harris CI, Nasar B, Finnerty CC. Nutritional implications of mast cell diseases. *J Acad Nutr Diet* 2024;124:1387–96.
128. Shaker M, Yuan I, Kennedy KL, Capucilli P, Spergel JM. Idiopathic anaphylaxis and undiagnosed anorexia nervosa. *Ann Allergy Asthma Immunol* 2019;122:215–17.
129. Katre M, Kaninde A, Biloliar H. Food allergy with idiopathic anaphylaxis and mast cell activation syndrome diagnostic challenge. *Arch Dis Child* 2021;106:A65–6.
130. Ratnaseelan AM, Tsilioni I, Theoharides TC. Effects of mycotoxins on neuropsychiatric symptoms and immune processes. *Clin Ther* 2018; 40:903–17.
131. Campbell AW, Weinstock LB. Molds, mycotoxins, the brain, the gut and misconceptions. *Altern Ther Health Med* 2022;28:8–12. Available from: https://www.alternative-therapies.com/oa/pdf/Campbel28_3l.pdf.
132. Afrin LB, Spruill LS, Schabel SI, Young-Pierce JL. Improved metastatic uterine papillary serous cancer outcome with treatment of mast cell activation syndrome. *Oncology (Williston Park)* 2014;28:129–31, 134; Available from: <https://www.cancernetwork.com/view/improved-metastatic-uterine-papillary-serous-cancer-outcome-treatment-mast-cell-activation-syndrome>.
133. Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. *Transl Res* 2016;174:33–59.
134. Thompson C, Trněný M, Morschhauser F, Salles G, Reagan PM, Hertzberg M, et al. PROs vs clinician-reported adverse events in a large clinical trial: findings from the phase 3 POLARIX study. *Blood* 2026;147:254–65.
135. Odejide OO, Abel GA. Patient-reported outcomes: a Polaris for POLARIX. *Blood* 2026;147:219–20.
136. Afrin LB, Cichocki F, Hoeschen A, Beckman KB, Gupta K, Nguyen J, et al. Mast cell regulatory gene variants are common in mast cell activation syndrome. *Blood* 2016;128:4878.
137. 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.
138. 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.
139. Soter NA, Austen KF, Wasserman SI. Oral disodium cromoglycate in the treatment of systemic mastocytosis. *N Engl J Med* 1979;301:465–9.
140. Yang Y, Lu JY, Wu X, Summer S, Whoriskey J, Saris C, et al. G-protein-coupled receptor 35 is a target of the asthma drugs cromolyn disodium and nedocromil sodium. *Pharmacol* 2010;86:1–5.
141. Edwards AM. The discovery of cromolyn sodium and its effect on research and practice in allergy and immunology. *J Allergy Clin Immunol* 2005;115:885–58.
142. Edwards AM, Hagberg H. Oral and inhaled sodium cromoglycate in the management of systemic mastocytosis: a case report. *J Med Case Rep* 2010;4:193.
143. Tolar J, Tope WD, Neglia JP. Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004;350:735–6.
144. Cikler E, Ersoy Y, Cetinel S, Ercan F. The leukotriene d4 receptor antagonist, montelukast, inhibits mast cell degranulation in the dermis induced by water avoidance stress. *Acta Histochem* 2009;111: 112–18.
145. 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.
146. Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 2009;102:155–60.
147. 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.
148. Butterfield JH. Survey of aspirin administration in systemic mastocytosis. *Prostag Other Lipid Mediat* 2009;88:122–4.
149. Finn DF, Walsh JJ. Twenty-first century mast cell stabilizers. *Br J Pharmacol* 2013;170:23–37.
150. Theoharides TC, Bielory L. Mast cells and mast cell mediators as targets of dietary supplements. *Ann Allergy Asthma Immunol* 2004; 93:S24–34.
151. Weinstock LB, Brook JB, Myers TL, Goodman B. Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment. *BMJ Case Rep* 2018;2018:bcr2017221405.
152. Kurosawa M, Amano H, Kanbe N, Igarashi Y, Nagata H, Yamashita T, et al. Response to cyclosporin and low-dose methylprednisolone in aggressive systemic mastocytosis. *J Allergy Clin Immunol* 1999;103: S412–20.
153. Zen M, Canova M, Campana C, Bettio S, Nalotto L, Rampudda M, et al. The kaleidoscope of glucocorticoid effects on immune system. *Autoimmun Rev* 2011;10:305–10.
154. Hagel AF, Layritz CM, Hagel WH, Hagel H-J, Hagel E, Dauth W, et al. Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases. *Naunyn-Schmied Arch Pharmacol* 2013;386:789–93.

155. Johnston CS, Martin LJ, Cai X. Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. *J Am Coll Nutr* 1992;11:172–6.
156. Masini E, Di Bello MG, Pistelli A, Raspanti S, Gambassi F, Mugnai L, et al. Generation of nitric oxide from nitrovasodilators modulates the release of histamine from mast cells. *J Physiol Pharmacol* 1994;45:41–53.
157. Schmidt H, Schmidt W, Müller T, Böhler H, Gebhard MM, Martin E. N-acetylcysteine attenuates endotoxin-induced leukocyte-endothelial cell adhesion and macromolecular leakage in vivo. *Crit Care Med* 1997;25:858–63.
158. Maxová H, Novotná J, Vajner L, Tomášová H, Vytásek R, Vízek M, et al. In vitro hypoxia increases production of matrix metalloproteinases and tryptase in isolated rat lung mast cells. *Physiol Res* 2008;57: 903–10.
159. Blesa S, Cortijo J, Mata M, Serrano A, Closa D, Santangelo F, et al. Oral N-acetylcysteine attenuates the rat pulmonary inflammatory response to antigen. *Eur Respir J* 2003;21:394–400.
160. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; 66:821–35.
161. Dimitrakov J, Kroenke K, Steers WD, Berde C, Zurakowski D, Freeman MR, et al. Pharmacologic management of painful bladder syndrome/interstitial cystitis: a systematic review. *Arch Intern Med* 2007;167:1922–9.
162. Nickel JC, Barkin J, Forrest J, Mosbaugh PG, Hernandez-Graulau J, Kaufman D, et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 2005;65: 654–8.
163. Hoffmann K, Xifró RA, Hartweg JL, Spitzlei P, Meis K, Molderings GJ, et al. Inhibitory effects of benzodiazepines on the adenosine A(2B) receptor mediated secretion of interleukin-8 in human mast cells. *Eur J Pharmacol* 2013;700:152–8.
164. Molderings GJ, Raithel M, Kratz F, Azemar M, Haenisch B, Harzer S, et al. Omalizumab treatment of systemic mast cell activation disease: experiences from four cases. *Intern Med* 2011;50:1–5.
165. Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. *Ann Allergy Asthma Immunol* 2012;108:383–4.
166. Kibsgaard L, Skjold T, Deleuran M, Vestergaard C. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. *Acta Derm Venereol* 2014;94: 363–4.
167. Kontou-Fili K, Filis CI, Voulgari C, Panayiotidis PG. Omalizumab monotherapy for bee sting and unprovoked “anaphylaxis” in a patient with systemic mastocytosis and undetectable specific IgE. *Ann Allergy Asthma Immunol* 2010;104:537–9.
168. Trojan TD, Khan DA. Calcineurin inhibitors in chronic urticaria. *Curr Opin Allergy Clin Immunol* 2012;12:412–20.
169. Broyd H, Koffer A, Assem ESKM. Effect of cyclosporin-A on secretion from intact and permeabilised mast cells. *Inflamm Res* 2005;54: S07–8.
170. Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. *J Urol* 2005;174:2235–8.
171. Whitcup SM, Chan CC, Luyo DA, Bo P, Li Q. Topical cyclosporine inhibits mast cell-mediated conjunctivitis. *Investig Ophthalmol Vis Sci* 1996;37:2686–93.
172. Serhat Inaloz H, Ozturk S, Akcali C, Kirtak N, Tarakcioglu M. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: a clinical and immunological evaluation. *J Dermatol* 2008;35:276–82.
173. Stellato C, de Paulis A, Ciccarelli A, Patella V, Casolaro V, Marone G, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. *J Invest Dermatol* 1992;98:800–4.
174. Harrison CA, Bastan R, Peirce MJ, Munday MR, Peachell PT. Role of calcineurin in the regulation of human lung mast cell and basophil function by cyclosporine and FK506. *Br J Pharmacol* 2007;150: 509–18.
175. Bridges AJ, Malone DG, Jicinsky J, Chen M, Ory P, Engber W, et al. Human synovial mast cell involvement in rheumatoid arthritis and osteoarthritis: relationship to disease type, clinical activity, and antirheumatic therapy. *Arthritis Rheum* 1991;34:1116–24.
176. Nielsen HJ. Histamine and histamine type-2 receptor antagonists in psoriasis. Mechanisms and speculations. *Dan Med Bull* 1991;38: 478–80.
177. Mulkins MA, Ng M, Lewis RA. Mycophenolic acid inhibits the degranulation of rat peritoneal mast cells. *Cell Immunol* 1992;141: 508–17.
178. Espinosa E, Valitutti S, Laroche M, Laurent C, Apoil PA, Hermine O, et al. Hydroxychloroquine as a novel therapeutic approach in mast cell activation diseases. *Clin Immunol* 2018;194:75–9.
179. Moraly J, Rossignol J, Rouzaud C, Gabas T, Bouktit LL, et al. Efficacy and safety of mammalian target of rapamycin inhibitors in systemic mastocytosis: a nationwide French pilot study. *Am J Hematol* 2024;99: 1095–102.
180. Afrin LB, Hamm LL. Polycythemia from mast cell activation syndrome: lessons learned. *Am J Med Sci* 2011;342:44–9.
181. Afrin LB. Mast cell activation disorder masquerading as pure red cell aplasia. *Int J Hematol* 2010;91:907–8.
182. Lim K-H, 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.
183. Afrin LB. Mast cell activation syndrome masquerading as agranulocytosis. *Military Med* 2012;177:113–17.
184. Droogendijk HJ, Kluin-Nelemans HJC, van Doormaal JJ, Oranje AR, van de Loosdrecht AA, van Daele PLA. Imatinib mesylate in the treatment of systemic mastocytosis: a phase II trial. *Cancer* 2006;107: 345–51.
185. Vega-Ruiz A, Cortes JE, Sever M, Manshoury T, Quintás-Cardama A, Luthra R, et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. *Leuk Res* 2009; 33:1481–4.
186. Pardanani A, Elliott M, Reeder T, Li C-Y, Baxter EJ, Cross NCP, et al. Imatinib for systemic mast-cell disease. *Lancet* 2003;362:535–6.
187. Aman J, Peters MJ, Weenink C, van Nieuw Amerongen GP, Vonk Noordegraaf A. Reversal of vascular leak with imatinib. *Am J Respir Crit Care Med* 2013;188:1171–3.
188. Vaali K, Lappalainen J, Lin AH, Mäyränpää MI, Kovanen PT, Berstad A, et al. Imatinib mesylate alleviates diarrhea in a mouse model of intestinal allergy. *Neuro Gastroenterol Motil* 2012;24:e325–335.
189. Quintás-Cardama A, Jain N, Verstovsek S. Advances and controversies in the diagnosis, pathogenesis, and treatment of systemic mastocytosis. *Cancer* 2011;117:5439–49.
190. Hochhaus A, Kantarjian H, Baccarani M, Cervantes F, Facon T, Goldberg S, et al. Dasatinib in patients with chronic phase chronic myeloid leukemia (CP-CML) who are resistant or intolerant to imatinib: results of the CA180013 “START-C” study. *J Clin Oncol* 2006; 24:6508. Available from: https://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.6508.

191. Verstovsek S, Tefferi A, Cortes J, O'Brien S, Garcia-Manero G, Pardanani A, et al. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. *Clin Cancer Res* 2008;14:3906–15.
192. Hantschel O, Rix U, Schmidt U, Bückstümmer T, Kneidinger M, Schütze G, et al. The Btk tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib. *Proc Natl Acad Sci USA* 2007;104:13283–8.
193. Gleixner KV, Mayerhofer M, Cerny-Reiterer S, Hörmann G, Rix U, Bennett KL, et al. KIT-D816V-independent oncogenic signaling in neoplastic cells in systemic mastocytosis: role of Lyn and Btk activation and disruption by dasatinib and bosutinib. *Blood* 2011;118:1885–98.
194. Gotlib J, Berubé C, Gowney JD, Chen C-C, George TI, Williams C, et al. Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V KIT mutation. *Blood* 2005;106:2865–70.
195. Papayannidis C, Soverini S, Benedittis CD, Abbenante MC, Sartor C, Iacobucci I, et al. PKC412 (Midostaurin) is safe and highly effective in systemic mastocytosis patients: follow up of a single-center Italian compassionate use. *Cancer Res* 2014;74:746.
196. Knapper S, Cullis J, Drummond MW, Evely R, Everington T, Hoyle C, et al. Midostaurin a multi-targeted oral kinase inhibitor in systemic mastocytosis: report of an open-label compassionate use program in the United Kingdom. *Blood* 2011;118:5145.
197. Sabato V, Beyens M, Toscano A, Van Gasse A, Ebo DG. Mast cell-targeting therapies in mast cell activation syndromes. *Curr Allergy Asthma Rep* 2024;24:63–71.
198. De Filippis D, D'Amico A, Iuvone T. Cannabinomimetic control of mast cell mediator release: new perspective in chronic inflammation. *J Neuroendocrinol* 2008;20:20–5.
199. Greineisen WE, Turner H. Immunoactive effects of cannabinoids: considerations for the therapeutic use of cannabinoid receptor agonists and antagonists. *Int Immunopharmacol* 2010;10:547–55.
200. 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.
201. Borzutzky A, Morales PS, Mezzano V, Nussbaum S, Burks AW. Induction of remission of idiopathic anaphylaxis with rituximab. *J Allergy Clin Immunol* 2014;134:981–3.
202. Sánchez-Ramón S, Eguíluz-Gracia I, Rodríguez-Mazariego ME, Paravisini A, Zubeldia-Ortuño JM, Gil-Herrera J, et al. Sequential combined therapy with omalizumab and rituximab: a new approach to severe atopic dermatitis. *J Investig Allergol Clin Immunol* 2013;23:190–6. Available from: <https://www.jiaci.org/issues/vol23issue3/8.pdf>.
203. Butterfield JH. Interferon treatment for hypereosinophilic syndromes and systemic mastocytosis. *Acta Haematol* 2005;114:26–40.
204. Casassus P, Caillat-Vigneron N, Martin A, Simon J, Gallais V, Beaudry P, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. *Br J Haematol* 2002;119:1090–7.
205. Butterfield JH, Tefferi A, Kozuh GF. Successful treatment of systemic mastocytosis with high-dose interferon-alfa: long-term follow-up of a case. *Leuk Res* 2005;29:131–4.
206. Yoshida C, Takeuchi M, Tsuchiyama J, Sadahira Y. Successful treatment of KIT D816V-positive, imatinib-resistant systemic mastocytosis with interferon-alpha. *Intern Med* 2009;48:1973–8.
207. Tefferi A, Li CY, Butterfield JH, Hoagland HC. Treatment of systemic mast-cell disease with cladribine. *N Engl J Med* 2001;344:307–9.
208. Kluin-Nelemans HC, Oldhoff JM, van Doormaal JJ, van't Wout JW, Verhoef G, Gerrits WBJ, et al. Cladribine therapy for systemic mastocytosis. *Blood* 2003;102:4270–6.
209. Pardanani A, Hoffbrand AV, Butterfield JH, Tefferi A. Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. *Leuk Res* 2004;28:127–31.
210. Böhm A, Sonneck K, Gleixner KV, Schuch K, Pickl WF, Blatt K, et al. In vitro and in vivo growth-inhibitory effects of cladribine on neoplastic mast cells exhibiting the imatinib-resistant KIT mutation D816V. *Exp Hematol* 2010;38:744–55.
211. Radojković M, Ristić S, Colović N, Terzić T, Colović M. Response to cladribine in patient with systemic mastocytosis. *Vojnosanit Pregl* 2011;68:444–6.
212. Marech I, Patruno R, Zizzo N, Gadaleta C, Introna M, Zito AF, et al. Masitinib (AB1010), from canine tumor model to human clinical development: where we are? *Crit Rev Oncol Hematol* 2014;91:98–111.
213. Paul C, Sans B, Suarez F, Casassus P, Barete S, Lanternier F, et al. Masitinib for the treatment of systemic and cutaneous mastocytosis with handicap: a phase 2a study. *Am J Hematol* 2010;85:921–5.
214. Ustun C, Keklik Karadag F, Linden MA, Valent P, Akin C. Systemic mastocytosis: current status and challenges in 2024. *Blood Adv* 2025;9:2048–62.
215. Aradhya A, Vidal R, Javaid A, Oganessian A, Fidler C. Imatinib in mast cell activation syndrome: a retrospective pilot study. *Blood* 2025;146(suppl 1):4775.
216. Maurer M, Berger W, Giménez-Arnau A, Hayama K, Jain V, Reich A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2022;150(6):1498–1506.e2.
217. Khan AA, Riaz AA, Naseer F, Fatima N, Abrar Z, Malik L, et al. Efficacy, safety, and quality-of-life outcomes of remibrutinib in chronic spontaneous urticaria: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2025;13(12):3406–19.

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