

**A Collection of publications on the subject  
of Mast Cell Activation Syndrome  
Jan 2018**

**Top Ten Papers – Pages 2 - 12**

**Detailed Bibliography of Other Papers**

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## **MCAS – Formally Recognised**

The American Centre for disease Control (CDC) has issued a revised edition (2017) of ICD 10, the International Classification of Diseases, for the first time this includes a diagnostic classification of Mast Cell Activation Syndrome.

ICD-10 Coordination and Maintenance Committee Meeting March 19-20, 2014  
Minutes of meeting (published online)

“The Committee on Mast Cell Disorders of the American Academy of Allergy, Asthma and Immunology (AAAAI) in conjunction with The Mastocytosis Society, Inc. (TMS), have proposed new codes for MCAS in ICD-10-CM. Because MCAS, in all of its forms, can cause tremendous suffering and disability due to symptomatology from daily mast cell mediator release and may not be as rare as previously thought, it is imperative that ICD-10-CM codes be established for this group of newly defined diseases. At present time most of the patients suffering from MCAS are categorized or coded as having anaphylaxis, which not does reflect the chronic nature of their symptoms and provides no insight into their treatment and long-term management needs.”

**D89.40 Mast cell activation, unspecified**

**Mast cell activation disorder, unspecified**

**Mast cell activation syndrome, NOS**

**D89.41 Monoclonal mast cell activation syndrome**

**D89.42 Idiopathic mast cell activation syndrome**

**D89.43 Secondary mast cell activation**

**Secondary mast cell activation syndrome**

**Code also underlying etiology, if known**

**D89.49 Other mast cell activation disorder**

**Other mast cell activation syndrome**

## TOP 10 MCAS MUST READ PAPERS

1. Afrin, L. B., Butterfield, J., Raithel, M. & Molderings. Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options. *Ann. Med.* **48**, 190–201 (2016).
2. Afrin, L. B. in *Mast Cells: Phenotypic Features, Biological Functions and Role in immunity* 155–232 (Nova Science Publishers, 2013). doi:10.1146/annurev.immunol.21.120601.141110
3. Valent, P. *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.* **157**, 215–225 (2012).
4. Seneviratne, S. L., Maitland, A. & Afrin, L. Mast cell disorders in Ehlers-Danlos syndrome. *Am. J. Med. Genet. Part C Semin. Med. Genet.* **236**, 226–236 (2017).
5. Molderings, G. J. *et al.* Pharmacological treatment options for mast cell activation disease. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **389**, 671–694 (2016).
6. Theoharides C, Valent, T. & Akin, C. Mast Cells, Mastocytosis, and Related Disorders. *N. Engl. J. Med.* **373**, 163–172 (2015).
7. Molderings, G. J. The genetic basis of mast cell activation disease - looking through a glass darkly. *Crit. Rev. Oncol. Hematol.* **93**, 75–89 (2015).
8. Wirz S, Molderings GJ. A Practical Guide for Treatment of Pain in Patients with Systemic Mast Cell Activation Disease. *Pain Physician.* 2017 Sep;20(6):E849-E861.
9. Lyons, J. J. *et al.* Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat. Genet.* **48**, (2016).
10. Afrin, L., Self, S., Menk, J. & Lazarchick, J. Characterization of Mast Cell Activation Syndrome. *Am. J. Med. Sci.* **353**, 207–215 (2017).

1. Afrin, L. B., Butterfield, J., Raithel, M. & Molderings. Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options. *Ann. Med.* **48**, 190–201 (2016).

## **Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options.**

Afrin LB, Butterfield JH, Raithel M, Molderings GJ.

### **Author information**

Division of Hematology, Oncology, and Transplantation, University of Minnesota , Minneapolis , MN , USA;  
Program for the Study of Mast Cell and Eosinophil Disorders, Mayo Clinic, Rochester, MN USA;  
Department of Internal Medicine , Waldkrankenhaus St. Marien, Erlangen, Germany;  
Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany.

### **Abstract**

Mast cell (MC) disease has long been thought to be just the rare disease of mastocytosis (in various forms, principally cutaneous and systemic), with aberrant MC mediator release at symptomatic levels due to neoplastic MC proliferation. Recent discoveries now show a new view is in order, with mastocytosis capping a metaphorical iceberg now called "MC activation disease" (MCAD, i.e. disease principally manifesting inappropriate MC activation), with the bulk of the iceberg being the recently recognized "MC activation syndrome" (MCAS), featuring inappropriate MC activation to symptomatic levels with little to no inappropriate MC proliferation. Given increasing appreciation of a great menagerie of mutations in MC regulatory elements in mastocytosis and MCAS, the great heterogeneity of MCAD's clinical presentation is unsurprising. Most MCAD patients present with decades of chronic multisystem polymorbidity generally of an inflammatory ± allergic theme. Preliminary epidemiologic investigation suggests MCAD, while often misrecognized, may be substantially prevalent, making it increasingly important that practitioners of all stripes learn how to recognize its more common forms such as MCAS. We review the diagnostically challenging presentation of MCAD (with an emphasis on MCAS) and current thoughts regarding its biology, epidemiology, natural history, diagnostic evaluation, and treatment.

PMID: [27012973](#) DOI: [10.3109/07853890.2016.1161231](#)

2. Afrin, L. B. in *Mast Cells: Phenotypic Features, Biological Functions and Role in immunity* 155–232 (Nova Science Publishers, 2013). doi:10.1146/annurev.immunol.21.120601.141110

## The presentation, diagnosis and treatment of mast cell activation syndrome

Lawrence B Afrin

### Author information

Division of Hematology/Oncology, Medical University of South Carolina, Charleston, SC, USA

### Abstract

First recognized in 1991 and finally termed such in 2007, “mast cell activation syndrome” (MCAS) is a large, likely quite prevalent collection of illnesses resulting from MCs which have been inappropriately activated but which, in contrast to the rare “mastocytosis,” are not proliferating, or otherwise accumulating, to any significant extent. Due to the marked diversity of direct and indirect, local and remote biological effects caused by the plethora of mediators released by MCs, MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. Suspected to be of clonal origin in most cases, MCAS usually is acquired relatively early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Initial manifestations often occur in childhood or adolescence but are non-specific; in fact, virtually all of the syndrome’s manifestations are non-specific, leading to decades of mysterious illness (and incorrect diagnoses often poorly responsive to empiric therapies) prior to diagnosis. A large menagerie of mutations in MC regulatory elements has been found in MCAS patients; most patients appear to have multiple such mutations, with no clear patterns, or genotype-phenotype correlations, yet apparent. Such mutational heterogeneity likely drives the heterogeneity of aberrant MC mediator expression, in turn causing the extreme heterogeneity of clinical presentation. Different MCAS patients can present with polar opposite clinical aberrancies. All of the body’s systems can be affected by MCAS. In addition to clinical heterogeneity, diagnosis is confounded by difficulty not only in detecting sensitive and specific biomarkers of primary MC disease but also in finding histologic evidence of a non-proliferative disease wrought by cells capable of great pleomorphism. For example, in contrast to proliferative mastocytosis which usually drives significantly elevated tryptase levels, relatively non- proliferative MCAS usually presents with normal tryptase levels; instead, histamine, MC specific prostaglandins, and other mediators need to be assessed in evaluations for MCAS. [abridged]

[https://www.novapublishers.com/catalog/product\\_info.php?products\\_id=42603](https://www.novapublishers.com/catalog/product_info.php?products_id=42603)

[Free full text]

3. Valent, P. *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*

## **Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal.**

Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, Castells M, Escribano L, Hartmann K, Lieberman P, Nedoszytko B, Orfao A, Schwartz LB, Sotlar K, Sperr WR, Triggiani M, Valenta R, Horny HP, Metcalfe DD.

### **Author information**

Division of Hematology and Hemostaseology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria.

### **Abstract**

Activation of tissue mast cells (MCs) and their abnormal growth and accumulation in various organs are typically found in primary MC disorders also referred to as mastocytosis. However, increasing numbers of patients are now being informed that their clinical findings are due to MC activation (MCA) that is neither associated with mastocytosis nor with a defined allergic or inflammatory reaction. In other patients with MCA, MCs appear to be clonal cells, but criteria for diagnosing mastocytosis are not met. A working conference was organized in 2010 with the aim to define criteria for diagnosing MCA and related disorders, and to propose a global unifying classification of all MC disorders and pathologic MC reactions. This classification includes three types of 'MCA syndromes' (MCASs), namely primary MCAS, secondary MCAS and idiopathic MCAS. MCA is now defined by robust and generally applicable criteria, including (1) typical clinical symptoms, (2) a substantial transient increase in serum total tryptase level or an increase in other MC-derived mediators, such as histamine or prostaglandin D<sub>2</sub>, or their urinary metabolites, and (3) a response of clinical symptoms to agents that attenuate the production or activities of MC mediators. These criteria should assist in the identification and diagnosis of patients with MCAS, and in avoiding misdiagnoses or overinterpretation of clinical symptoms in daily practice. Moreover, the MCAS concept should stimulate research in order to identify and exploit new molecular mechanisms and therapeutic targets.

PMID: [22041891](#) PMID: [PMC3224511](#) DOI: [10.1159/000328760](#) [Free full text]

4. Seneviratne, S. L., Maitland, A. & Afrin, L. Mast cell disorders in Ehlers-Danlos syndrome. *Am. J. Med. Genet. Part C Semin. Med. Genet.* **236**, 226–236 (2017).

## **Mast cell disorders in Ehlers-Danlos syndrome.**

Seneviratne SL, Maitland A, Afrin L

### **Author information**

Institute of Immunity and Transplantation, Royal Free Hospital and University College London, UK and Faculty of Medicine, University of Colombo, Sri Lanka

### **Abstract**

Well known for their role in allergic disorders, mast cells (MCs) play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury, with an array of chemical mediators. After being recruited to connective tissues, resident MCs progenitors undergo further differentiation, under the influence of signals from surrounding microenvironment. It is the differential tissue homing and local maturation factors which result in a diverse population of resident MC phenotypes. An abundance of MC reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts). Situated near nerve fibers, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, MCs can modulate the function of local and distant structures (e.g., other immune cell populations, fibroblasts, angiogenesis), and MC dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs). This report reviews basic biology of mast cells and mast cell activation as well as recent research efforts, which implicate a role of MC dysregulation beyond atopic disorders and in a cluster of Ehlers-Danlos Syndromes, non-IGE mediated hypersensitivity disorders, and dysautonomia

PMID: 28261938

DOI:[10.1002/ajmg.c.31555](https://doi.org/10.1002/ajmg.c.31555)

5. Molderings, G. J. *et al.* Pharmacological treatment options for mast cell activation disease. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **389**, 671–694 (2016).

## Pharmacological treatment options for mast cell activation disease

Molderings GJ, Haenisch B, Brettner S, Homann J, Menzen M, Dumoulin FL, Panse J, Butterfield J, Afrin LB

### Author information

Department of Oncology, Hematology and Palliative Care, Kreiskrankenhaus Waldbröl, Waldbröl, Germany.

### Abstract

Mast cell activation disease (MCAD) is a term referring to a heterogeneous group of disorders characterized by aberrant release of variable subsets of mast cell (MC) mediators together with accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs due to MC proliferation (systemic mastocytosis [SM] and MC leukemia [MCL]) or morphologically ordinary MCs due to decreased apoptosis (MC activation syndrome [MCAS] and well-differentiated SM). Clinical signs and symptoms in MCAD vary depending on disease subtype and result from excessive mediator release by MCs and, in aggressive forms, from organ failure related to MC infiltration. In most cases, treatment of MCAD is directed primarily at controlling the symptoms associated with MC mediator release. In advanced forms, such as aggressive SM and MCL, agents targeting MC proliferation such as kinase inhibitors may be provided. Targeted therapies aimed at blocking mutant protein variants and/or downstream signaling pathways are currently being developed. Other targets, such as specific surface antigens expressed on neoplastic MCs, might be considered for the development of future therapies. Since clinicians are often underprepared to evaluate, diagnose, and effectively treat this clinically heterogeneous disease, we seek to familiarize clinicians with MCAD and review current and future treatment approaches.

PMID: [27132234](#) PMCID: [PMC4903110](#) DOI: [10.1007/s00210-016-1247-1](#) [Free full text]

6. Theoharides C, Valent, T. & Akin, C. Mast Cells, Mastocytosis, and Related Disorders. *N. Engl. J. Med.* **373**, 163–172 (2015).

## **Mast Cells, Mastocytosis, and Related Disorders.**

Theoharides TC, Valent P, Akin C.

### **Author information**

Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, and Department of Internal Medicine, Tufts University School of Medicine, Tufts Medical Center Mastocytosis Center, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School Department of Internal Medicine I, Division of Hematology and Hemostaseology and Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Vienna.

### **Abstract**

Mast cells, which are present in most tissues, mature in situ from hematopoietic progenitors and acquire unique features of local effector cells. These features vary, depending on the tissue microenvironment. This article provides an overview of recent developments concerning the physiology and pathobiology of mast cells. We discuss current diagnostic and therapeutic approaches to mast cell disorders, with an emphasis on mastocytosis.

PMID: [26154789](#) DOI: [10.1056/NEJMra1409760](#)

### **See comments in:**

Theoharides TC, Valent P, Akin C.  
*N Engl J Med.* 2015 Nov 5;373(19):1885-6.

PMID: [26535528](#) DOI: [10.1056/NEJMc1510021](#)



7. Molderings, G. J. The genetic basis of mast cell activation disease - looking through a glass darkly. *Crit. Rev. Oncol. Hematol.* **93**, 75–89 (2015).

## **The genetic basis of mast cell activation disease - looking through a glass darkly.**

Molderings GJ.

### **Author information**

Institute of Human Genetics, University Hospital of Bonn, Sigmund-Freud-Str. 25, D-53127 Bonn, Germany.  
Electronic address:.

### **Abstract**

Within the last decade, and in particular since 2012, research has greatly extended our understanding of the molecular basis of systemic mast cell activation disease (MCAD). Initial studies demonstrated that somatic mutations in the tyrosine kinase KIT led to the establishment of a clonal mast cell population. Recent studies, in particular those involving next generation sequencing analyses of advanced systemic mastocytosis, have revealed mutations in additional genes. The respective genes encode proteins for various signaling pathways, epigenetic regulators, the RNA splicing machinery, and transcription factors. Although almost all of the detected mutations are somatic in nature, transgenerational transmission of MCAD appears to be quite common. However, the molecular mechanisms underlying genetic predestination, e.g. germline mutations and the contribution of epigenetic processes, still await identification. The aim of the present review is to present and discuss available genetic findings, and to outline the relationship between adult-onset systemic MCAD and childhood-onset mastocytosis, often termed cutaneous mastocytosis, on the basis of current genetic data. Finally, the implications of increased knowledge of the molecular basis of MCAD in terms of diagnostics and therapy are discussed.

PMID: [25305106](#) DOI: [10.1016/j.critrevonc.2014.09.001](#) [**Free full text**]

8. Wirz S, Molderings GJ. A Practical Guide for Treatment of Pain in Patients with Systemic Mast Cell Activation Disease. *Pain Physician*. 2017 Sep;20(6):E849-E861.

## **A Practical Guide for Treatment of Pain in Patients with Systemic Mast Cell Activation Disease.**

### Abstract

Systemic mast cell activation disease (MCAD, a subclass of mastocytosis), which has a prevalence of around 17% (at least in the German population), is characterized by accumulation of genetically altered dysfunctional mast cells with abnormal release of these cells' mediators. Since mast cells affect functions in potentially every organ system, often without causing abnormalities in routine laboratory or radiologic testing, this disease has to be considered routinely in the differential diagnosis of patients with chronic multisystem polymorbidity of a generally inflammatory and allergic theme. Pain in its different manifestations is a common symptom in MCAD found in more than three-quarters of the MCAD patients. Because of the specific mast cell-related causes of pain in MCAD it should be treated specifically, if possible, deduced from their putative mast cell mediator-related causes. As yet, there is no official guideline for treatment of MCAD at all. The present review focuses on mast cell mediator-induced acute and chronic pain and the current state of analgesic drug therapy options in MCAD. Due to the high prevalence of MCAD, many physicians are often faced with the issue of pain management in MCAD patients. Hence, our practical guide should contribute to the improvement of patient care. Key words: Pain therapy, mast cell activation disease, mast cell activation syndrome, systemic mastocytosis, mast cell.

PMID: [28934791](#) [Free full text]

9. Lyons, J. J. *et al.* Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat. Genet.* **48**, (2016).

## **Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number**

Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, Ho N, Zhao M, Liu Y, O'Connell MP, Trivedi NN, Nelson C, DiMaggio T, Jones N, Matthews H, Lewis KL, Oler AJ, Carlson RJ, Arkwright PD, Hong C, Agama S, Wilson TM, Tucker S, Zhang Y, McElwee JJ, Pao M, Glover SC, Rothenberg ME, Hohman RJ, Stone KD, Caughey GH, Heller T, Metcalfe DD, Biesecker LG, Schwartz LB, Milner JD.

### **Author Information**

Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, US National Institutes of Health, Bethesda, Maryland, USA.

### **Abstract**

Elevated basal serum tryptase levels are present in 4-6% of the general population, but the cause and relevance of such increases are unknown. Previously, we described subjects with dominantly inherited elevated basal serum tryptase levels associated with multisystem complaints including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility. Here we report the identification of germline duplications and triplications in the TPSAB1 gene encoding  $\alpha$ -tryptase that segregate with inherited increases in basal serum tryptase levels in 35 families presenting with associated multisystem complaints. Individuals harboring alleles encoding three copies of  $\alpha$ -tryptase had higher basal serum levels of tryptase and were more symptomatic than those with alleles encoding two copies, suggesting a gene-dose effect. Further, we found in two additional cohorts (172 individuals) that elevated basal serum tryptase levels were exclusively associated with duplication of  $\alpha$ -tryptase-encoding sequence in TPSAB1, and affected individuals reported symptom complexes seen in our initial familial cohort. Thus, our findings link duplications in TPSAB1 with irritable bowel syndrome, cutaneous complaints, connective tissue abnormalities, and dysautonomia.

PMID: 27749843      PMCID: [PMC5397297](https://pubmed.ncbi.nlm.nih.gov/PMC5397297/)    DOI: [10.1038/ng.3696](https://doi.org/10.1038/ng.3696)

10. Afrin, L., Self, S., Menk, J. & Lazarchick, J. Characterization of Mast Cell Activation Syndrome. *Am. J. Med. Sci.* **353**, 207–215 (2017).

## Characterization of Mast Cell Activation Syndrome

Afrin LB, Self S, Menk J, Lazarchick J.

### Author Information

Division of Hematology, Oncology and Transplantation, University of Minnesota (UMN), Minneapolis, Minnesota.

Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina.

Clinical and Translational Science Institute (CTSI), University of Minnesota, Minneapolis, Minnesota.

### Abstract

**Background:** Mast cell activation syndrome (MCAS), a recently recognized nonneoplastic mast cell disease driving chronic multisystem inflammation and allergy, appears prevalent and thus important. We report the first systematic characterization of a large MCAS population.

**Method:** Demographics, comorbidities, symptoms, family histories, physical examination and laboratory findings were reviewed in 298 retrospective and 115 prospective patients with MCAS. Blood samples from prospective subjects were examined by flow cytometry for clonal mast cell disease and tested for cytokines potentially driving the monocytosis frequent in MCAS.

**Results:** Demographically, white females dominated. Median ages at symptom onset and diagnosis were 9 and 49 years, respectively (range: 0-88 and 16-92, respectively) and median time from symptom onset to diagnosis was 30 years (range: 1-85). Median numbers of comorbidities, symptoms, and family medical issues were 11, 20, and 4, respectively (range: 1-66, 2-84, and 0-33, respectively). Gastroesophageal reflux, fatigue and dermatographism were the most common comorbidity, symptom and examination finding. Abnormalities in routine laboratories were common and diverse but typically modest. The most useful diagnostic markers were heparin, prostaglandin D<sub>2</sub>, histamine and chromogranin A. Flow cytometric and cytokine assessments were unhelpful.

**Conclusions:** Our study highlights MCAS's morbidity burden and challenging heterogeneity. Recognition is important given good survival and treatment prospects.

PMID: 28262205

PMCID: [PMC5341697](#)

DOI: [10.1016/j.amjms.2016.12.013](#)

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PMID: [27012973](#) DOI: [10.3109/07853890.2016.1161231](#)

1.2 Afrin LD. 2013 Nova Science Publishers, Mast Cells: Phenotypic Features, Biological Functions and Role in Immunity. Chapters. Presentation, Diagnosis, and Management of Mast Cell Activation Syndrome (pp. 155-232)

[https://www.novapublishers.com/catalog/product\\_info.php?products\\_id=42603](https://www.novapublishers.com/catalog/product_info.php?products_id=42603)

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PMID: [28780942](#) DOI: [10.1016/j.jaci.2017.06.007](#)

1.4 Baretto RL, Beck S, Heslegrave J et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: A perioperative perspective. *Allergy*. 2017 Dec;72(12):2031-2034.

PMID: [28609557](#) DOI: [10.1111/all.13226](#)

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PMID: [29094472](#) DOI: [10.1111/1742-6723.12875](#)

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1.7 Cookson H, Grattan C. An update on mast cell disorders. *Clin Med (Lond)*. 2016 Dec;16(6):580-583.

PMID: [27927825](#) DOI: [10.7861/clinmedicine.16-6-580](#)

1.8 Frieri M, Patel R, Celestin J. Mast cell activation syndrome: a review. *Curr Allergy Asthma Rep*. 2013 Feb;13(1):27-32.

PMID: [23179866](#) DOI: [10.1007/s11882-012-0322-z](#)

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## MAST CELL ACTION

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1.14 Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. *N Engl J Med.* 2015;373(2):163-72. PMID: [26154789](#) DOI: [10.1056/NEJMra1409760](#)

1.15 Valent P, Akin C, Arock M 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(3):215-25. PMID: [22041891](#) PMCID: [PMC3224511](#) DOI: [10.1159/000328760](#) [Free full text]

1.16 Wirz S, Hertfelder HJ, Seidel H, Homann J, Molderings GJ. Lower prevalence of vitamin D insufficiency in German patients with systemic mast cell activation syndrome compared with the general population. *Z Gastroenterol.* 2017 Dec;55(12):1297-1306. PMID: [29212100](#) DOI: [10.1055/s-0043-121346](#)

1.17 Afrin, L., Self, S., Menk, J. & Lazarchick, J. Characterization of Mast Cell Activation Syndrome. *Am. J. Med. Sci.* 2017; 353, 207-215. PMID: [28262205](#) PMCID: [PMC5341697](#) DOI: [10.1016/j.amjms.2016.12.013](#)

## 2. Testing

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