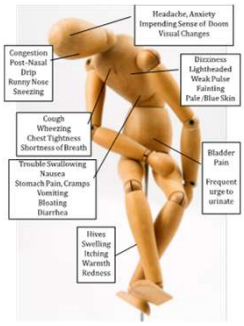


Anaphylaxis,

Mast Cell Activation Syndrome,

Or

Something Else

Anne Maitland, MD, PhD

Attending Physician, Metrodora Institute

Medical Director, Comprehensive Allergy & Asthma Care, PLLC

Assistant Professor, Icahn School of Medicine at Mt SinAi- Dept of medicine- Allergy & Clinical immunology

1

Learning Objectives

- A case report
- To review the scope of mast cell activation disease, including mast cell activation syndrome (MCAS)
- To understand the spectrum and heterogeneity of anaphylaxis
- To review diagnostic and management options for anaphylaxis and mast cell activation disease (MCAD)

2

What's in Name? [MCAS? Anaphylaxis?]

A doctor begins by examining the words of his patient to determine their clinical significance. He then translates the words into medical language, describing how the condition came to be, what it means, and how it may evolve.

Of all the words a doctor uses, the name he gives the illness has the greatest weight.

It forms the foundation of all subsequent discussion, not only between doctor and patient but also between doctor and doctor and between patient and patient.

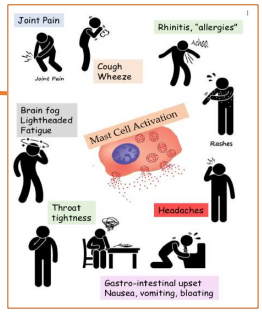
With a name, the patient can construct an explanation of his illness not only for others but for himself …

The name can also provide an instant community.

Jerome Groopman, Hurting All Over (2000)

3

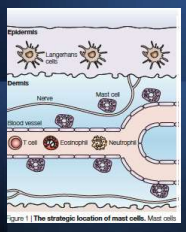
A case report:
Anaphylaxis? MCAS?

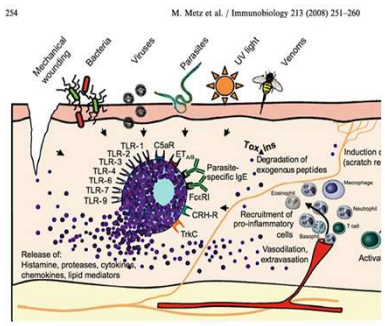


Or Something Else?

4

Spoiler Alert?





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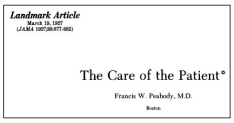


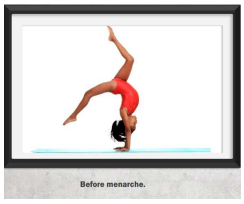
Landmark Article
March 16, 1927
(JAMA. 1927;88:877-882)

The Care of the Patient*

Francis W. Peabody, M.D.
Boston.

Take the case of a young woman, for instance, who entered the hospital with a history of nausea and discomfort in the upper part of the abdomen after eating. Mrs. Brown had "suffered many things of many physicians." Each of them gave her a tonic and limited her diet. She stopped eating everything that any of her physicians advised her to omit, and is now living on a little milk and a few crackers; but her symptoms persist

A patient
"who has nothing the matter with [her]"



Meet Sara.

6

After her 12th birthday, Sara started to experience

- increased frequency of headaches
- fatigue
- nausea and abdominal pain.

This coincided with the onset of her menstrual cycle and recurrent upper respiratory infection, after moving to a new home.

After several visits by her local pediatrician, her parents took her to a local allergy specialist and a pediatric gastroenterologist.

❖Histamine blockade,

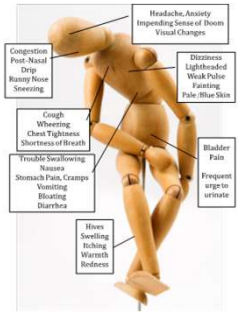
❖tricyclic agents,

❖FODmap diet was tried,

no change in her symptoms.

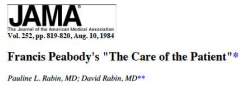
All of Sara's testing, requested by her general practitioner and several clinical specialists, were within normal limits: blood tests, X-rays, CAT scans, and endoscopy examinations.

Tryptase 9.4 ng/ml (Range < 11.4)



7

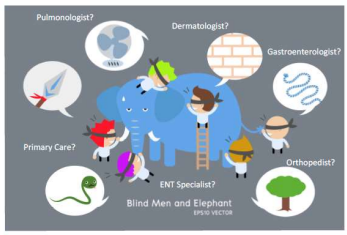
patients who do not show objective, organic pathological conditions and who are generally spoken of as having "nothing the matter with them."



Francis Peabody's "The Care of the Patient"*

*Pauline L. Rubin, MD; David Rubin, MD***

- Sara's local pediatrician tried her best, sending the family to various specialists to decode the cause of her ailments, while holding off school administrators, concerned about Sara's mounting absences.
- A neurologist diagnosed Sara with a migraine disorder, postural orthostatic tachycardia syndrome and suspected joint hypermobility.
- A local gastroenterologist tried to counter Sara's weight loss with different hypoallergenic formulas, via nasogastric tube feeds, but each formula caused pain.



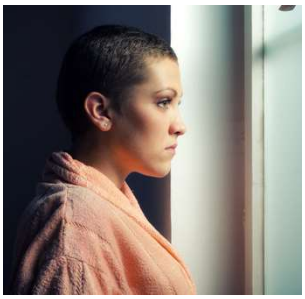
8

Functional Disorder? Dysfunctional Order?

An in-patient stay, at an out of state, pediatric hospital = amplified pain program = failed to alleviate any of her pain and ultimately entertained another psychiatric diagnosis.

Another allergy evaluation = detected pollen, but no food allergies.

Despite numerous doctors' appointments, across state lines, Sara went to bed in pain and awoke with nausea and fatigue, for over a year.



Shutterstock image

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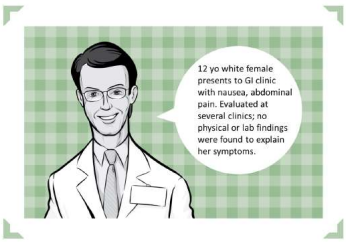

Food Aversion Disorder

Rx: NG feeds with hypoallergenic formulas. Psychiatry consult.

Rx: NG feeds with hypoallergenic formulas. Psychiatry consult.
Sara resisted having to go through another week of NG tube feeds;
Her mother asked for another opinion and the request was denied;
so Sara was placed in soft restraints for 3 days to receive NG tube feeds.
No change in pain, no gain in her weight; so Sara was discharged home.

10

Sara's Diagnosis?

MCAD/MCAS

MCAS Masqueraders

Cardiac conditions
Coronary hypersensitivity (the Kounis syndrome)*
Postural orthostatic tachycardia syndrome

Endocrine conditions
Fibromyalgia
Parathyroid tumor
Pheochromocytoma
Carcinoid syndrome

Digestive conditions
Adverse reaction to food*
Eosinophilic esophagitis*
Eosinophilic gastroenteritis*
Gastroesophageal reflux disease
Gluten enteropathy
Irritable bowel syndrome
Vasoactive intestinal peptide–secreting tumor

Immunologic conditions
Autoinflammatory disorders such as deficiency of interleukin 1–receptor antagonist*
Familial hyper-IgE syndrome
Vasculitis*

Neurologic and psychiatric conditions
Anxiety
Chronic fatigue syndrome
Depression
Headaches
Mixed organic brain syndrome
Somatization disorder
Autonomic dysfunction
Multiple sclerosis

Skin conditions
Angioedema*
Atopic dermatitis*
Chronic urticaria*
Scleroderma*

Localized mast-cell activation can occur.

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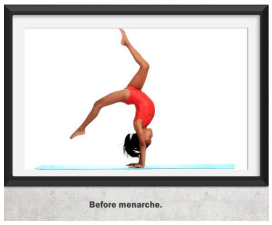
Hereditary Alpha Tryptasemia




SCIENCE

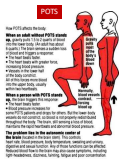
One Gene Mutation Links Three Mysterious, Debilitating Diseases

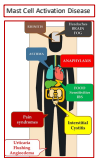
By Kate Horowitz
Oct 27, 2016

Ehlers-Danlos Syndrome (EDS), Postural Orthostatic Tachycardia Syndrome (POTS), and Mast Cell Activation Syndrome (MCAS) —a trifecta of weird diseases. POTS, EDS, and MCAS are so obscure that many doctors have never even heard of

12

HYPER-ALPHA TRYPTASEMIA
(HαT)





nature genetics

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

Findings associated with multiplications of TPSAB1 gene:

- Connective Tissue Abnormalities
- Dysautonomia
- Mast Cell Activation

13

209 **A New Disease Cluster: Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome, and Ehlers-Danlos Syndrome**

Ingrid Cheung, Peter Vadas, MD, PhD; St. Michael's Hospital, Toronto, ON, Canada.

RATIONALE: Patients with postural orthostatic tachycardia syndrome (POTS) and hypermobility often describe symptoms suggestive of mast cell activation. Herein, we describe a new, unique phenotype, characterized by the co-segregation of three disorders: POTS, Ehlers Danlos syndrome (EDS) and mast cell activation syndrome (MCAS).

METHODS: Participants with diagnoses of POTS and EDS were recruited from throughout North America through a patient support group and evaluated by questionnaire and supporting documentation. A formal diagnosis of POTS by a cardiologist included confirmation via tilt-table test. A formal diagnosis of EDS required assessment by a dermatologist, a Beighton score of ≥ 5/9 and a diagnostic skin biopsy. A questionnaire for MCAS was based on diagnostic criteria and validated symptoms as reported by Akin, Valent and Metcalfe (2010).

RESULTS: 15 participants completed questionnaires with required documentation. All eligible participants were female. 12 of these people had formal diagnoses of POTS (80%); 9 were diagnosed with both POTS and EDS, 6 of 9 patients with both POTS and EDS had validated symptoms of a mast cell disorder (66%), suggestive of MCAS.

CONCLUSIONS: From these pilot data, it appears that a mast cell disorder may frequently co-segregate with POTS and a collagen disorder such as EDS.

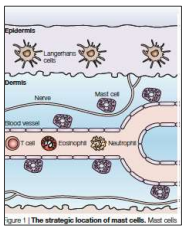


Figure 1 | **The strategic location of mast cells.** Mast cells

36

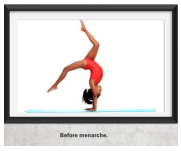
PREVALENCE OF ALLERGIC DISORDERS AND MAST CELL ACTIVATION SYNDROME IN PATIENTS WITH EHLERS DANLOS SYNDROME.

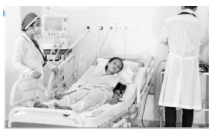
M. Lococo[1], S. Silverman[*2], A. Mailland[3]. *1. Boston, MA; 2. Philadelphia, PA; 3. New York, NY.*

Background: Patients with Ehlers Danlos Syndrome appear to have a significant prevalence of allergic disease and mast cell activation syndrome, a recurrent non-IgE mediated allergic reaction. This study aims to determine the prevalence of allergic disease and mast cell activation syndrome in Ehlers Danlos Syndrome patients. Methods: Patients with confirmed genetic diagnosis of Ehlers Danlos Syndrome were identified at an allergist's clinical practice. Information regarding patients' allergic rhinitis, asthma, urticaria and anaphylaxis were obtained via validated questionnaires. Chart review was also conducted

Earlier observations of disorders traveling with
Mast Cells/Connective Tissue/Nerve Crosstalk

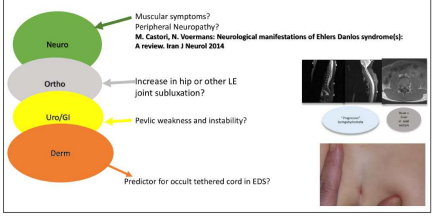
14



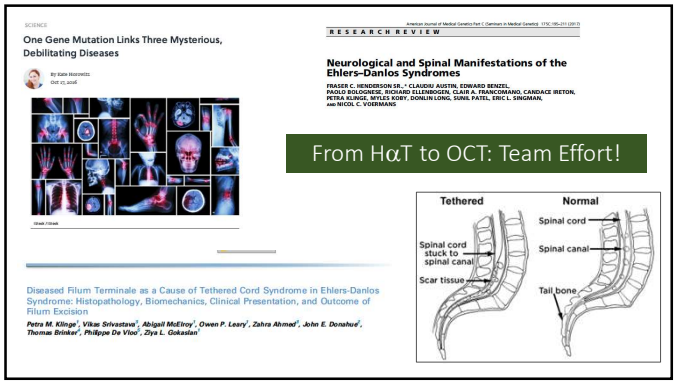


Etiology of Sara's pain with eating?

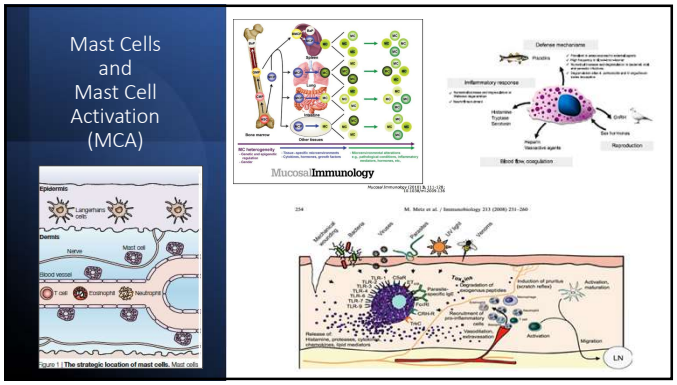
The occult tethered cord syndrome - EDS



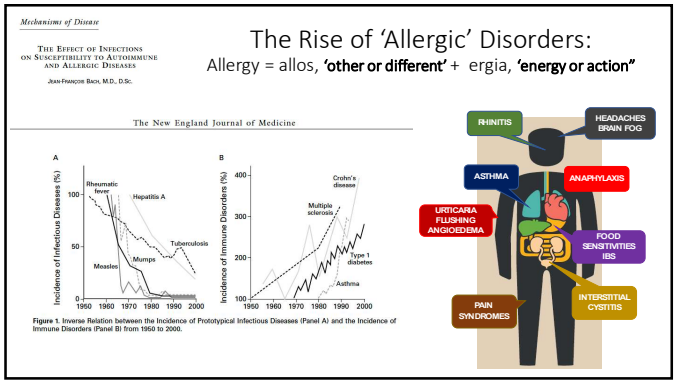
15


One Gene Mutation Links Three Mysterious, Debilitating Diseases
RESEARCH REVIEW
Neurological and Spinal Manifestations of the Ehlers–Danlos Syndromes
From HαT to OCT: Team Effort!
Tethered
Normal
Spinal cord
Spinal canal
Spinal cord stuck to spinal canal
Scar tissue
Tail bone
Diseased Filum Terminale as a Cause of Tethered Cord Syndrome in Ehlers-Danlos Syndrome: Histopathology, Biomechanics, Clinical Presentation, and Outcome of Filum Excision

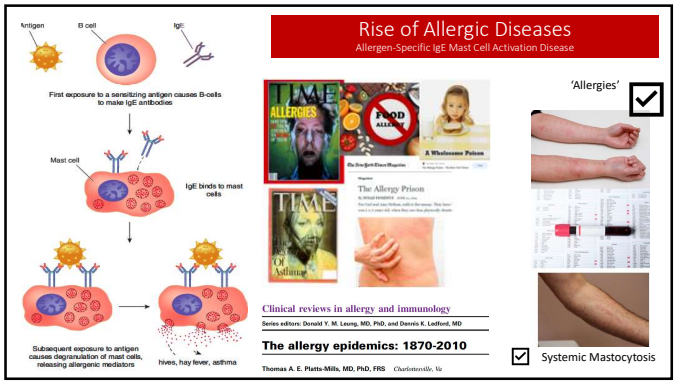
16


Mast Cells and Mast Cell Activation (MCA)
MucosalImmunology

17


Mechanisms of Disease
The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases
Jean-François Bach, M.D., D.Sc.
The Rise of 'Allergic' Disorders:
Allergy = allos, 'other or different' + ergia, 'energy or action"
The New England Journal of Medicine
Incidence of Infectious Diseases (%)
Incidence of Immune Disorders (%)
Rheumatic fever
Hepatitis A
Tuberculosis
Mumps
Measles
Crohn's disease
Multiple sclerosis
Type 1 diabetes
Asthma
RHINITIS
HEADACHES BRAIN FOG
ASTHMA
ANAPHYLAXIS
URTICARIA FLUSHING ANGIOEDEMA
FOOD SENSITIVITIES IBS
PAIN SYNDROMES
INTERSTITIAL CYSTITIS

18


Antigen
B cell
IgE
First exposure to a sensitizing antigen causes B-cells to make IgE antibodies
Mast cell
IgE binds to mast cells
Subsequent exposure to antigen causes degranulation of mast cells, releasing allergenic mediators
hives, hay fever, asthma
Rise of Allergic Diseases
Allergen-Specific IgE Mast Cell Activation Disease
Clinical reviews in allergy and immunology
The allergy epidemics: 1870-2010
Thomas A. E. Platts-Mills, MD, PhD, FRS
'Allergies'
Systemic Mastocytosis

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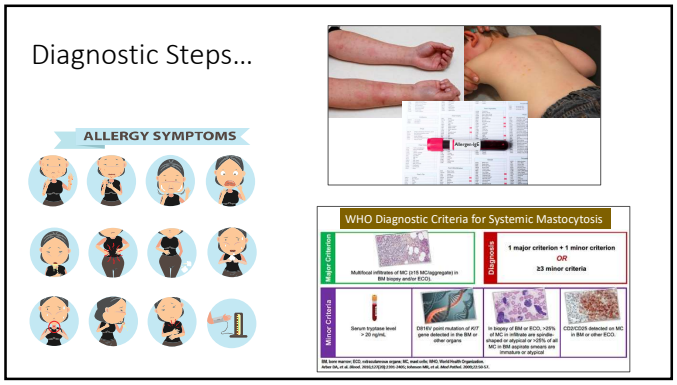
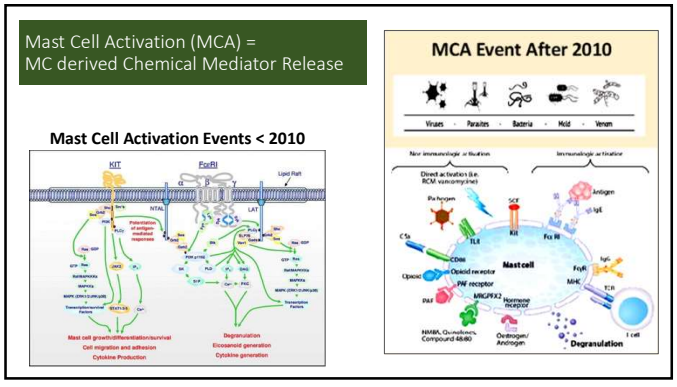

Diagnostic Steps…
ALLERGY SYMPTOMS
WHO Diagnostic Criteria for Systemic Mastocytosis
Major Criterion
Diagnosis
1 major criterion + 1 minor criterion
OR
≥3 minor criteria
Minor Criteria

20


Mast Cell Activation (MCA) =
MC derived Chemical Mediator Release
Mast Cell Activation Events < 2010
KIT
FcεRI
MCA Event After 2010
Viruses
Parasites
Bacteria
Mold
Venom
Mast cell
Degranulation

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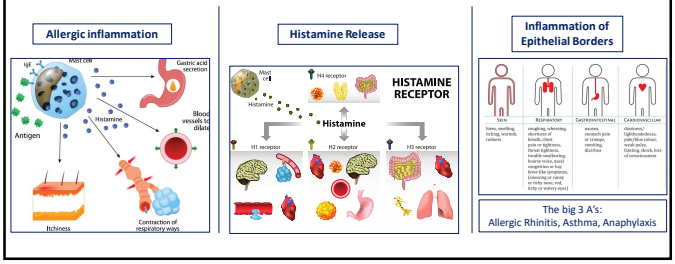
By 2010,
a growing number of patients and practitioners recognize MCA events beyond …



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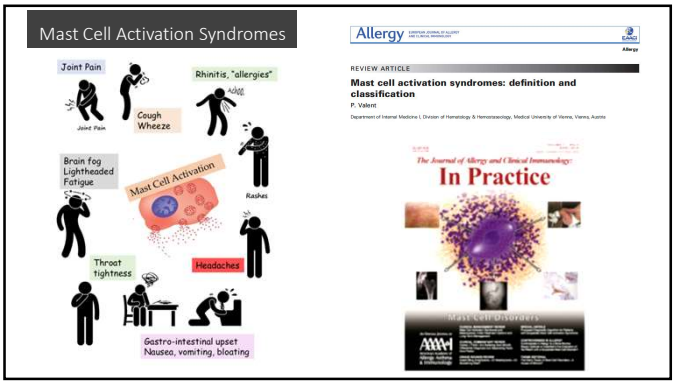

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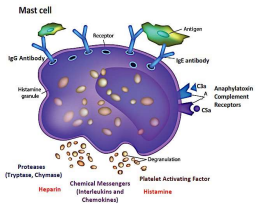
Mast Cell Activation Syndrome

When symptoms are

- recurrent,
- accompanied by an increase in mast cell–derived mediators in biological fluids, and
- responsive to treatment with
- mast cell–stabilizing or mediator-targeting drugs



the diagnosis of mast cell activation syndrome (MCAS) is appropriate.

MCAS = increased capacity of mast cells and basophils to release mediators of anaphylaxis, in response to cell activation, also termed 'releasability'

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MCA in 2 or more organ systems?

Mast Cell Activation Disorders

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,[a] Jason L. Hornick, MD, PhD,[b] Cem Akin, MD, PhD,[a] Mariana C. Castells, MD, PhD,[a] and Norton J. Greenberger, MD[a] *Boston, Mass*

Better with anti-MC/MC mediator medications?

- Histamine Blockade
- Leukotriene Antagonists
- Cromones
- Omalizumab
- Ketotifen

MCA events associated w/ validated MCA markers

- Tryptase
- Urine Methylhistamine
- Urine Prostaglandin D2
- Urine 11- Beta Prostaglandin F2alpha
- C kit mutation- tissue, peripheral blood
- CD25+ MC in biopsies
- Clustered MC in biopsies

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Criterion #1 MCAS Signs and Symptoms

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,[a] Jason L. Hornick, MD, PhD,[b] Cem Akin, MD, PhD,[a] Mariana C. Castells, MD, PhD,[a] and Norton J. Greenberger, MD[a] *Boston, Mass*

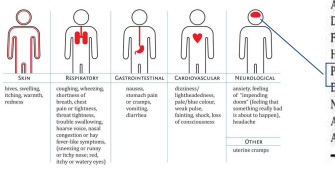
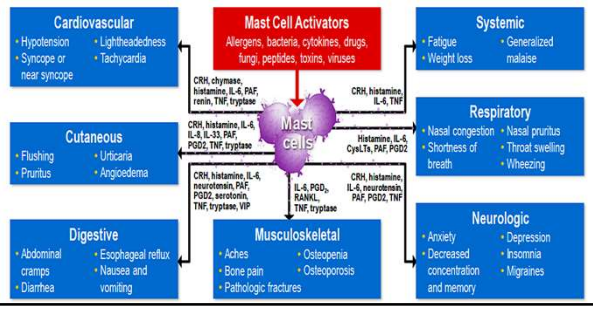


TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

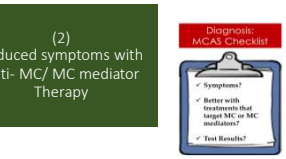
26

Clinical Consequences of MC Derived Chemical Mediator Release (MCAD/MCAS)



27

(2)
Reduced symptoms with Anti- MC/ MC mediator Therapy



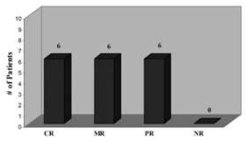


FIG 1. Assessment of treatment response. The total number of patients in each response-to-treatment category is shown by using the criteria established for mastocytosis. Complete regression (CR) was resolution of all symptoms, major regression (MR) was improvement in symptoms by greater than 50%, partial regression (PR) was improvement in symptoms by 10% to 50%, and no regression (NR) was less than 10% improvement in symptoms.

Non-clonal/ Clonal MCAD symptom relief	Clonal MCAD w/ increased MC burden
Histamine R1 Blockade (diphenhydramine, cetirizine, e.g.)	Protein Tyrosine Kinase Inhibitors (Imatinib, Avapritinib, Midostaurin)
Histamine R2 Blockade (famotidine, cimetidine, e.g.)	
Tricyclic Agents (doxepin, nortriptyline)	
Leukotriene Antagonists (montelukast, zafirlukast, zileuton)	Stem cell transplant
Aspirin	
Ketotifen Cromolyn	Anti-CD30?

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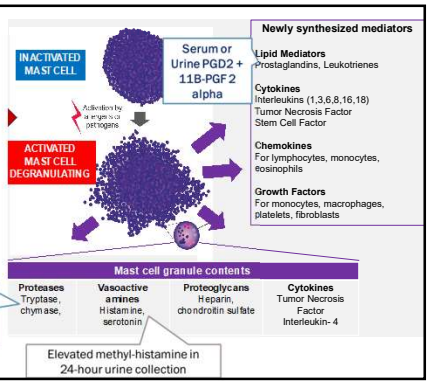
(3)
Measuring validated Mast Cell Activation Markers

Elevated Basal Serum Tryptase

Serum tryptase > 1.2 serum BT + 2 ng/ml



Serum or Urine PGD2 + 11B-PGF2 alpha

Elevated methyl-histamine in 24-hour urine collection

Newly synthesized mediators

Lipid Mediators
Prostaglandins, Leukotrienes

Cytokines
Interleukins (1,3,6,8,16,18)
Tumor Necrosis Factor
Stem Cell Factor

Chemokines
For lymphocytes, monocytes, eosinophils

Growth Factors
For monocytes, macrophages, platelets, fibroblasts

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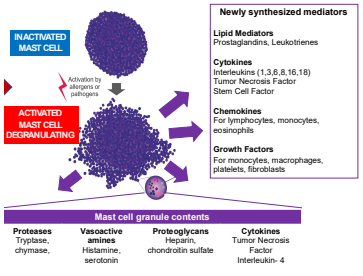
Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,* Jason L. Hornick, MD, PhD,* Cem Akin, MD, PhD,* Mariana C. Castells, MD, PhD,* and Norton J. Greenberger, MD* Boston, Mass



Newly synthesized mediators

Lipid Mediators
Prostaglandins, Leukotrienes

Cytokines
Interleukins (1,3,6,8,16,18)
Tumor Necrosis Factor
Stem Cell Factor

Chemokines
For lymphocytes, monocytes, eosinophils

Growth Factors
For monocytes, macrophages, platelets, fibroblasts

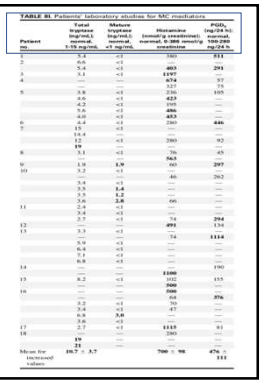


TABLE III. Patients' laboratory studies for MC mediators

Patient no.	Total tryptase (ng/mL) (normal, 3-11.5 ng/mL)	Mature tryptase (ng/mL) (normal, <7 ng/mL)	Histamine (normal g creatinine; normal, 0-300 nmol/g creatinine)	PGD_2 (ng/24 h) (normal, 0-300 ng/24 h)
1	5.4	<1	380	811
2	5.6	<1	—	—
3	5.4	<1	403	291
4	5.1	<1	1197	—
5	—	—	674	57
	3.8	<1	327	78
	4.6	<1	230	105
	4.2	<1	555	—
	3.6	<1	486	—
6	4.0	<1	453	—
7	6.4	<1	280	646
	15	<1	—	—
	11.4	—	—	—
	11.4	<1	280	92
8	5.1	<1	76	45
	—	—	563	—
9	3.9	1.9	60	297
10	5.2	<1	46	262
	5.4	<1	—	—
	3.5	1.4	—	—
	3.5	1.2	—	—
	3.6	2.8	66	—
11	2.4	<1	—	—
	3.4	<1	—	—
	2.7	<1	74	294
12	—	—	491	134
13	3.3	<1	74	1114
	5.9	<1	—	—
	6.4	<1	—	—
	7.1	<1	—	—
	6.8	<1	—	—
14	—	—	—	190
	—	—	1190	—
15	8.2	<1	102	155
	—	—	500	—
16	—	—	500	—
	—	—	64	376
	3.2	<1	70	—
	3.3	<1	47	—
	6.8	3.0	—	—
	3.6	<3	—	—
17	2.7	<3	1115	91
18	—	—	280	—
	19	—	—	—
	21	—	—	—
Mean for increased values	10.7 ± 3.7		700 ± 98	476 ± 111

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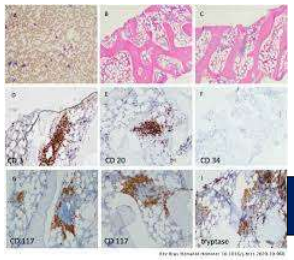


Small clusters

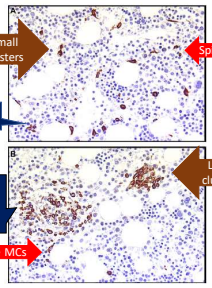
Spindle MCs

MMAS

Large clusters

Systemic mastocytosis

Spindle MCs



Histopathology: Clonal MCAD

Systemic mastocytosis (SM), monoclonal MC activation syndrome (MMAs)

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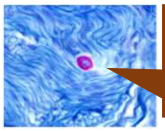
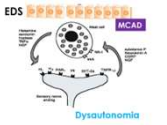
Hyper-Alpha Tryptasemia (HαT) : EDS-MCAS-POTS



Multiplication of alpha tryptase gene (HαT) 5-7% population



nature genetics

" Our findings link findings (germline) duplication in TPSAB1 (the alpha-tryptase gene) with **Irritable bowel syndrome / Cutaneous complaints /Connective Tissue Abnormalities / Dysautonomia**

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

Jonathan J Lyons[1], Xiaomin Yu[1], Jason D Hughes[2], Quang T Le[1], Ali Jamil[1], Yun Bai[1], Nancy Ho[1], Ming Zhao[2], Yihui Liu[1], Michael P O'Connell[1], Neil N Trivedi[4,7], Celeste Nelson[1], Thomas DiMaggio[1], Nina Jones[8], Helen Matthews[8], Katie L Lewis[10], Andrew J Oler[11], Ryan J Carlson[1], Peter D Arkwright[12], Celine Hong[13], Sherene Agama[1], Todd M Wilson[1], Sofie Tucker[1], Yu Zhang[2,3], Joshua I McElwee[1], Maryland Pao[14], Sarah C Glover[15], Marc E Rothenberg[16], Robert I Hohman[17], Kelly D Stone[1], George H Caughey[4,7], Theo Heller[4], Dean D Metcalfe[1], Leslie G Biesecker[18], Lawrence B Schwartz[2] & Joshua D Milner[1]

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Conclusions: patients with clinical manifestations of MC activation and a baseline serum tryptase > 8 ng/mL and who are undergoing upper endoscopy for intestinal symptoms should have specific stains to identify MCs

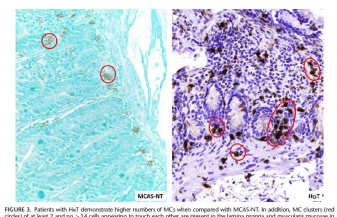
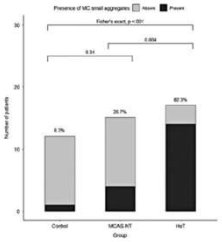


FIGURE 3. Patients with HαT demonstrate higher numbers of MCs when compared with MCAS-NT. In addition, MC clusters (red circles) of at least 2 and no > 14 cells appearing to touch each other are present in the lamina propria and muscularis mucosae in HαT patients and in the lamina propria in MCAS-NT patients (CD117 stain).



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- [Hypersensitivity disorders, including MCAD/MCAS and anaphylaxis are sometimes applied to patients with vague yet suggestive symptoms.
- These patients may suffer from an unrelated, overlooked disease.
- Applying solid diagnostic criteria, when considering the MCAD/MCAS-anaphylaxis diagnosis, helps avoid wasting time and money.

"I'll do some tests rather than give you a guess."

Mast Cell Activation Disorders On the Rise

By Mark L. Fuerst
Reviewed By Miriam K. Anand, MD, FAAAAI, FACAAI, Clinical Associate Professor, Arizona College of Osteopathic Medicine, Midwestern University; President, Allergy Associates & Asthma, Tempe, Arizona

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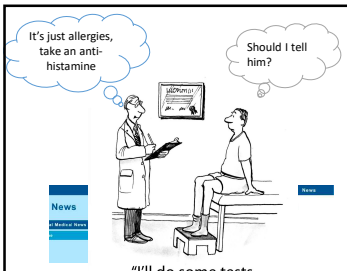

"I'll do some tests rather than give you a guess."

Delayed Diagnosis of MCAS is common

- patient has to recognize that they have a medical problem that warrants mention
- Next, the PCP has to recognize that the patient may have an inflammatory disorder that may benefit from referral to a specialist
- Specialist has to recognize that there is a lack of objective markers for MCAD/MCAS

Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

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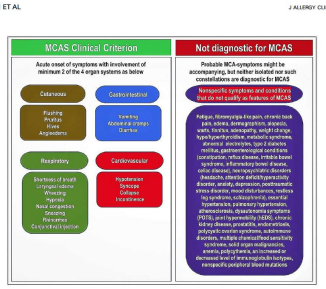

GÜLEN ET AL — J ALLERGY CLIN IMMUNOL PRACT — NOVEMBER 2021

DE GRUYTER — Diagnosis 2020; aop

Review

Lawrence B. Afrin*, Mary B. Ackerley, Linda S. Bluestein, Joseph H. Brewer, Jill B. Brook, Anjana D. Buchanan, Jill R. Cuni, William P. Davey, Tania T. Dempsey, Shanda R. Dorff, Martin S. Dubravec, Alena G. Guggenheim, Kimberly J. Hindman, Bruce Hoffman, David L. Kaufman, Stephanie J. Kratzer, Theodore M. Lee, Mindy S. Marantz, Andrew J. Maxwell, Kelly K. McCann, Dwight L. McKee, Laurie Menk Otto, Laura A. Pace, Dahra D. Perkins, Laurie Radovsky, Mary S. Raleigh, Sonia A. Rapaport, Emma J. Reinhold, Mark L. Rennaker, William A. Robinson, Aaron M. Roland, E. Scott Rosenbloom, Peter C. Rowe, Bene S. Ruhoy, David S. Sapersein, David A. Schlosser, Jill R. Schofield, Janet E. Settle, Leonard B. Weinstock, Martina Wengenroth, Mark Westaway, Shijun Cindy Xi and Gerhard J. Molderings

Diagnosis of mast cell activation syndrome: a global "consensus-2"

Overdiagnosis by "consensus-2" criteria has potential to be problematic, but underdiagnosis by "consensus-1" criteria seems the far larger problem given (1) increasing appreciation that MCAS is prevalent (up to 17o/o of the general population), and (2) most MCAS patients, regard less of illness duration prior to diagnosis, can eventually identify treatment yielding sustained improvement.

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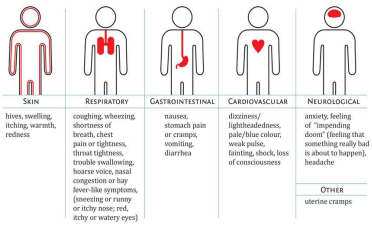
Unspoken 4th Criterion: r/o MCAS mimics



Skin	Respiratory	Gastrointestinal	Cardiovascular	Neurological
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever–like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bad is about to happen), headache

Other: uterine cramps

Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome

Digestive conditions

Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor

Immunologic conditions

Auto-inflammatory disorders such as deficiency of inter- leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

Neurologic/psychiatric conditions

Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction; Multiple sclerosis

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HHS Public Access
Author manuscript
Immunol Allergy Clin North Am. Author manuscript; available in PMC 2019 August 01.
Published in final edited form as:
Immunol Allergy Clin North Am. 2018 August ; 38(3): 469–481. doi:10.1016/j.iac.2018.04.002.

Non-Clonal Mast Cell Activation: A Growing Body of Evidence

Matthew J. Hamilton, M.D.
Assistant Professor, Harvard Medical School, Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Boston, MA. U.S.A.

patients present with … signs and symptoms suggesting mast cell activation disease without

- systemic mastocytosis (SM)
- autoimmune urticaria, or
- IgE-mediated allergy.

Other medical inflammatory conditions, auto-immune diseases, malignant processes, and infections have been ruled out.

Objective markers for MCAD/MCAS are lacking at this time.

Consider a diagnosis of MCAS and optimize management,

use of therapies to block MCA/ MC-mediator action
Diagnosis and therapy of any associated conditions

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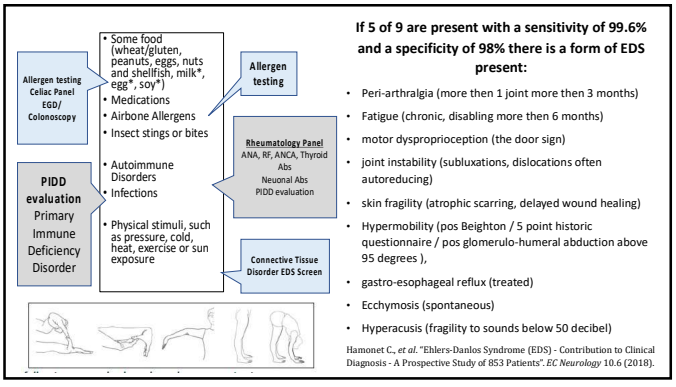

If 5 of 9 are present with a sensitivity of 99.6% and a specificity of 98% there is a form of EDS present:

- Peri-arthralgia (more then 1 joint more then 3 months)
- Fatigue (chronic, disabling more then 6 months)
- motor dysproprioception (the door sign)
- joint instability (subluxations, dislocations often autoreducing)
- skin fragility (atrophic scarring, delayed wound healing)
- Hypermobility (pos Beighton / 5 point historic questionnaire / pos glomerulo-humeral abduction above 95 degrees),
- gastro-esophageal reflux (treated)
- Ecchymosis (spontaneous)
- Hyperacusis (fragility to sounds below 50 decibel)

Hamonet C., *et al.* "Ehlers-Danlos Syndrome (EDS) - Contribution to Clinical Diagnosis - A Prospective Study of 853 Patients". *EC Neurology* 10.6 (2018).

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MCAD evaluation:
retrospective study of 986 patients at a single site

Clinical Commentary Review

Doctor, I Think I Am Suffering from MCAS: Differential Diagnosis and Separating Facts from Fiction

Peter Valent, MD[1], and Cem Akin, MD[2] *Vienna, Austria; and Ann Arbor, Mich*

Received: 12 October 2021 | Accepted: 16 October 2021
DOI: 10.1002/ajmg.c.31940

RESEARCH ARTICLE

Mast cell activation disease and immunoglobulin deficiency in patients with hypermobile Ehlers-Danlos syndrome/ hypermobility spectrum disorder

Isabelle Brock[1,2,3] | Walter Prendergast[1] | Anne Maitland[1,4]

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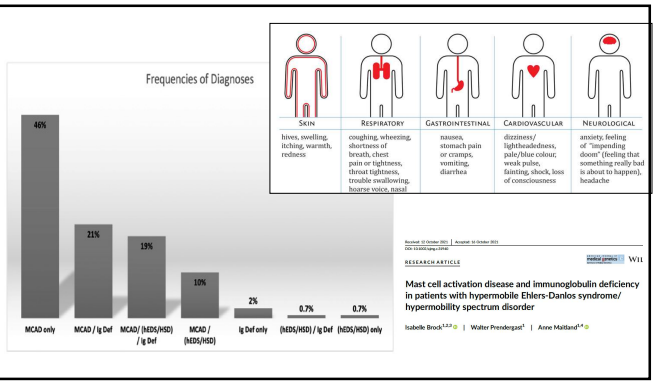

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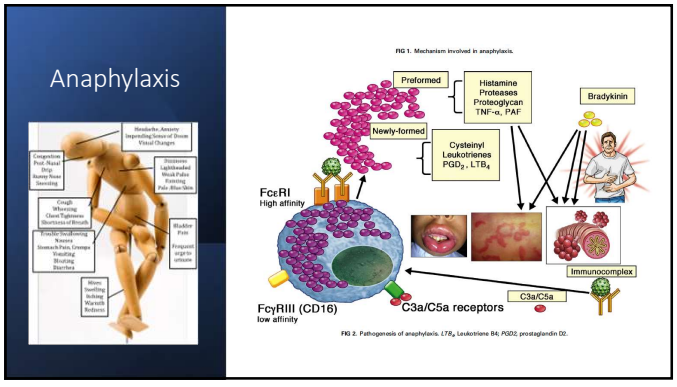

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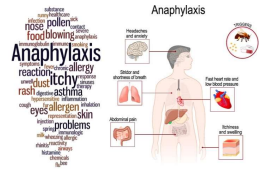
Grand Rounds Review

Insect Sting Anaphylaxis—Or Mastocytosis—Or Something Else?

David B.K. Golden, MD[a], and Melody C. Carter, MD[b] *Baltimore and Bethesda, Md*



Case Report

62 yo Caucasian female, former nurse,

- h/o cardiac vasospasm (cardiac cath-1991),
- complex regional pain syndrome (1992);
- b/l DCIS = underwent b/l mastectomy 1999);
- Thoracic Outlet Syndrome (1991); carpal tunnel syndome
- rx for GERD;
- h/o DVT and pulmonary emobili, prothrombin gene Mutation Heterozygotic (2002)
- h/o cat and pollen allergy, migraine headaches
- In 2010 - Previously evaluated for insect venom allergy by local NJ allergist; honey bee and wasp sting caused flushing and lightheadedness, started VIT but had anaphylaxis; referred to Maryland A/I practice – accused of malinguering
- Consumed fish, elevated Mercury level 1.6

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Evaluated in 2012 for recurrent infections- sinusitis, bronchitis, moderate persistent asthma

- PST +ve Alternaria, cat, dog,
- neg venom Immunocap
- Found to Selective IGA and IGG deficiency- no change with prophylactic abx, ICS and adjuvant therapy
- Scratched by her cat with CNS effects – suspected Bartonella Henselae and empiric treatment doxycycline and rifampin by ID specialist
- started on Gammagard 2015 and Xolair (2017), persistent moderate asthma and CRS
- 2017 Beighton Screen 9/9
- 2018 Gene-by Gene Test = calculated alpha tryptase copy number = n3, beta copy = 2

lab test	value
Tryptase	11.0 ng/ml (< 11.4) 2012 10.0 ng/ml (2-10) 2013 9.0 ng/ml (2-10) 2015
IGG	815 (694-1618 mg/Dl)
IGA	70 (81 -463 mg/Dl)
IGM	81 (48-271 mg/Dl)
IGE	15 (< 100 IU/ml)
WBC	4.8 (3.8-10.8)

Allergen Specific IgE
Primary Immune Deficiency
Autoimmune Disease (Hashimoto's dz)
Hyper Alpha Tryptasemia (HaT)
Hypermobile Ehlers Danlos Syndrome
Autonomic Dysfunction – Dysproprioception/ Small Fiber Neuro.

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

Case Report:

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1st experimental evidence of Hypersensitivity

ana (against)
+
phylaxis (protection)

Hakai Magazine

Coastal Science and Societies
www.hakaimagazine.com

The discovery of anaphylaxis began aboard one of Prince Albert of Monaco's yachts. Monaco commemorated the accomplishment with a series of stamps, but unfortunately depicted the wrong vessel. Background photo courtesy of Freshwater and Marine Image Bank/University of Washington

The Unexpected Discovery of Anaphylaxis

How the sting of the Portuguese man-of-war led to one of the most significant medical advances rooted in oceanographic work.

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Anaphylaxis is rare?

Anaphylaxis is More Common than Many Thought, Most Patients are Not Prepared

Hakai Magazine — 1902

The Unexpected Discovery of Anaphylaxis

How the sting of the Portuguese man-of-war led to one of the most significant medical advances rooted in oceanographic work.

JACI, 2014

Food, drug, insect sting allergy, and anaphylaxis

Anaphylaxis in America: The prevalence and characteristics of anaphylaxis in the United States

Robert A. Wood, MD,[a] Carlos A. Camargo, Jr, MD, DrPH,[b] Philip Lieberman, MD,[c] Hugh A. Sampson, MD,[d] Lawrence B. Schwartz, MD, PhD,[e] Myron Zitt, MD,[f] Charlotte Collins, JD,[g] Michael Tringale, MSM,[g] Marilyn Wilkinson, ScD,[h] John Boyle, PhD,[i] and F. Estelle R. Simons, MD[j] *Baltimore, Londonvc, Silver Spring, and Culverton, Md, Boston, Mass, Memphis, Tenn, New York and Stony Brook, NY, Richmond, Va, and Winnipeg, Manitoba, Canada*

According to [this 2014] study, anaphylaxis very likely occurs in nearly 1-in-50 Americans (1.6%), and the rate is probably higher, close to 1-in-20 (5.1%).

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Clinical Management Review

Diagnostic Challenges in Anaphylaxis

Jay A. Lieberman, MD*, Theresa A. Bingemann, MD*, and Julie Wang, MD*

What is anaphylaxis?

- Signs + Symptoms?
- Triggers?
- Effector Cells?
- Chemical Mediators?

There are many diagnostic challenges in anaphylaxis, but the first and most important is "what is anaphylaxis?" Because of not having a clear definition, one perspective has likened anaphylaxis to Justice Potter Stewarts's definition of pornography when he stated he could not define it but that "I know if when I see it."

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Anaphylaxis is Heterogeneous Syndrome

Anaphylaxis Is a Complex Disease with Clinical Variability

- **Anaphylaxis Definitions**
  - Signs and Symptoms
  - Clinical Severity
  - Risk Factors for Anaphylaxis
    - Atopy
    - Mast Cell Disease
      - Systemic Mastocytosis, HαT, MMAS
- Phenotypes and Endotypes
- Response to therapy

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Allergy, Asthma & Clinical Immunology

Critical view of anaphylaxis epidemiology: open questions and new perspectives

Similiarities and Differences in anaphylaxis definitions worldwide

AAAAI/ACAAI Guidelines (Liberman et al., 2010) (6)	NIAID (Sampson et al., 2006) (1)	EAACI Guidelines (Muraro et al., 2014) (3)	WAO Guidelines (Simons et al., 2011) (7)	ASCIA Practice Essentials (Brown et al., 2006) (8)
"an acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils"	"a serious allergic reaction that involves more than one organ system (e.g. skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening"	"a severe life-threatening generalized or systemic hypersensitivity reaction"	"a serious life-threatening generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death"	"a serious, rapid-onset, allergic reaction that may cause death"

ences in anaphylaxis definitions worldwide [1, 3, 6–8]

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Anaphylaxis: Signs and Symptoms

Systemic anaphylaxis represents the most dramatic and potentially catastrophic manifestation of immediate hypersensitivity.

REVIEW

CURRENT CONCEPTS

ANAPHYLAXIS

Skin	Respiratory	Gastrointestinal	Cardiovascular	Neurological
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever-like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bad is about to happen), headache
				Other: uterine cramps

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Anaphylaxis: Phenotypes and Endotypes

Skin	Respiratory	Gastrointestinal	Cardiovascular	Neurological
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever-like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bad is about to happen), headache
				Other: uterine cramps

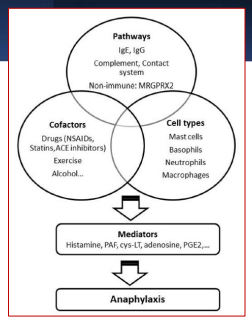

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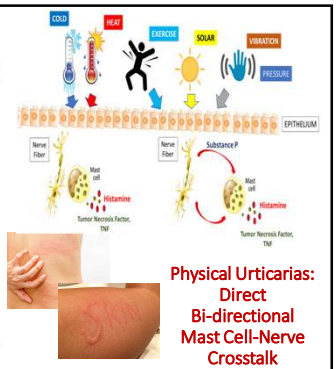
Table I. *Classification of urticaria*

Group/Subgroup	Characteristics
Spontaneous urticaria	*Definition*
Acute urticaria	Spontaneous wheals < 6 weeks
Chronic urticaria	Spontaneous wheals > 6 weeks
Physical urticaria	*Eliciting factors*
Acquired cold urticaria	Cold air/water/wind/food/objects
Delayed pressure urticaria	Vertical pressure (wheals arising with a 3–8 h latency)
Heat urticaria	Localized heat
Solar urticaria	UV and/or visible light
Dermographic urticaria/urticaria factitia/	Mechanical shearing forces (wheals arising after 1–5 min)
Vibratory urticaria/angioedema	Vibratory forces, e.g. pneumatic hammer
Other urticaria disorders	
Aquagenic urticaria	Water
Cholinergic urticaria	Increase of body temperature
Contact urticaria	Contact with urticariogenic substance
Exercise-induced anaphylaxis/ urticaria	Physical exercise

UV: ultraviolet



Physical Urticarias: Direct Bi-directional Mast Cell-Nerve Crosstalk

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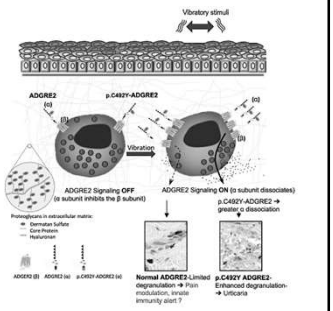
Autosomal Dominant mast cell activation disorder

Localized hives at the site of mechanoreceptor-vibration or

Systemic manifestations in response to local friction stimulus



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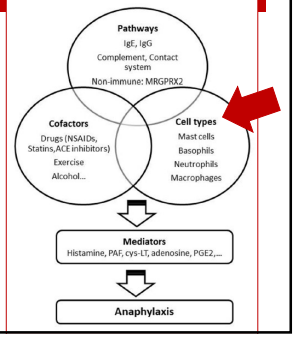
- Atopy
- Gender
  - Females, during reproductive years
- Mast Cell Disease
  - Systemic Mastocytosis, Monoclonal Mast Cell Activation Disease and Hereditary alpha Tryptasemia
- Cardiovascular disease and Medications for CV dz
  - Statins (impacts PAF-Bradykinin pathways)
  - ACEi/BBlockers
- Asthma
- Older Age
- Antigen
  - Food,
  - Drugs
    - Antibiotics, RCM, NSAIDs, ACEi/BBlockers Neuromuscular Blocking Agents- tubocurarine, atracurium, or ciprofloxacin
  - Latex
  - Venom Stings
- Exercise
- Alcohol

Anaphylaxis: Risk Factors



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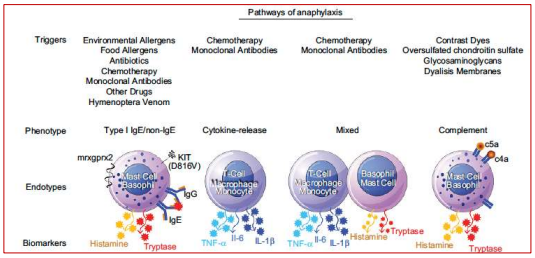
Pathophysiologic Mechanisms

Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers M. Castells - J Asthma Allergy 2018:11, 121–142



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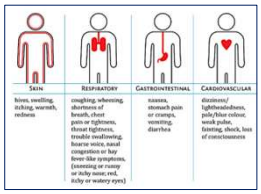
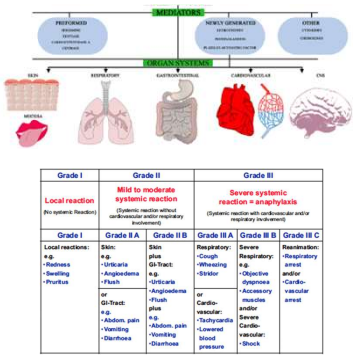
Anaphylaxis: Severity



Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis



Grade I	Grade II		Grade III		
Local reaction (No systemic Reaction)	Mild to moderate systemic reaction (Systemic reaction without cardiovascular and/or respiratory involvement)		Severe systemic reaction = anaphylaxis (Systemic reaction with cardiovascular and/or respiratory involvement)		
Grade I	Grade II A	Grade II B	Grade III A	Grade III B	Grade III C
Local reactions: e.g. • Redness • Swelling • Pruritus	Skin: e.g. • Urticaria • Angioedema • Flush or GI-Tract: e.g. • Abdom. pain • Vomiting • Diarrhoea	Skin plus GI-Tract: e.g. • Urticaria • Angioedema • Flush plus e.g. • Abdom. pain • Vomiting • Diarrhoea	Respiratory: e.g. • Cough • Wheezing • Stridor or Cardio-vascular: • Tachycardia • Lowered blood pressure	Severe Respiratory: e.g. • Objective dyspnoea • Accessory muscles and/or Severe Cardio-vascular: • Shock	Reanimation: • Respiratory arrest and/or • Cardio-vascular arrest

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Anaphylaxis is Heterogeneous Syndrome

Anaphylaxis Is a Complex Disease with Clinical Variability

- Anaphylaxis Definitions
  - Signs and Symptoms
  - Clinical Severity
  - Risk Factors for Anaphylaxis
    - Atopy
    - Mast Cell Disease
      - Systemic Mastocytosis, HαT, MMAS
- **Phenotypes and Endotypes**
- Response to therapy

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Anaphylaxis is a rapidly evolving, acute, life-threatening reaction that occurs rapidly on contact with a trigger.

Contact via:

FcεRI Receptors:
Allergen-Specific IgE
IgG autoantibodies against FcεR

FcγRIII Receptors:
IgG complexes

Complement Receptors
C3A, C5A

Contact

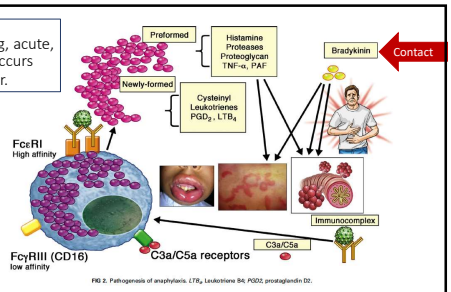

FIG 2. Pathogenesis of anaphylaxis. LTB_4, Leukotriene B4; PGD_2, prostaglandin D2.

Clinical reviews in allergy and immunology

Non–IgE-mediated anaphylaxis

Antonella Cianferoni, MD, PhD Philadelphia, Pa

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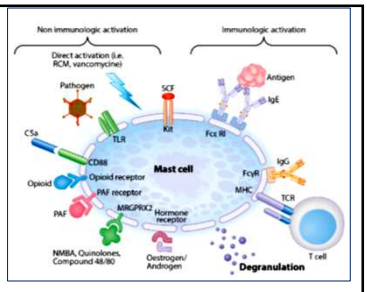
Anaphylaxis

IgE Mediated
Effector cells:
- Mast Cells
- Basophils

Not IgE Mediated
Activation pathways:
- IgG
- Complement
- Bradykinin
- Leukotrienes
- Prostaglandin-E 2

Effector Cells
- Neutrophils
- Endothelial cell
- Smooth Muscle
- Mast cells
- Basophils
- Eosinophils



Anaphylaxis =
Not Just Allergen-IgE triggered Mast Cells / Basophil Degranulation

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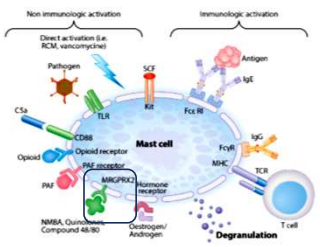
Mas-related G protein-coupled receptor-X2 (MRGPRX2) in drug hypersensitivity reactions.
Front Immunol 2018;9:3027.

Clinical reviews in allergy and immunology

Multifaceted MRGPRX2: New insight into the role of mast cells in health and disease

Soptarshi Roy, PhD, Chalatip Chompunud Na Ayudhya, DDS, Monica Thapaliya, BS, Vishwa Deepak, PhD, and Hyder Ali, PhD Philadelphia, Pa



Benjamin D. McNeil

Division of Allergy and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States

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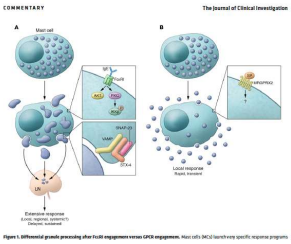
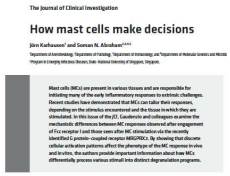
Two Degranulation Pathways: Monophasic vs Biphasic Reactions?

Mast cells (MCs), basophils and eosinophils express MRGPRX2 receptors





The Journal of Clinical Investigation

How mast cells make decisions

MCs launch very specific response programs depending on the nature of the stimulus: FcR vs. MRGPRX2 receptors

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Anaphylaxis is Heterogeneous Syndrome

Anaphylaxis Is a Complex Disease with Clinical Variability

- Anaphylaxis Definitions
  - Signs and Symptoms
  - Clinical Severity
  - Risk Factors for Anaphylaxis
    - Atopy
    - Mast Cell Disease
      - Systemic Mastocytosis, HαT, MMAS
- Phenotypes and Endotypes
- **Response to therapy**

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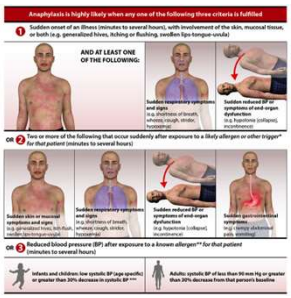
Anaphylaxis Diagnosis is highly likely:

1) acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both with either respiratory involvement or reduced blood pressure (BP)/associated symptom of end-organ dysfunction

2) >2 of the following that occur rapidly after exposure to a likely allergen for the patient, including
   1) involvement of skin-mucosal tissue,
   2) respiratory involvement,
   3) reduced blood pressure or associated symptoms

3) reduced blood pressure as a result of exposure to a known [allergen] trigger.

Shaker et al, JACI 145 (4):1082-1123 (2020)



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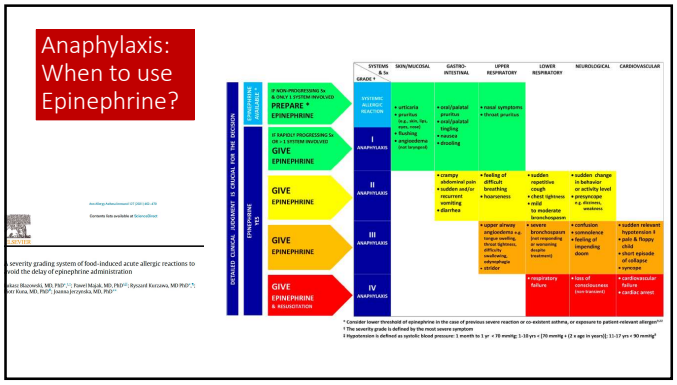
Anaphylaxis: When to use Epinephrine?



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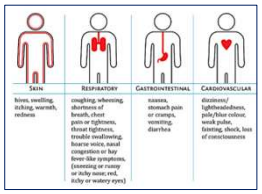
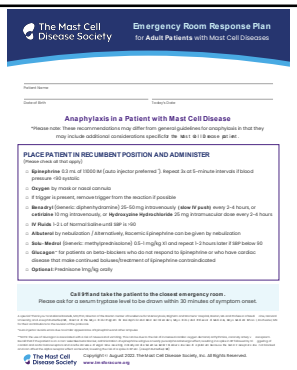
Anaphylaxis: Severity



Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis



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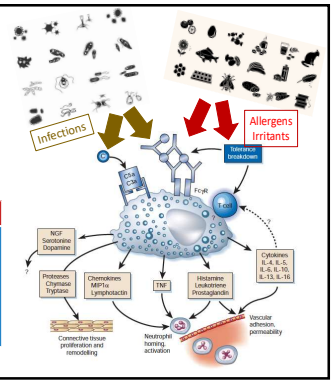
Allergen-IgE	Infections
Avoidance measures (Diet, Environment)	Lyme, Borrelia
Medications: histamine, Leukotriene blockade	Bacterial infections (Strep- ASO/DNAse Ig)
Tricyclic agents	
Ketotifen, Cromolyn	EBV, HSV, Hepatitis
Desensitization/Immunotherapy	
Omalizumab	COVID

Primary Immune Deficiency	Autoimmune Disorders
Prophylactic Antibiotics	Anti-inflammatory Agents
Immune Globulin	Immune Globulin
Anti-inflammatory Agents	



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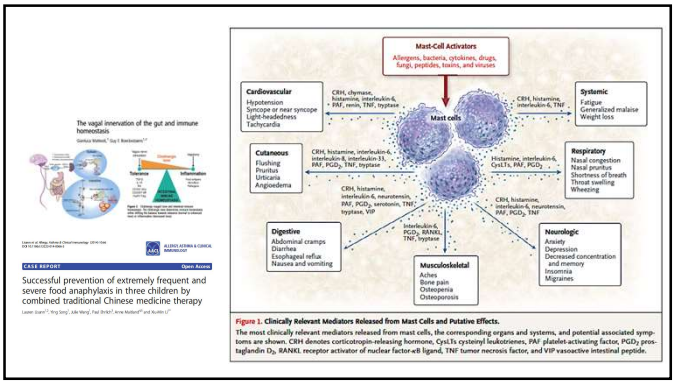

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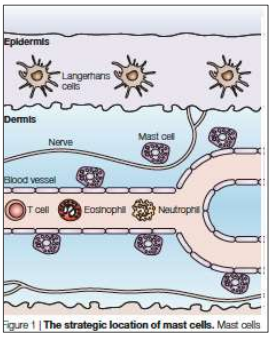
Re: Something else? Consider this…

- Mast cells arise from bone marrow and embryonal progenitor cells, resident broadly in vascularized tissues, throughout the the body.
- Signals from surrounding microenvironment direct MC progenitor differentiation.
- Mast cells are common at sites in the body that are exposed to the external environment, contributing to barrier function, situated near nerves and blood vessels.
- Responses to external and internal stimuli must be tightly regulated to prevent the pathology associated with unnecessary immune activation.
- The crucial role of the tissues in regulating immunity is increasingly being recognized.



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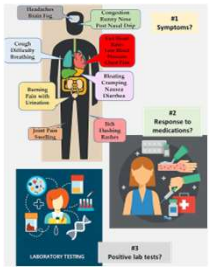
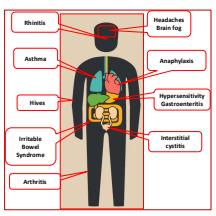
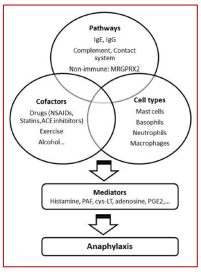
MCAD/MCAS vs Anaphylaxis







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Contents lists available at ScienceDirect

ELSEVIER

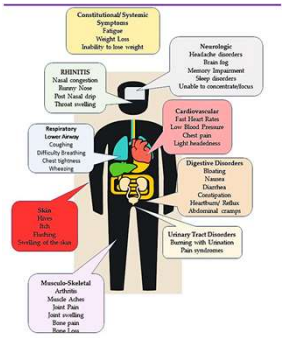
Perspective

Mast cell activation syndromes and anaphylaxis

Multiple diseases part of the same spectrum

David González-de-Olano, MD, PhD [1,*]; Almudena Matito, MD, PhD [1,2]; Iván Alvarez-Twose, MD, PhD [1,2]

[1] Allergy Department, Hospital Universitario Ramón y Cajal, IRYCIS, ARADyAL, Center RD16/0006/0022, Madrid, Spain
[2] Instituto de Estudios de Mastocitosis de Castilla-La Mancha (CMast), CIBERONC CB16/12/00400, Madrid, Spain
[3] Spanish Network on Mastocytosis (REMA), Madrid, Spain



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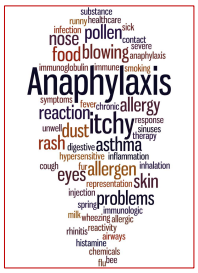
Anaphylaxis Is a Complex Disease with Clinical Variability



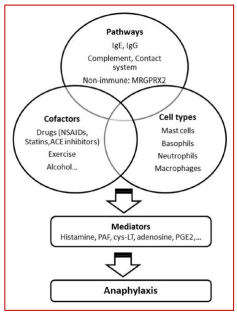
Severity of Signs and Symptoms

Natural History
- Age of Onset
- Disease Progression

Risk of adverse anaphylaxis outcomes
- Loss of life or diminished organ function

Pathophysiologic Characteristics

Response to therapy



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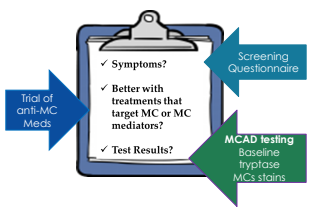
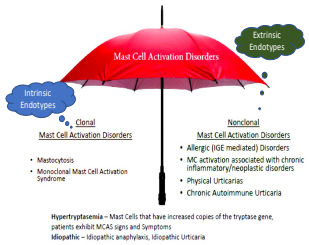
Mast Cell Activation Disease, including MCAS





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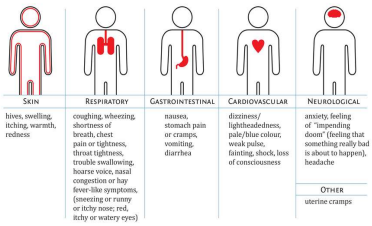
R/O Disorders that Mimic these Multi-system, Hypersensitivity Syndromes



Skin	Respiratory	Gastrointestinal	Cardiovascular	Neurological
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever–like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bad is about to happen), headache

Other

uterine cramps

Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome

Digestive conditions

Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor

Immunologic conditions

Auto-inflammatory disorders such as deficiency of inter- leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

Neurologic/psychiatric conditions

Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction; Multiple sclerosis

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Prevention of MCA / Anaphylactic Event

Pre-Medication Plan

For major and minor procedures/surgery and for radiology procedures, including ultrasound, with and without dyes.

ADMINISTER

At 12 hours and 1 hour prior to surgery or dye administration give:
(please select all that apply)

- ☐ **Benadryl** (Generic: diphenhydramine) 25 mg orally or IV, or **Atarax** (Generic: hydroxyzine) 25 mg orally, or equivalent nonsedating antihistamine. Examples: Zyrtec (cetirizine) 10 mg IV or PO may be used as a long-acting alternative. Claritin (loratidine), Allegra (fexofenadine)
- ☐ **Pepcid** (Generic: famotidine) 20 mg orally. Another H2 antagonist is tagamet/cimetidine
- ☐ **Singulair** (montelukast) Examples: Accolate (zafirlukast), Zyflo CR (zileuton)

Medications to Be Avoided

AVOID

- Any medication to which the patient has a listed allergy
- Aspirin and nonsteroidal anti-inflammatory medicines if the patient has a known adverse reaction
- Morphine and codeine derivatives (fentanyl is the preferred opioid)
- Vancomycin given IV. Oral route may be tolerated in some patients.
- Quinolones

STOP

Please note this is a standardized protocol. Each protocol should be personalized for the patient with the help of a mast cell specialist. Some institutions/medical departments have their own protocols. **Be sure to discuss IN ADVANCE with your physicians and those departments.**

Additional Orders

Physician Signature Date

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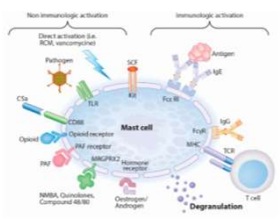
At Risk for MCA event / Anaphylaxis: Medications to use and Avoid



The Mast Cell Disease Society

Medications to Use and Avoid
Quick Reference Guide

Medications *to avoid* or *use with caution* in patients with mast cell disease in emergency situations

Please note: *Some of the Medications to Avoid may be given if absolutely necessary, if given with a prep to stabilize mast cells. Please refer to one of our mast cell experts for instructions.*

Medication Type	Avoid or Use With Caution	Medications That Are Typically Tolerated
General Medications	• alcohol • amphotericin b • codeine • dextromethorphan • polymyxin B • quinine • vancomycin IV • alpha-adrenergic blockers • beta-adrenergic blockers	• calcium channel blockers • centrally acting alpha 2 adrenergic agonists • aldosterone antagonists • Oral doses of Vancomycin may be tolerated in some cases.
Pain Medications	• opioid narcotics (may be tolerated by some individuals) • Toradol (ketorolac) • Non-steroidal anti-inflammatory drugs (unless the patient is already taking a drug from this class)	• fentanyl (may require adjunct treatment with Zofran (ondansetron)) • tramadol
General Anesthetics	• atracurium • doxacurium • rocuronium • mivacurium	• pancuronium • vecuronium
Local Anesthetics	• benzocaine • chloroprocaine • procaine • tetracaine	• bupivacaine • lidocaine • mepivacaine • prilocaine • levobupivacaine • ropivacaine
Intraoperative Induction Medications		• ketamine • midazolam • propofol
Inhaled Anesthetics		• sevoflurane

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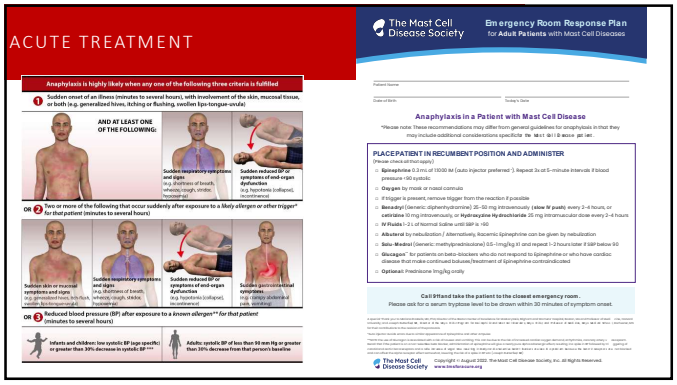
ACUTE TREATMENT
Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
Sudden respiratory symptoms and signs
Sudden reduced BP or symptoms of end-organ dysfunction
OR 2 Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours)
Sudden skin or mucosal symptoms and signs
Sudden respiratory symptoms and signs
Sudden reduced BP or symptoms of end-organ dysfunction
Sudden gastrointestinal symptoms
OR 3 Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours)
Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP***
Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
The Mast Cell Disease Society
Emergency Room Response Plan for Adult Patients with Mast Cell Diseases
Anaphylaxis in a Patient with Mast Cell Disease
PLACE PATIENT IN RECUMBENT POSITION AND ADMINISTER
Epinephrine 0.3 mL of 1:1000 IM (auto injector preferred *). Repeat 2x at 5-minute intervals if blood pressure <90 systolic
Oxygen by mask or nasal cannula
If trigger is present, remove trigger from the reaction if possible
Benadryl (Generic: diphenhydramine) 25-50 mg intravenously (slow IV push) every 2-4 hours, or cetirizine 10 mg intravenously, or Hydroxyzine Hydrochloride 25 mg intramuscular dose every 2-4 hours
IV Fluids 1-2 L of Normal Saline until SBP is >90
Albuterol by nebulization / Alternatively, Racemic Epinephrine can be given by nebulization
Solu-Medrol (Generic: methylprednisolone) 0.5-1mg/kg IV and repeat 1-2 hours later if SBP below 90
Glucagon** for patients on beta-blockers who do not respond to Epinephrine or who have cardiac disease that make continued boluses/treatment of Epinephrine contraindicated
Optional: Prednisone 1mg/kg orally
Call 911and take the patient to the closest emergency room.
Please ask for a serum tryptase level to be drawn within 30 minutes of symptom onset.
The Mast Cell Disease Society www.tmsforacure.org
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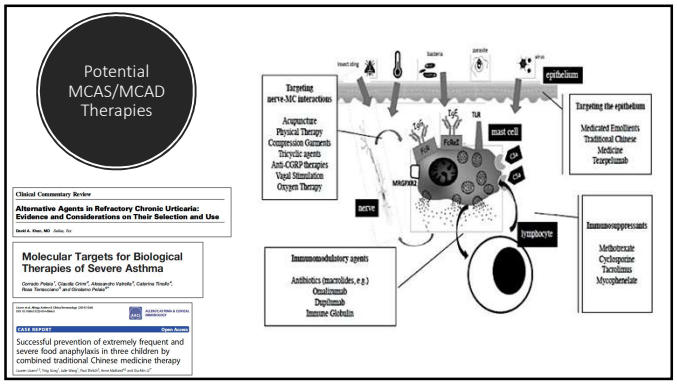
Potential MCAS/MCAD Therapies
Clinical Commentary Review
Alternative Agents in Refractory Chronic Urticaria: Evidence and Considerations on Their Selection and Use
Molecular Targets for Biological Therapies of Severe Asthma
CASE REPORT
Open Access
Successful prevention of extremely frequent and severe food anaphylaxis in three children by combined traditional Chinese medicine therapy
Targeting nerve-MC interactions
Acupuncture
Physical Therapy
Compression Garments
Tricyclic agents
Anti-CGRP therapies
Vagal Stimulation
Oxygen Therapy
epithelium
Targeting the epithelium
Medicated Emollients
Traditional Chinese Medicine
Tezepelumab
mast cell
nerve
lymphocyte
Immunosuppressants
Methotrexate
Cyclosporine
Tacrolimus
Mycophenolate
Immunomodulatory agents
Antibiotics (macrolides, e.g.)
Omalizumab
Dupilumab
Immune Globulin

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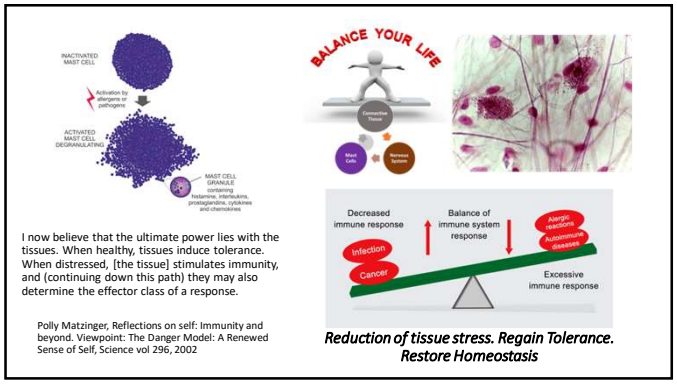
INACTIVATED MAST CELL
Activation by allergens or pathogens
ACTIVATED MAST CELL DEGRANULATING
MAST CELL GRANULE containing histamine, interleukins, prostaglandins, cytokines and chemokines
I now believe that the ultimate power lies with the tissues. When healthy, tissues induce tolerance. When distressed, [the tissue] stimulates immunity, and (continuing down this path) they may also determine the effector class of a response.
Polly Matzinger, Reflections on self: Immunity and beyond. Viewpoint: The Danger Model: A Renewed Sense of Self, Science vol 296, 2002
BALANCE YOUR LIFE
Connective Tissue
Mast Cells
Nervous System
Decreased immune response
Balance of immune system response
Allergic reactions
Autoimmune diseases
Infection
Cancer
Excessive immune response
Reduction of tissue stress. Regain Tolerance. Restore Homeostasis

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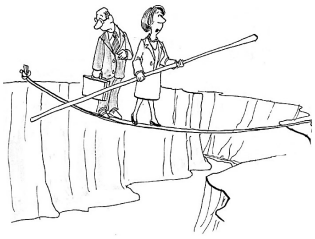

"We want someone who's willing to take risks."

Gratitude!

Contact info:
anne.maitland@metrodora.co

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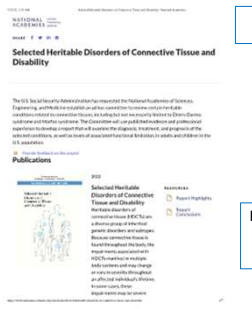

Selected Heritable Disorders of Connective Tissue and Disability

Publications

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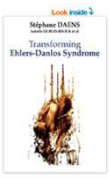

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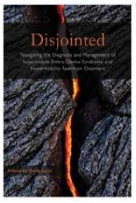

Mast Cell Activation Disease Society
tmsforacure.org

https://www.nationalacademies.org/our-work/selected-heritable-disorders-of-connective-tissue-and-disability

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