Australian
Chronic Infectious &
Inflammatory Disease
Society

Mast Cell Activation Syndrome
ACIIDS Conference 2022

Mark W Westaway

MBBS; DCH; MLCOM; MRSB; MACNEM; Grad Dip Allergy

Coronation Medical
Suite 1 301 Coronation Drive. Qld 4064
Phone 07 38899996 Fax 07 30410448
Email: reception@coronationmedical.com.au

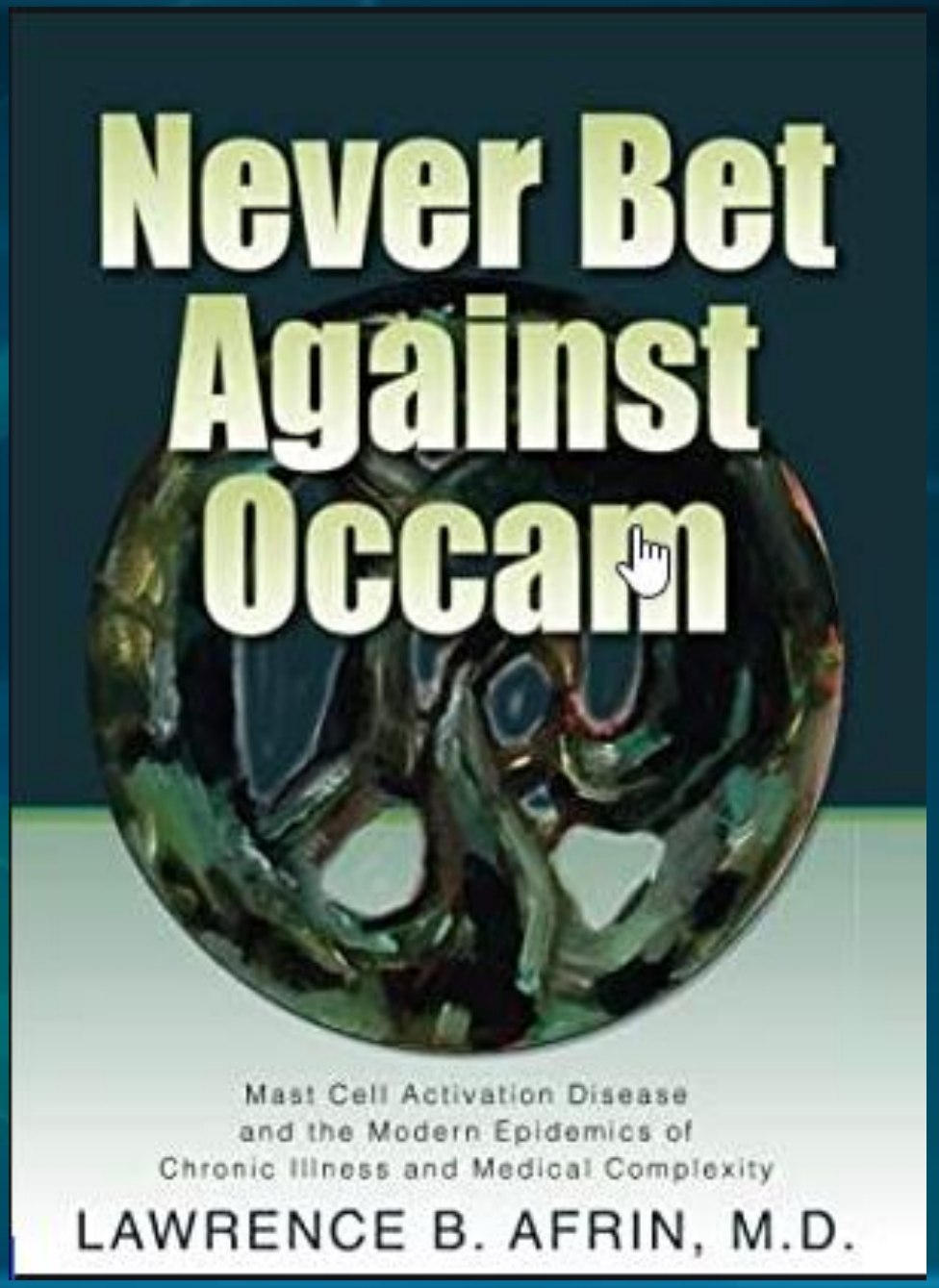
Paid speaker for Viatris

Recommended reading…

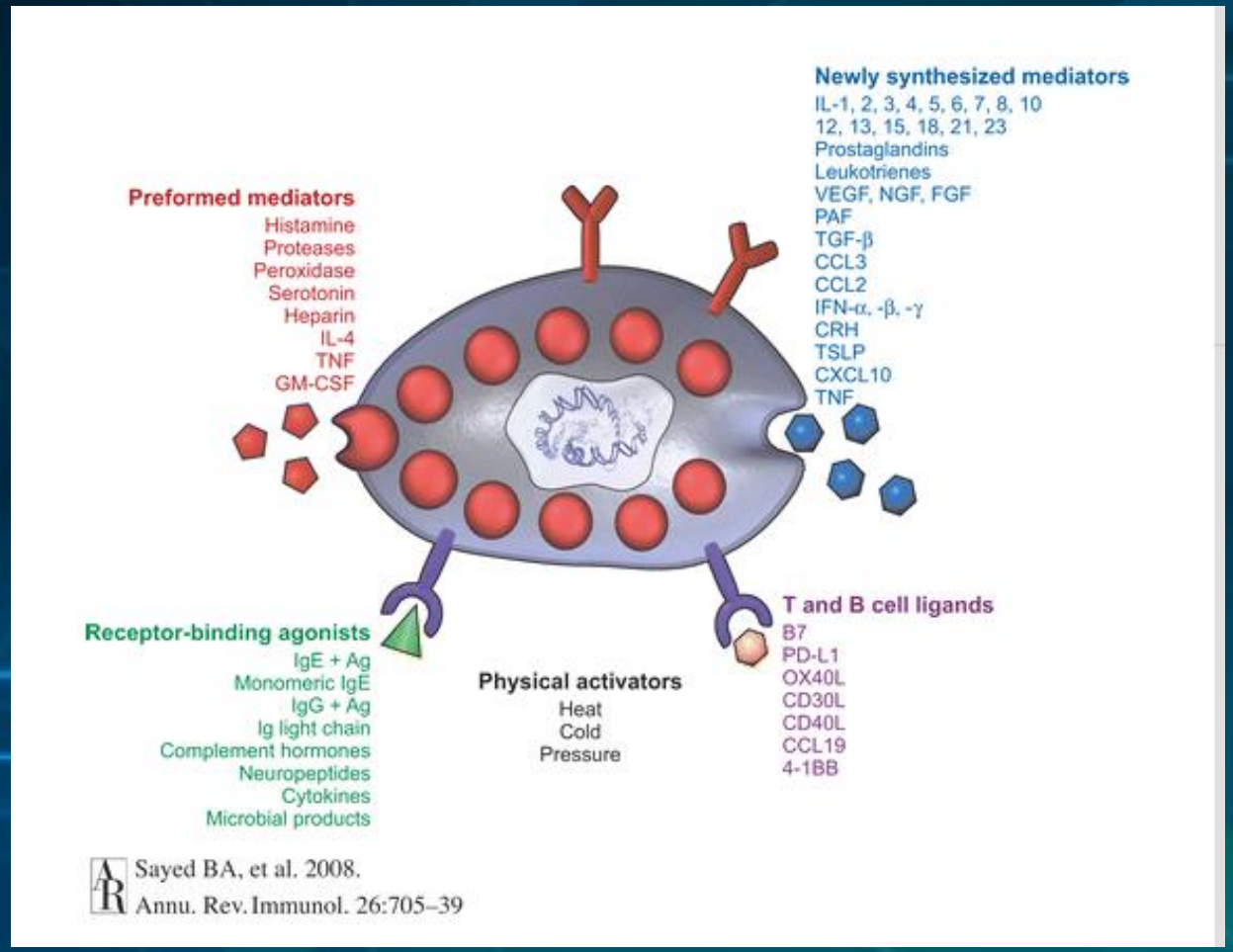
Recommended reading for both patients and physicians

Never Bet Against Occam

Dr Lawrence B Afrin M.D.



Mast Cell Mediators



Over 1,000 mast cell mediators have been discovered

Not all mast cell activation is allergic

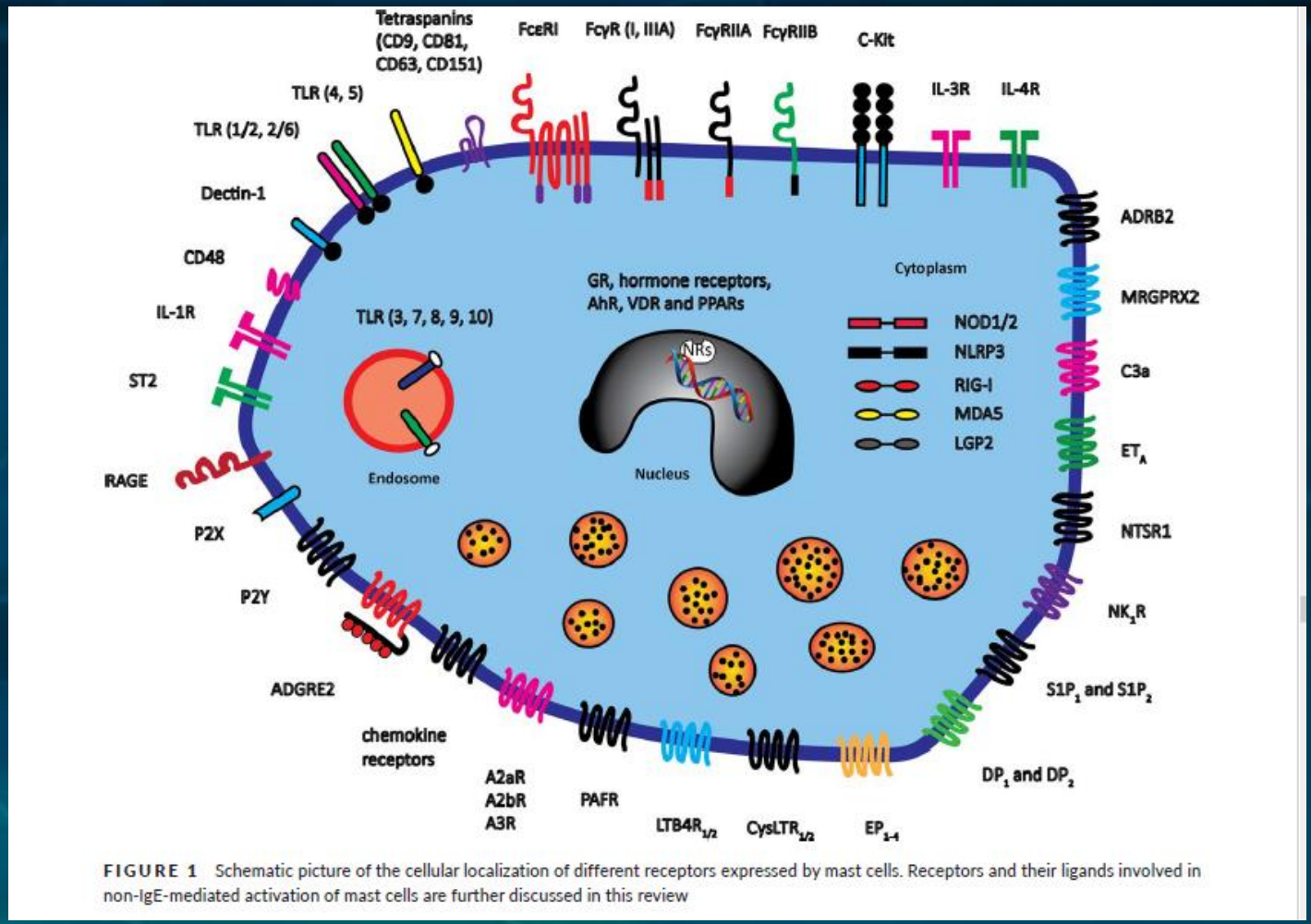


FIGURE 1 Schematic picture of the cellular localization of different receptors expressed by mast cells. Receptors and their ligands involved in non-IgE-mediated activation of mast cells are further discussed in this review

DOI: 10.1111/imr.12629

INVITED REVIEW

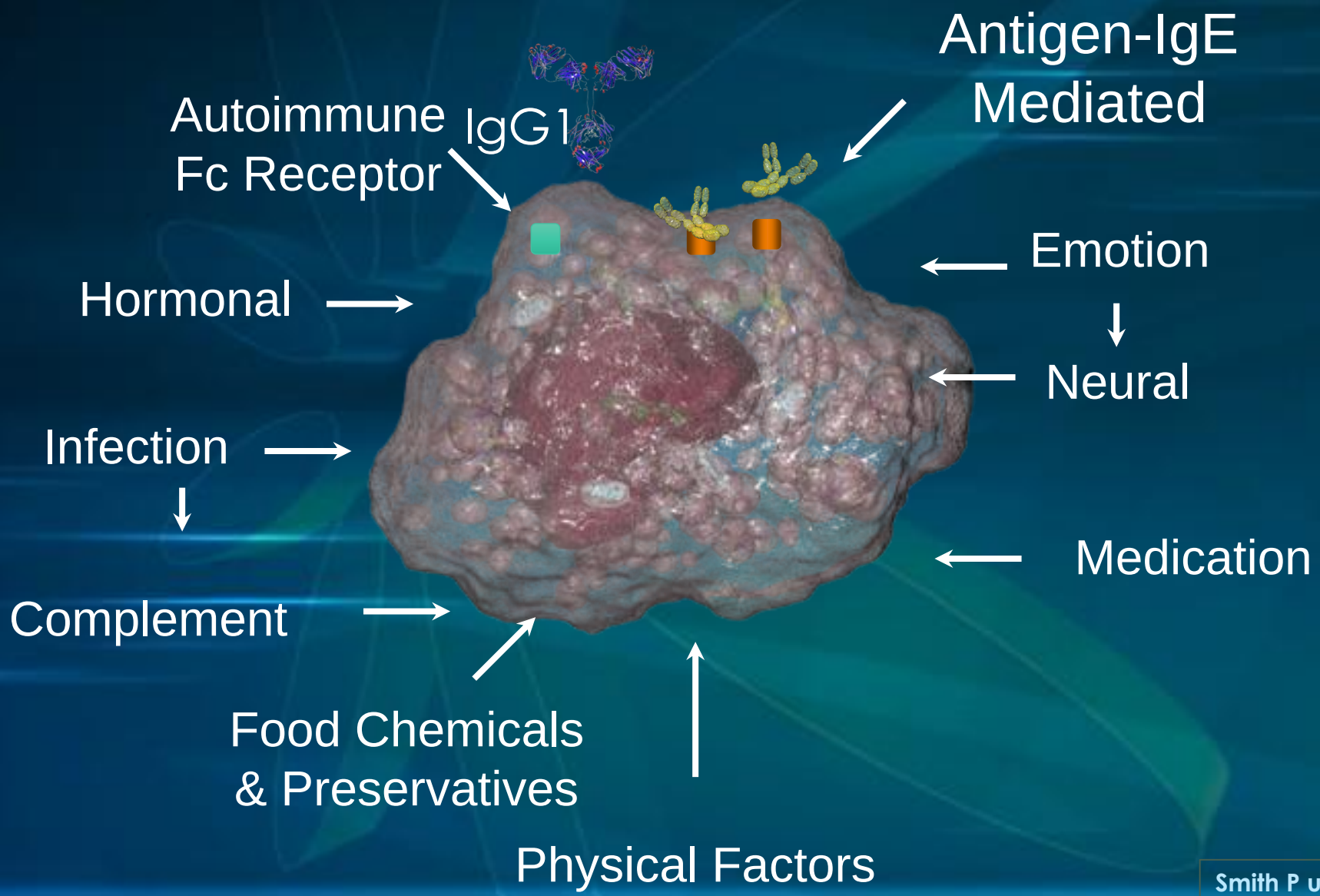
WILEY Immunological Reviews

Non-IgE mediated mast cell activation

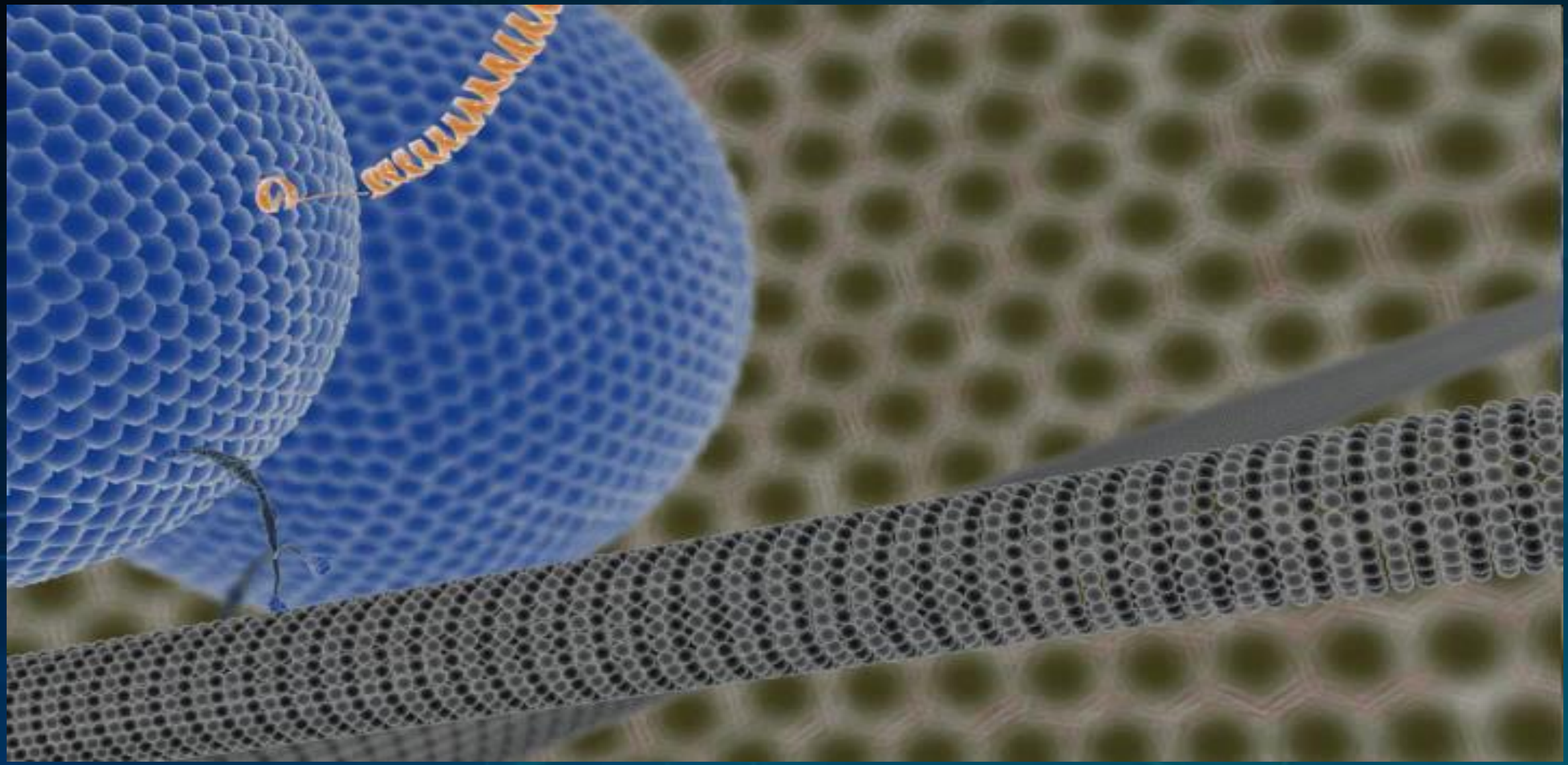
Frank A. Redegeld[1] | Yingxin Yu[1] | Sangeeta Kumari[1] | Nicolas Charles[2,3,4] | Ulrich Blank[2,3,4,5]

Redegeld, FA, Yu, Y, Kumari, S, Charles, N, Blank, U. Non-IgE mediated mast cell activation. *Immunol Rev*. 2018; 282: 87– 113. https://doi.org/10.1111/imr.12629

A Mast Cell



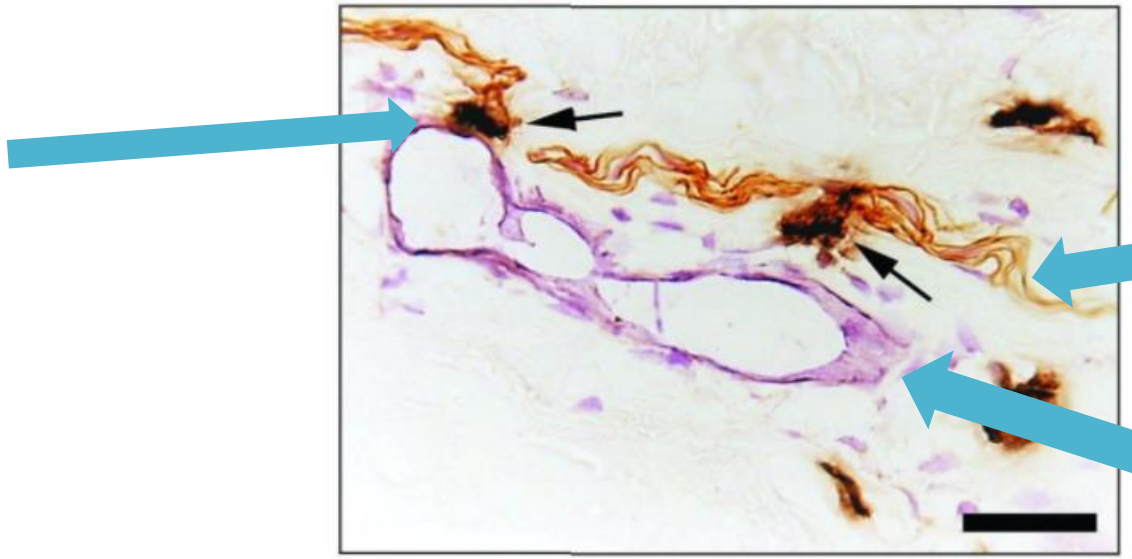
Kinesin, a bipedal protein, that walks along microtubules with the pre-filled vesicles to bring to the SNARE complex to allow degranulation



Smith ,P with permission

Triple immunoperoxidase labelled frozen section of a Mast Cell

Mast Cell



Nerves

Blood Vessels

Figure 2. Triple-immunoperoxidase-labeled frozen section showing the relationship among mast cells, blood vessels, and nerves. Peripheral nerves stained with antibodies to neurofilament protein are brown, while the CD31 (PECAM-1) adhesion molecule on the luminal surface of the blood vessel is stained pink. Tryptase in mast cells is stained black. Several mast cells are present in the section. Two of these (indicated by arrows) are juxtaposed between nerves and blood vessels. Original magnification X400. Scale bar represents 20 μm.

Walsh LJ, Murphy GF. Role of adhesion molecules in cutaneous inflammation and neoplasia. *J Cutan Pathol*. 1992;19(3):161-171. doi:10.1111/j.16000560.1992.tb01654.x

Comparison between Allergic Diseases, Mastocystosis and Mast Cell Activation

- Allergic Diseases = Allergy + inflammation
- Mastocytosis = Mast Cell Neoplasia+/- Allergy + Inflammation
- Mast Cell Activation = Inflammation+/-Allergy +/- Aberrant Growth

WHO 2008 diagnostic criteria for systemic mastocytosis[33]

Major criterion:

Multifocal, dense aggregates of MCs (15 or more) in sections of bone marrow or other extracutaneous tissues and confirmed by tryptase immunohistochemistry or other special stains

Minor criteria:

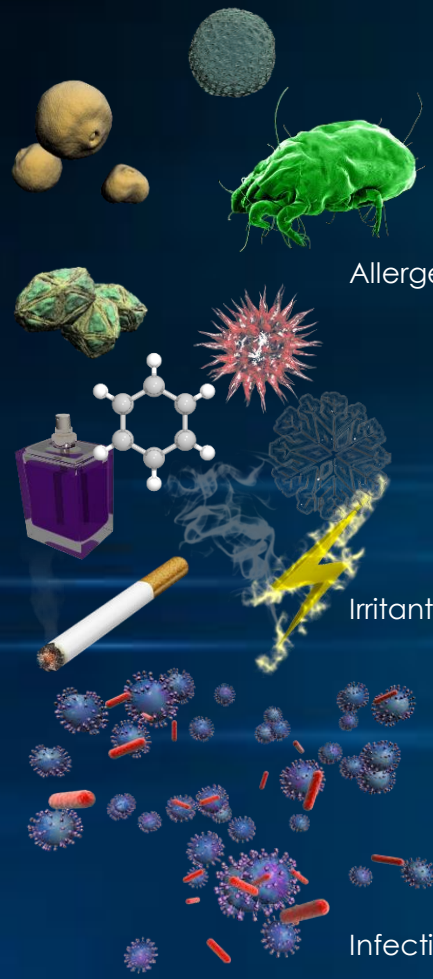
1 Atypical or spindled appearance of at least 25% of the MCs in the diagnostic biopsy
2 Expression of CD2 and/or CD25 by MCs in marrow, blood, or extracutaneous organs
3 KIT codon 816 mutation in marrow, blood or extracutaneous organs
4 Persistent elevation of serum total tryptase > 20 ng/mL

Diagnosis of SM made by either (1) major criterion + any one or more minor criteria; or (2) any three minor criteria

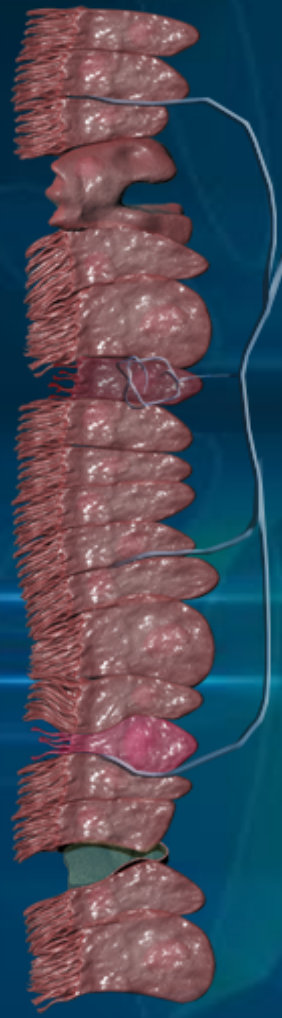
Molderings, G.J., Brettner, S., Homann, J. *et al.* Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J Hematol Oncol* 4, 10 (2011).

How does It Happen?

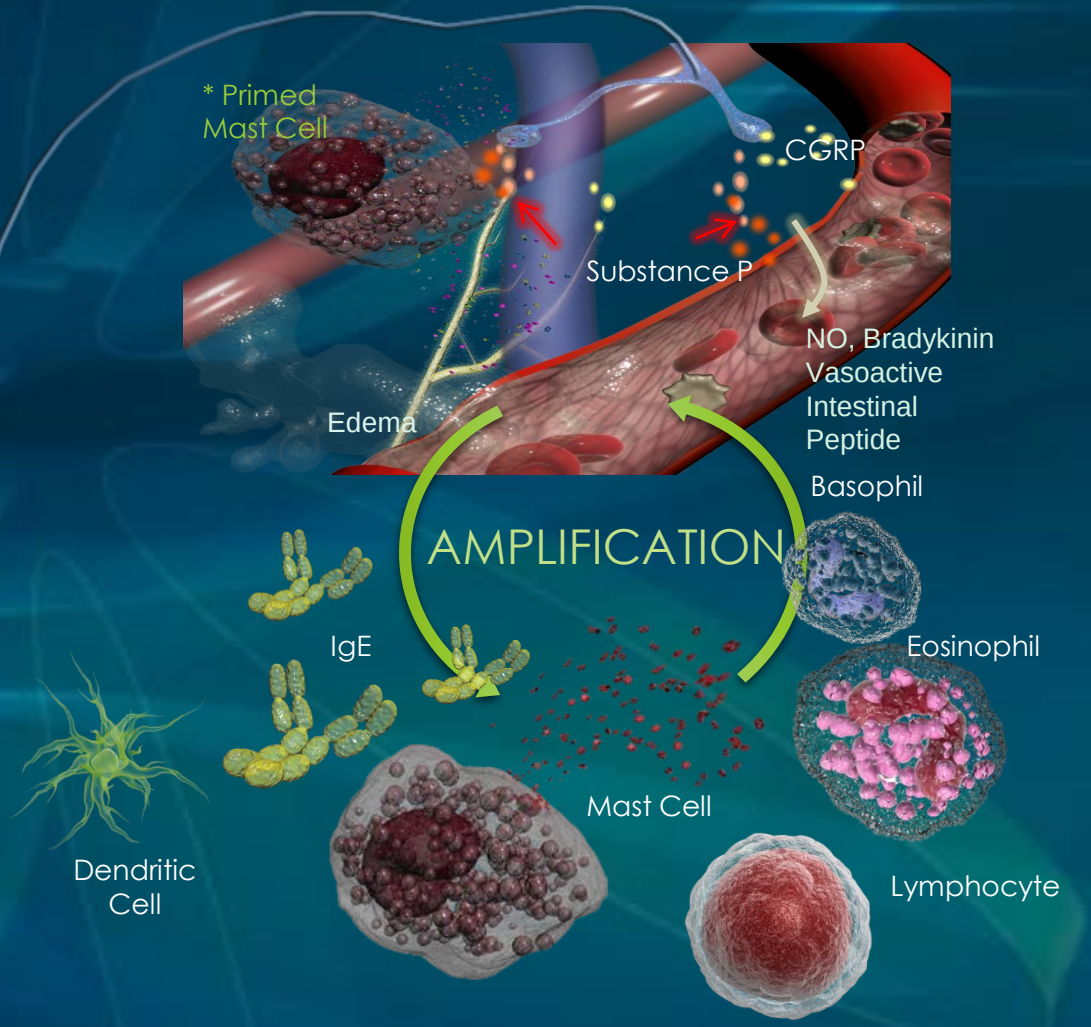
Threats



Receptors



Effectors

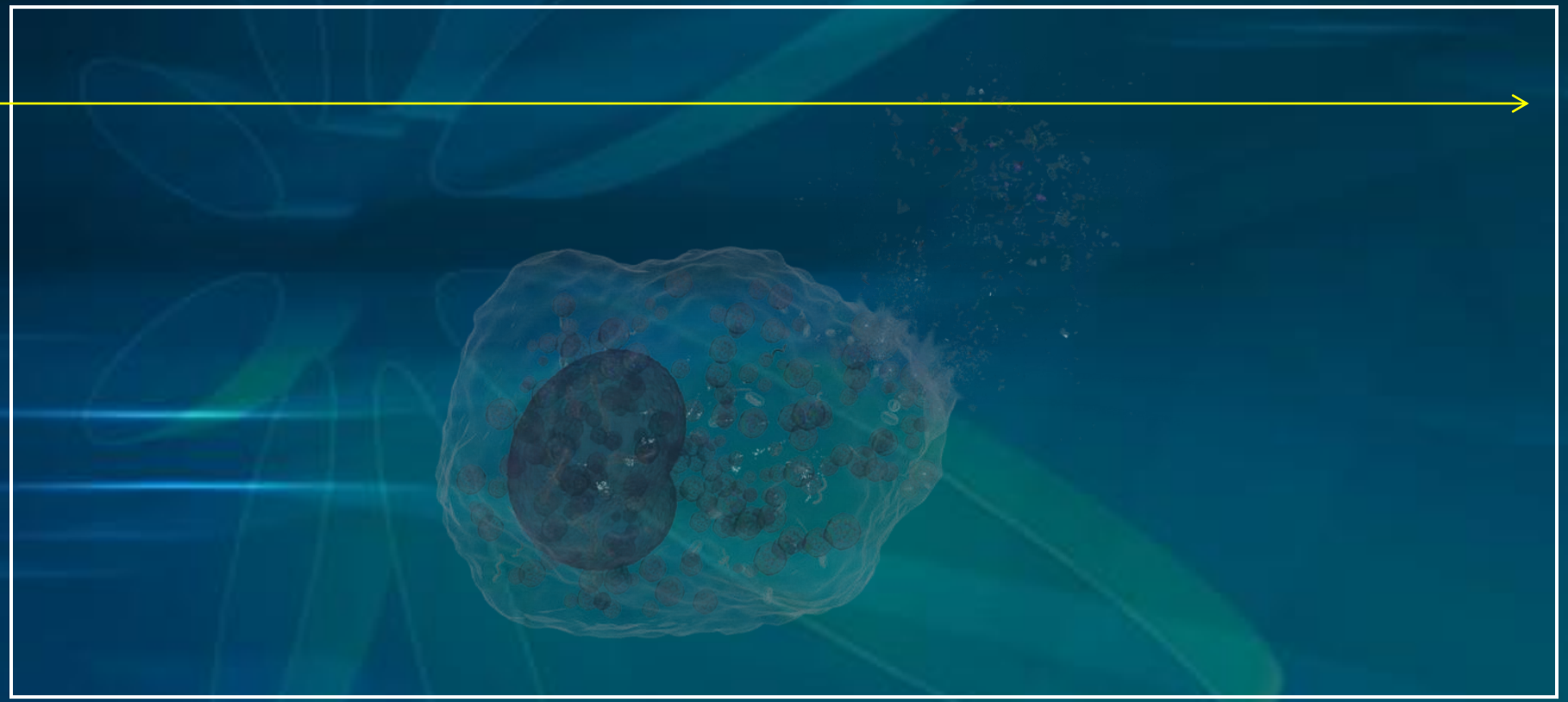


Perception

AMPLIFICATION AMPLIFICATION AMPLIFICATION

Thresholds

mast cell activation

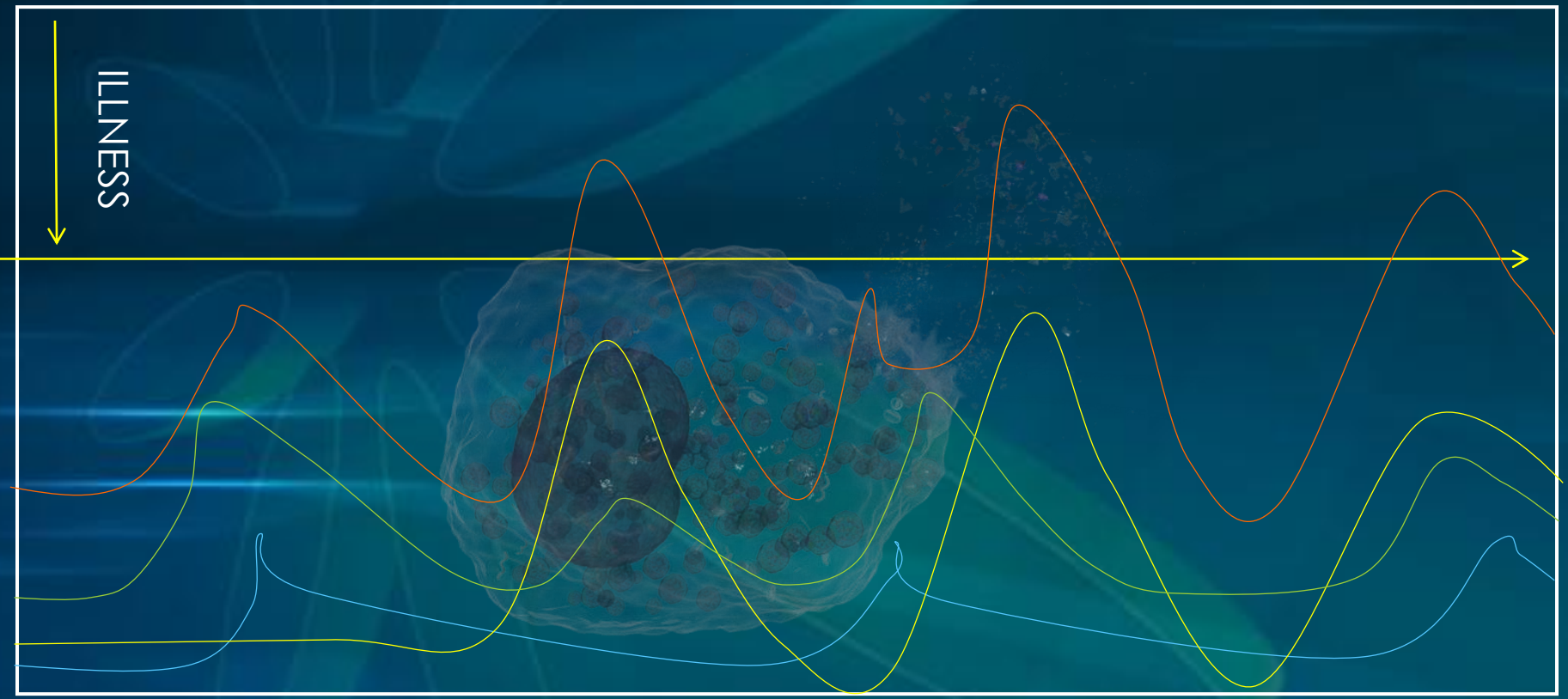


Symptoms

Asymptomatic

Smith P used with permission

Thresholds



Smith,P used with permission

What is Mast Cell Activation Syndrome?

MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. It is usually acquired early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Variable and numerous mutations in MC regulation lead to heterogeneity of presentations.

Afrin, 2011

Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options

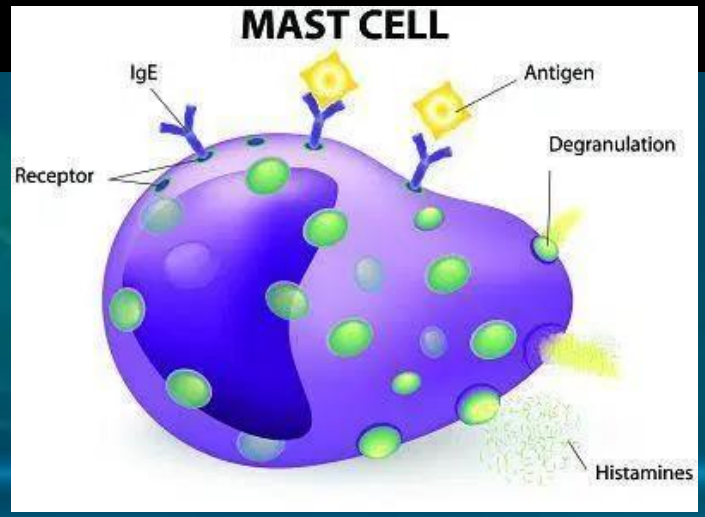
Gerhard J Molderings,[1] Stefan Brettner,[2] Jürgen Homann,[3] and Lawrence B Afrin[4]

Abstract

Mast cell activation disease comprises disorders characterized by accumulation of genetically altered mast cells and/or abnormal release of these cells' mediators, affecting functions in potentially every organ system, often without causing abnormalities in routine laboratory or radiologic testing. In most cases of mast cell activation disease, diagnosis is possible by relatively non-invasive investigation. Effective therapy often consists simply of antihistamines and mast cell membrane-stabilising compounds supplemented with medications targeted at specific symptoms and complications. Mast cell activation disease is now appreciated to likely be considerably prevalent and thus should be considered routinely in the differential diagnosis of patients with chronic multisystem polymorbidity or patients in whom a definitively diagnosed major illness does not well account for the entirety of the patient's presentation.

Introduction

The term *mast cell activation disease* (MCAD) denotes a collection of disorders characterized by (1) accumulation of pathological mast cells in potentially any or all organs and tissues and/or (2) aberrant release of variable subsets of mast cell mediators. A classification has been proposed which differentiates several types and subclasses of MCAD (Table 1). The traditionally recognized subclass termed *systemic mastocytosis* (SM) includes disorders characterized by certain pathological immunohistochemical and mutational findings (the WHO criteria; Table 2; [1,2]) which are divided into several subtypes (Table 1). On the other hand, *mast cell activation syndrome* (MCAS) presents a complex clinical picture of multiple mast cell mediator-induced symptoms, failure to meet the WHO criteria for diagnosis of SM, and exclusion of relevant differential diagnoses [1,3-5]. Symptoms observed in patients with MCAS are little, if any,



Consensus 1

> Int Arch Allergy Immunol. 2012;157(3):215-25. doi: 10.1159/000328760. Epub 2011 Oct 27.

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

Peter Valent [1], Cem Akin, Michel Arock, Knut Brockow, Joseph H Butterfield, Melody C Carter, Mariana Castells, Luis Escribano, Karin Hartmann, Philip Lieberman, Boguslaw Nedoszytko, Alberto Orfao, Lawrence B Schwartz, Karl Sotlar, Wolfgang R Sperr, Massimo Triggiani, Rudolf Valenta, Hans-Peter Horny, Dean D Metcalfe

Affiliations + expand

PMID: 22041891 PMCID: PMC3224511 DOI: 10.1159/000328760

Mast cell activation syndrome: Proposed diagnostic criteria

Cem Akin, MD, PhD,[a*] Peter Valent, MD,[b] and Dean D. Metcalfe, MD[c] *Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md*

Consensus 1 – Criteria for MCAS Diagnosis

- Must have ≥ 2 of flushing, pruritis, urticaria, angioedema, nasal congestion, nasal pruritis, wheezing, throat swelling, headache, hypotension, diarrhea.
- Increase in serum total tryptase by at least 20% above an asymptomatic baseline + 2ng/ml during or within 4 hours of a symptomatic period.
- Response of clinical symptoms to histamine receptor blockers or other 'Mast Cell targeting agents"

Akin C *et al*. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010; 126:1099-1104.e4.
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* 2012 Jan;157:215-225.
Valent P *et al*. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *JACI In Pract* 2019;7(4):1125-33

Potential issues with 'Consensus 1'

- Methodology of 'consensus' was obtained (closed meeting)
- Requires a rise in tryptase (within 4 hours of flare)of 20%+2ng/ml over asymptomatic baseline
  - What is 'asymptomatic baseline' in MCAS patient?
  - No published data whether this distinguishes normal/abnormal fluctuation in MCAS population
  - Having blood drawn within 4 hours of flare
- Requires response to Mast Cell targeted therapy
  - Treating prior to diagnosis?
  - Assumes all types of presentations of MCAS will respond

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* 2012 Jan;157:215-225.
Akin C *et al*. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 2010; 126:1099-1104.e4.
Valent P *et al*. Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe mast cell activation and mast cell activation syndrome. *Int Arch Allergy Immunol* 2019;180(1):44-51, doi: 10.1159/000501079.

Consensus 2

DE GRUYTER

Diagnosis 2020; aop

Review

Lawrence B. Afrin*, Mary B. Ackerley, Linda S. Bluestein, Joseph H. Brewer, Jill B. Brook, Ariana 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. Renneker, William A. Robinson, Aaron M. Roland, E. Scott Rosenbloom, Peter C. Rowe, Ilene S. Ruhoy, David S. Saperstein, 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"

https://doi.org/10.1515/dx-2020-0005
Received January 5, 2020; accepted February 15, 2020

some respects but differing in others, leading to substantial differences between these proposals in the numbers

‘Consensus 2’ Criteria for MCAS Dx

Diagnosis made upon fulfillment of the major criterion + ≥ 1 minor criterion

Major criterion

- Constellation of complaints attributable to pathologically increased Mast Cell Activity ≥ 2 organ systems involved

Minor criterion

- Multifocal or disseminated infiltrates of Mast Cells in marrow and /or extracutaneous organs ≥20 MC/high powered field (CD117)
- Evidence of increased production of Mast Cell mediators
- Symptomatic response to inhibitors of Mast Cell activation or mediator production.

No other diagnosis made that explains symptoms

Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". *Diagnosis (Berl)*. 2020;8(2):137-152. Published 2020 Apr 22. doi:10.1515/dx-2020-0005

MCAS Diagnostic work-up: 2022

Establish Suspicion:

Signs of mastocytosis (e.g., urticaria pigmentosa, unprovoked flushing or anaphylaxis, wasting, end-organ dysfunction, etc.)?

Symptoms of MC activation (Table 1)? MC mediator release syndrome per validated questionnaire (Figure 4)?

More symptoms/findings than can be explained by definitively established diagnoses? Odd/strange symptoms/findings?

Poor response to treatment of definitively established diagnoses?

↓

Initial Testing:

Biopsy of lesions of suspected cutaneous mastocytosis

Serum tryptase persistently > 20 ng/ml:

- bilateral marrow aspiration/biopsy including MC-specific immunohistochemical staining (e.g., CD117, tryptase, toluidine blue, Giemsa, Alcian blue), multicolor flow cytometry for co-expression of CD117/CD25, CD117/CD2, and molecular testing for KIT mutations as available (PCR for KIT^{D816V} at a minimum)
- biopsy of other extracutaneous tissues (e.g., GI tract) as appropriate, for MC-specific testing as above

Complete blood count (CBC) with manual differential
Common serum chemistries
Quant. Ig profile if frequent infections and/or delayed healing
PT/PTT if easy bruising or bleeding or thromboembolic events

↓

Additional MC Mediator Testing:

Serum chromogranin A (avoid PPIs for 5+ days before testing)
Chilled plasma for PGD_2 (and/or 11-β-$PGF_{2\alpha}$) (avoid NSAIDs for 5+ days before testing)
Chilled plasma histamine
Chilled plasma heparin (if not on exogenous heparin products)
Chilled random and 24-hour urine collections for PGD_2 (and/or 11-β-$PGF_{2\alpha}$) and *N*-methylhistamine
Chilled urine for leukotrienes B4, C4, D4, and E4 (if necessary)

Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol* 2014 Mar;3(1):1-17.

Systems involved in MCAS

Table 1. Symptoms and findings in mast cell (MC) activation disease (73).

System	Potential manifestations of mast cell disease
Constitutional	Fatigue (83%), malaise, asthenia, "chronic fatigue syndrome," subjective (rarely, objective) hyperthermia (40%) and/or hypothermia (56%), "sense of feeling cold much of the time," heat and/or cold intolerance (13%), diaphoresis or sweats (47%) (not always nocturnal), flushing, plethora or pallor, increased or decreased appetite, early satiety, weight gain (17%) or loss (16%), pruritus, environmental sensitivities (40%; often odd (16%))
Dermatologic	Rashes (49%) and lesions of many sorts (classic urticaria pigmentosa, "freckles," telangiectatic/angiomatous lesions, xerosis, warts, tags, folliculitis, ulcers, diffusely migratory but sometimes focally persistent patchy erythema), pruritus (often diffusely migratory, sometimes aquagenic) (63%), flushing (31%), angioedema, striae, dermatographism, excessive hair loss (15%), brittle nails (13%; often also longitudinally ridged), poor healing (23%)
Ophthalmologic	Irritated (often described as "dry") eyes (53%), increased or decreased lacrimation, suffusion, conjunctivitis, difficulty focusing (30%), lid tremor/tic, solar sensitivity, infectious or sterile inflammation
Otologic	Infectious or sterile otitis externa and/or media, hearing loss or hyperacusis, tinnitus, otosclerosis
Oral/oropharyngeal	Pain (sometimes "burning"), leukoplakia, fibrosis, lichen planus, ulcers, sores (30%), angioedema, dental decay (17%), dysgeusia, throat tickle/discomfort/irritation/pain, post-nasal drip
Lymphatic	Adenopathy (28%), usually sub-pathologic and often waxing/waning in size, sometimes asymptomatic but not uncommonly tender, sometimes focal, sometimes migratory, pathology usually shows a reactive lymphocytosis or sometimes an atypical non-specific lymphoproliferative disorder; left upper quadrant discomfort (likely from release of mediators from splenic MCs with or without detectable splenomegaly)
Pulmonary	Rhinitis, sinusitis (17%), pharyngitis (48%), laryngitis, bronchitis, pneumonitis (often confused with infectious pneumonia), cough (16%), dyspnea (often low-grade, inconstant, "I just can't catch a deep breath" despite normal pulmonary function tests) (53%), wheezing (15%), obstructive sleep apnea, pulmonary hypertension
Cardiovascular	Presyncope (lightheadedness, weakness, dizziness, vertigo) and/or syncope (71%), hypertension and/or hypotension, palpitations and dysrhythmias (47%), chest discomfort or pain (usually non-anginal in character (40%)), coronary and peripheral arterial atherosclerosis/spasm/infarction, aneurysms, hemorrhoids, varicosities, aberrant angiogenesis (hemangiomas, arteriovenous malformations, telangiectasias), migratory edema (often non-dependent and in spite of normal cardiac and renal function) (56%)
Gastrointestinal	Aerophagia, angioedema in any segment of the luminal tract, dysphagia (often proximal (35%), possibly due to pharyngeal angioedema), pain (48%) and inflammation (often migratory) in one or more segments of the luminal tract (from esophagitis to proctitis) and/or one or more solid organs (e.g., hepatitis, pancreatitis), queasiness, nausea ± vomiting (57%), diarrhea (27%) and/or constipation (14%) (often alternating (36%)), malabsorption (more often selective micronutrient malabsorption than general protein-calorie malabsorption), ascites either from portal hypertension and/or peritoneal serositis; gastroesophageal reflux disease (50%; often "treatment-refractory") and inflammatory/irritable bowel syndrome are common pre-existing diagnoses
Genitourinary	Inflammation (27%; often migratory) in one or more segments of the luminal tracts (ureteritis, cystitis, urethritis, vaginitis, vestibulitis) and/or one or more solid organs (e.g., nephritis, prostatitis), chronic kidney disease, endometriosis, chronic low back pain or flank pain or abdominal pain, hydronephrosis (likely from ureteral angioedema), infertility, erectile dysfunction, decreased libido; in the appropriate setting of multisystem morbidity, miscarriages should prompt consideration of antiphospholipid antibody syndrome potentially due to MCAS
Musculoskeletal	Clinical myositis, often diffusely migratory (fibromyalgia is a common pre-existing diagnosis), subclinical myositis (i.e., asymptomatic elevated creatine kinase not otherwise explained), arthritis (typically migratory), joint laxity/hypermobility, osteoporosis/osteopenia, osteosclerosis, sometimes mixed osteoporosis/osteopenia/osteosclerosis; MCAS-driven musculoskeletal pain (75%) not uncommonly is poorly responsive to non-steroidal anti-inflammatory drugs and narcotics
Neurologic	Headache (especially migraine) (63%), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies including paresthesias (58%), tics, tremors (13%; typically resting), chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be "treatment-refractory")
Psychiatric	Mood disturbances (e.g., anger, depression (13%)), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, other anxiety and panic disorders (16%), psychoses, memory and concentration and word-finding difficulties and other cognitive dysfunction (49%), wide variety of sleep disruptions (including insomnia (35%) and obstructive sleep apnea regardless of weight)
Endocrinologic/metabolic	Abnormal electrolytes (including magnesium) and liver function tests, delayed puberty, dysmenorrhea (11%), endometriosis, osteosclerosis and/or osteoporosis, hypothyroidism, hyperthyroidism, dyslipidemia, hyperferritinemia, selective vitamin and/or other micronutrient deficiencies, weight change, possibly diabetes mellitus
Hematologic/coagulopathic	Polycythemia or anemia, leukocytosis or leukopenia, chronic (usually mild) monocytosis or eosinophilia or basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, aberrant bruising and bleeding (39%); in MCAS the marrow usually does not show increased or even flow-cytometrically aberrant MCs and marrow histology is often interpreted as normal or as unspecified myelodysplastic/myeloproliferative syndrome; standard cytogenetic studies are almost always normal or show culture failure
Immunologic	Types I, II, III, and IV hypersensitivity reactions (e.g., allergy, delayed-type hypersensitivity, etc.), increased risk for malignancy, autoimmunity, impaired healing, increased susceptibility to infection, elevated or decreased levels of one or more isotypes of immunoglobulin; modest monoclonal gammopathy of undetermined significance not uncommon

Most are chronic, low-grade; some are persistent but many are either episodic or waxing/waning. Prevalences of the most common symptoms (≥10% of patients) in an MCAD population ($N = 413$; LBA, unpublished data) are indicated parenthetically.

The Triad

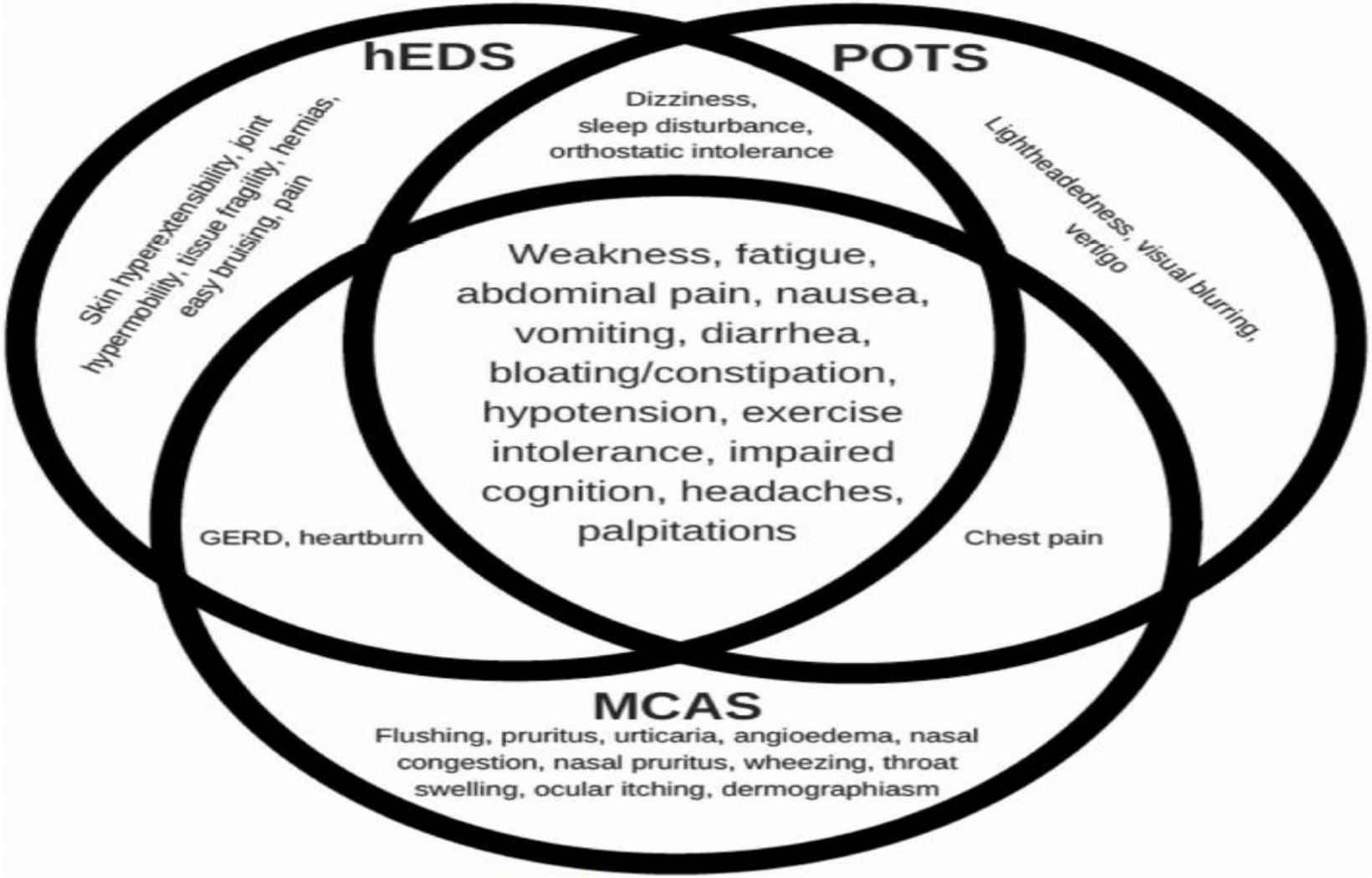


Fig. 3 Patient reported symptoms in hEDS, POTS, and MCAS. (*MCAS* mast cell activation syndrome, *POTS* postural orthostatic tachycardia syndrome, *hEDS* hypermobile Ehlers-Danlos syndrome)

MCAS neurology and psychiatry

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

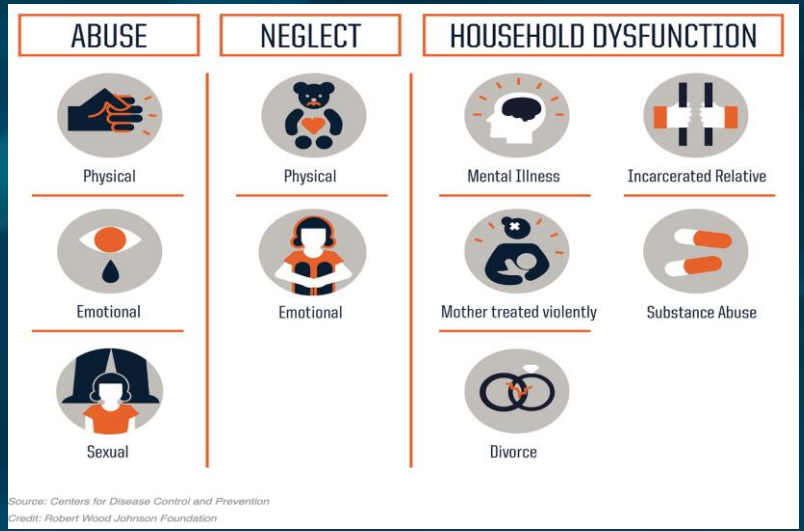
Lawrence B. Afrin[a], Dieter Pöhlau[b], Martin Raithel[c], Britta Haenisch[d,e], Franz L. Dumoulin[f], Juergen Homann[f], Uwe M. Mauer[g], Sabrina Harzer[h], Gerhard J. Molderings[h,*]

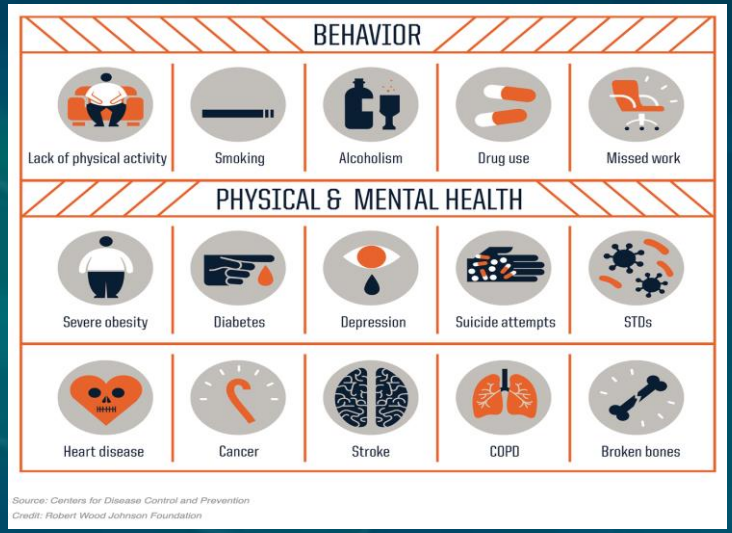
[a] Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN 55455, USA
[b] Department of Neurology, Kamillus Klinik, Asbach, Germany
[c] Medizinische Klinik 1, Universitätsklinikum Erlangen, Erlangen, Germany
[d] Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Standort Bonn, Bonn, Germany
[e] Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany
[f] Community Hospital St. Elisabeth, Bonn, Germany
[g] Department of Neurosurgery, Hospital of the German Armed Forces, Ulm, Germany
[h] Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany

MCAS – To make a diagnosis, you need a good history

- History – Crucial
  - Life long range of problems
  - Family history
    - 75% chance of 1st degree relative
    - Chronological
      - Often starting early in life
      - Puberty often trigger
    - Social Stressors
      - Major life Events
        - Puberty
        - Tertiary education
        - Employment
        - Marriage/Divorce
        - Pregnancies
    - Physical Stressors
      - Surgery
      - Trauma
      - Illnesses
    - Medication/Allergies

ACES: Adverse Childhood Events





https://www.npr.org/sections/health-shots/2015/03/02/387007941/take-the-ace-quiz-and-learn-what-it-does-and-doesnt-mean

MCAS – History taking continued

Symptoms are often chronic/recurrent, waxing/waning.

'Flares' may be temporary (minutes /months), may be permanent)

Roberts LJ, Anthony LB, Oates JA. "Disorders of Vasodilator Hormones: Carcinoid Syndrome and Mastocytosis" in Wilson JD, Foster DW, Kronenberg HM, *et al., eds., Williams Textbook of Endocrinology, 9th ed.*, 1998, W. B. Saunders Company, Philadelphia, pp. 1718-1732.

Lim K-H, *et al.* Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-5736.

Afrin –with permission

Circadian Control of Mast Cells

Allergology International 71 (2022) 425–431

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

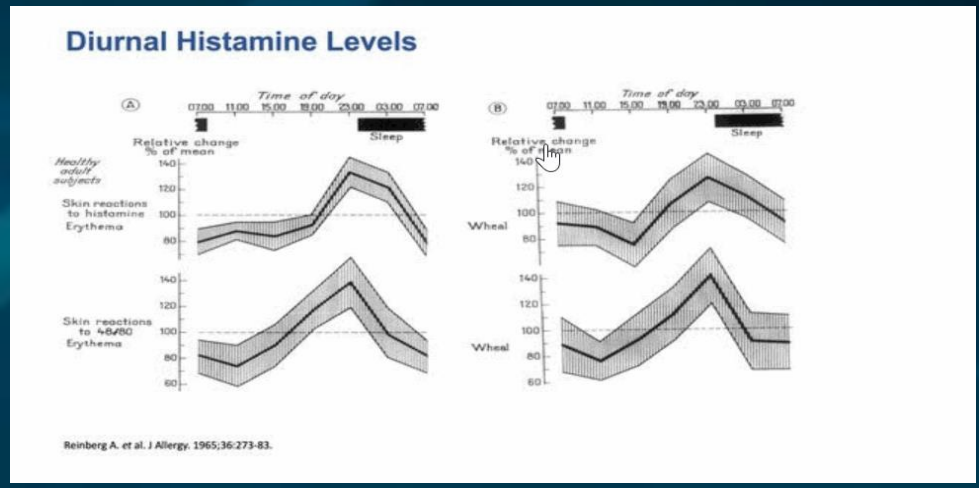
Invited Review Article

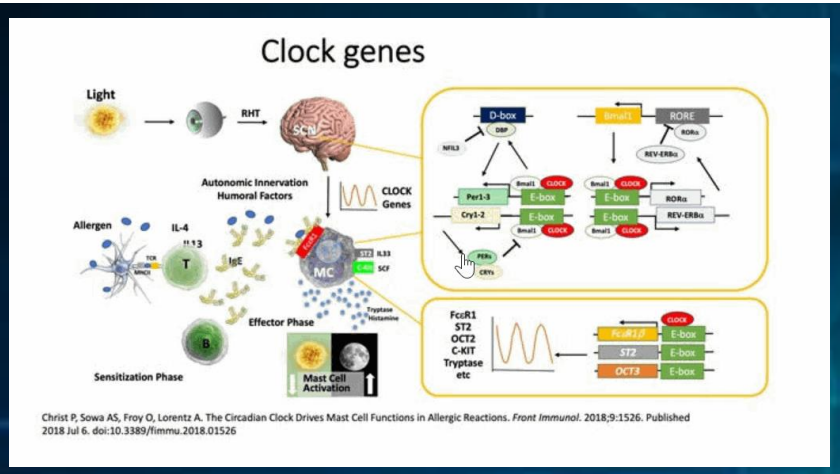
Time will tell about mast cells: Circadian control of mast cell activation

Atsuhito Nakao [a, b, *], Yuki Nakamura [a]

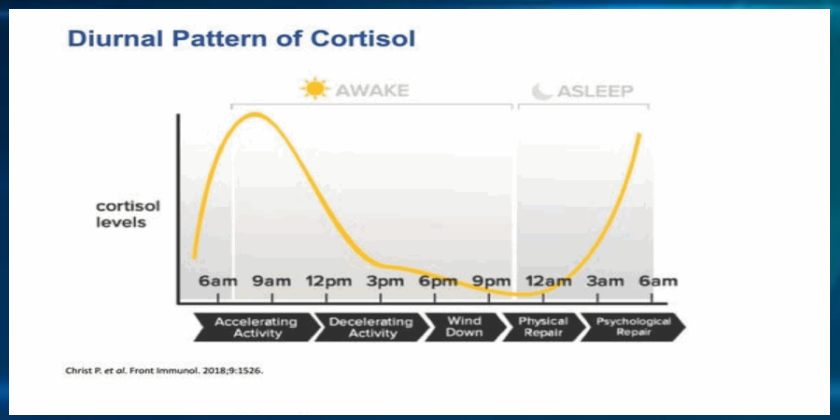
[a] Department of Immunology, University of Yamanashi Faculty of Medicine, Yamanashi, Japan
[b] Atopy Research Center, Juntendo University School of Medicine, Tokyo, Japan

Histamine levels rise during day





Cortisol levels low at 2am



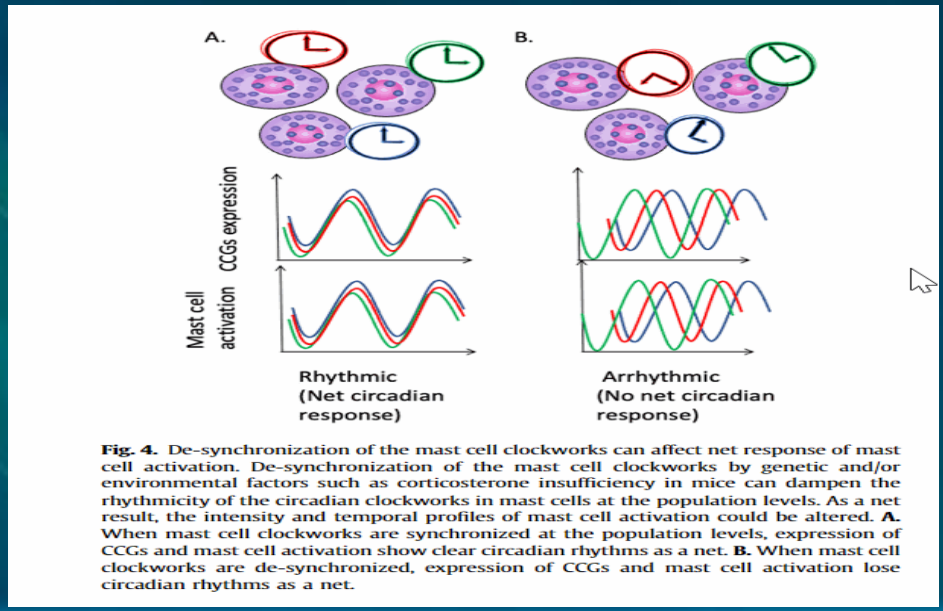


Fig. 4. De-synchronization of the mast cell clockworks can affect net response of mast cell activation. De-synchronization of the mast cell clockworks by genetic and/or environmental factors such as corticosterone insufficiency in mice can dampen the rhythmicity of the circadian clockworks in mast cells at the population levels. As a net result, the intensity and temporal profiles of mast cell activation could be altered. **A.** When mast cell clockworks are synchronized at the population levels, expression of CCGs and mast cell activation show clear circadian rhythms as a net. **B.** When mast cell clockworks are de-synchronized, expression of CCGs and mast cell activation lose circadian rhythms as a net.

TILT Syndrome – Toxicant Induced Loss of Tolerance

Miller et al. Environmental Sciences Europe (2021) 33:129
https://doi.org/10.1186/s12302-021-00570-3

Environmental Sciences Europe

DISCUSSION Open Access

Mast cell activation may explain many cases of chemical intolerance

Claudia S. Miller[1], Raymond F. Palmer[1*], Tania T. Dempsey[2], Nicholas A. Ashford[3] and Lawrence B. Afrin[2]

BREESI

Brief Environmental Exposure and Sensitivity Inventory

Instructions: Please answer these three questions by checking Yes or No

1. Do you feel sick when you are exposed to tobacco smoke, certain fragrances, nail polish/remover, engine exhaust, gasoline, air fresheners, pesticides, paint/thinner, fresh tar/asphalt, cleaning supplies, new carpet or furnishings? By sick we mean: headache, difficulty thinking, difficulty breathing, weakness, dizziness, upset stomach, etc.

❑ *Yes* ❑ *No*

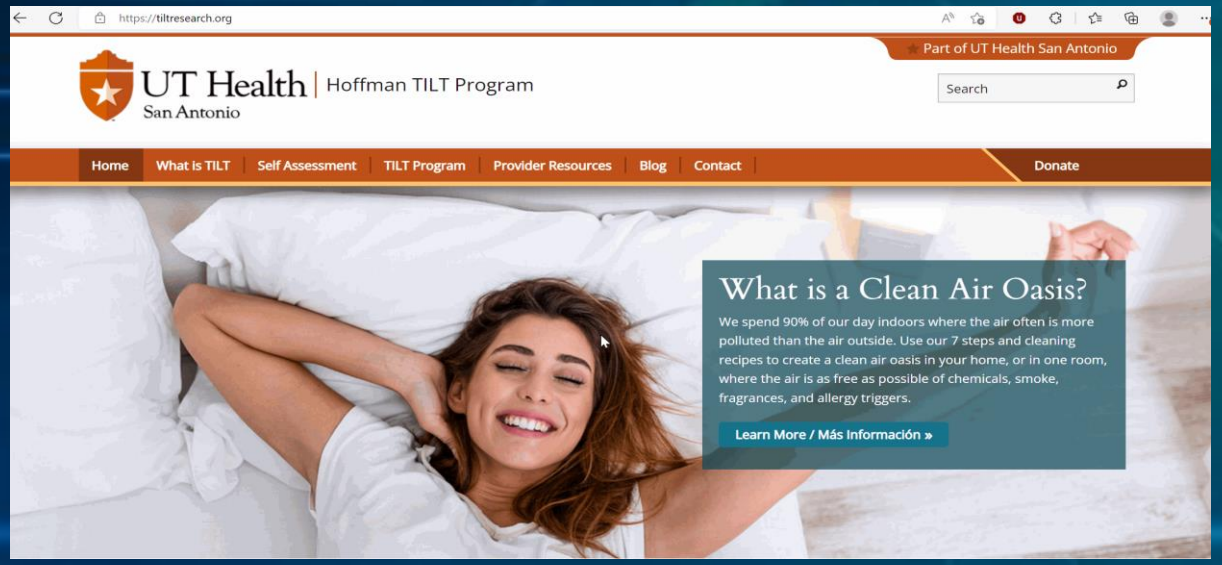
2. Are you unable to tolerate or do you have adverse or allergic reactions to any drugs or medications (such as antibiotics, anesthetics, pain relievers, X-ray contrast dye, vaccines or birth control pills), or to an implant, prosthesis, contraceptive chemical or device, or other medical/surgical/dental material or procedure?

❑ *Yes* ❑ *No*

3. Are you unable to tolerate or do you have adverse reactions to any foods such as dairy products, wheat, corn, eggs, caffeine, alcoholic beverages, or food additives (e.g., MSG, food dye)?

❑ *Yes* ❑ *No*

www.tiltresearch.org

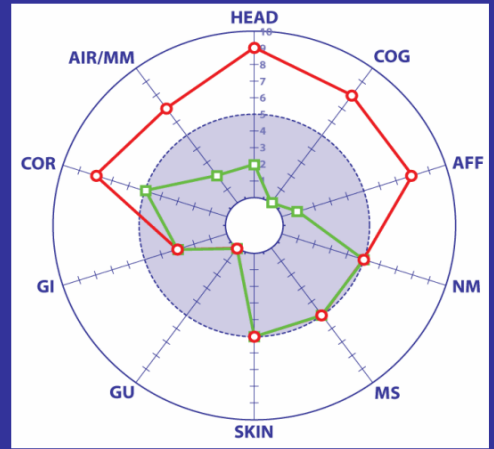


QEESI

Symptom Star

HEAD = Head-related symptoms
COG = Cognitive symptoms
AFF = Affective symptoms
NM = Neuromuscular symptoms
MS = Musculoskeletal symptoms
SKIN = Skin-related symptoms
GU = Genitourinary symptoms
GI = Gastrointestinal symptoms
COR = Heart/chest-related symptoms
AIR/MM = Airway or mucous membrane symptoms

Before exposure event
After exposure event



Mast Cell Mediator Release Syndrome Questionnaire

Mast Cell Mediator Release Syndrome Questionnaire

Patient name _____

Date _____

Date of birth _____

Answer all of the following symptoms/questions, even if they are only slightly bothersome, rarely occurring (for instance, not necessary present currently but in the past), or may seem not be related to your main problems.
Contact your doctor if you have difficulty completing the questionnaire.

Check (✓) inside the box if the statement applies to you.

If the statement applies to you, enter the intensity level when it was present the last time it occurred on the line next to the box. Please use the range of 1 (very mild) to 10 (unbearable) to reflect the level of your discomfort.

MCMRS: 5 page, validated, self-administered

57 questions - symptoms potential of 40 points

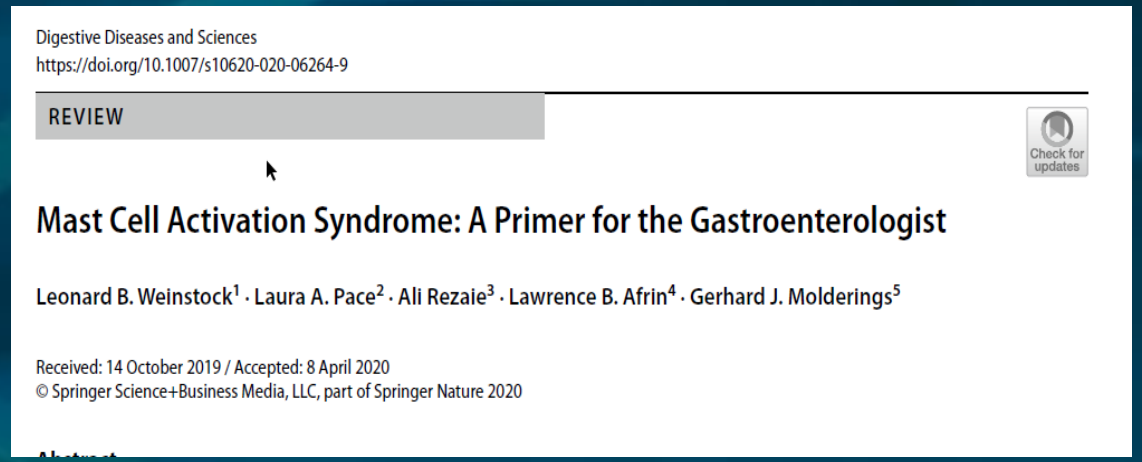
Additional points for pathology and biopsies

≥ 14 consistent with MCAS

Testing for Mast Cell Activation Syndrome

STOP medication prior to testing

1. Chilled serum tryptase
2. Chromogranin A
3. Plasma prostaglandin D2
4. Histamine
5. Heparin
6. Random urine N-Methylhistamine
7. Random urine Leukotriene E4
8. 24 hour urine Prostaglandin D2
9. 24 hour urine N-Methylhistamine
10. 24 hour urine Leukotriene E4
11. 24 hour urine 2,3-dinor-11beta-prostaglandin F2 alpha



Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-020-06264-9

REVIEW

Check for updates

Mast Cell Activation Syndrome: A Primer for the Gastroenterologist

Leonard B. Weinstock[1] · Laura A. Pace[2] · Ali Rezaie[3] · Lawrence B. Afrin[4] · Gerhard J. Molderings[5]

Received: 14 October 2019 / Accepted: 8 April 2020

Tissue biopsy with CD117 stains – must request specifically

Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol* 2014 Mar;3(1):1-17.

Testing for Mast Cell Activation Syndrome

AUSTRALIAN TESTING

- Available through major NATA accredited pathology labs:
  - Whole blood histamine
  - Tryptase
  - Chromogranin A
  - N-methyl histamine 24 hour
  - Heparin
  - CD 117 stain.
- Nutripath have additional testing available – contact Nutripath directly for further information

Mast Cell detection: CD117 Staining

- Biopsies with CD117 stain – attaches to KIT protein (transmembrane tyrosine kinase) – best for number but not activity

  - MCAS – tissue speckled with MC >20/HPF is “abnormal”

    vs.

  - Mastocytosis – cells are in aggregates and are mainly spindle shaped >100/hpf

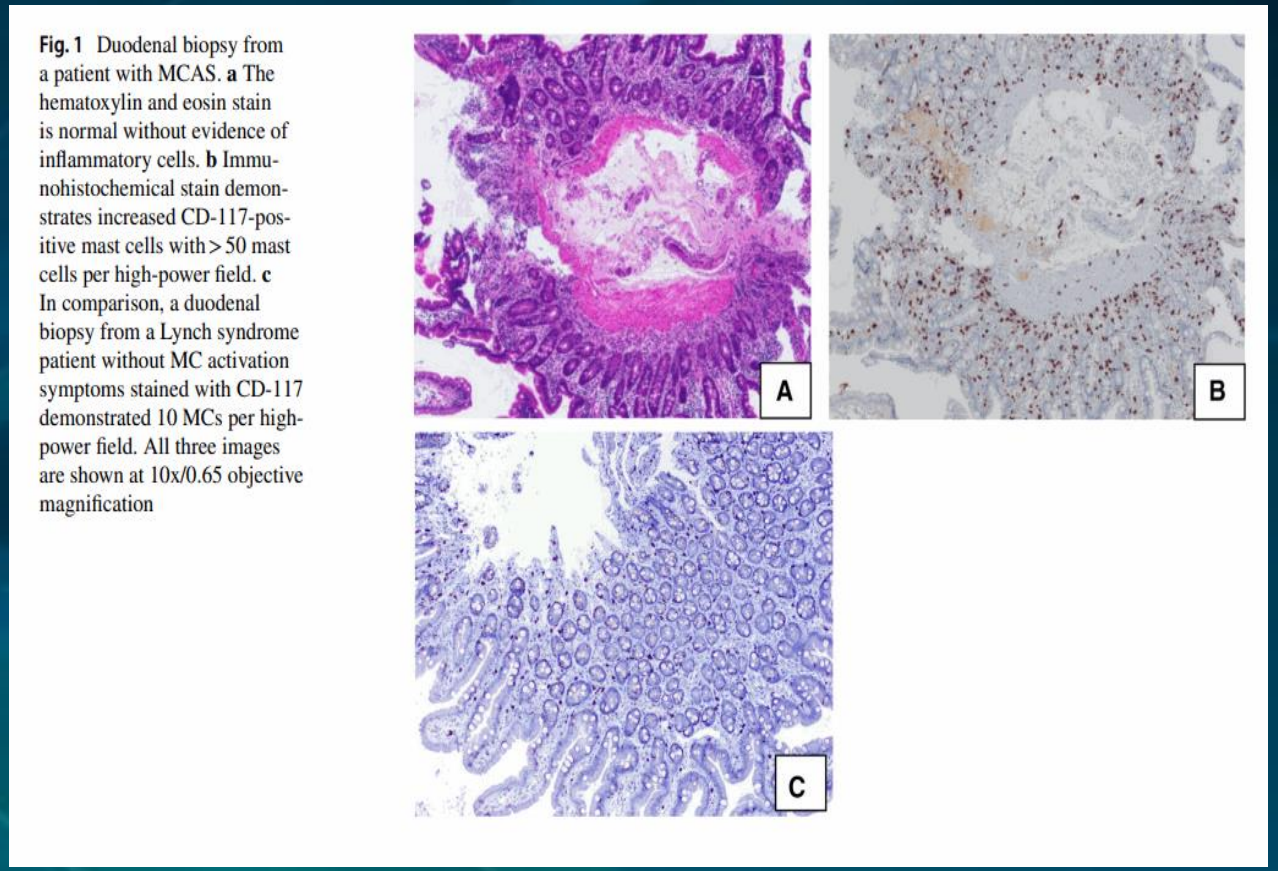


Fig. 1 Duodenal biopsy from a patient with MCAS. **a** The hematoxylin and eosin stain is normal without evidence of inflammatory cells. **b** Immunohistochemical stain demonstrates increased CD-117-positive mast cells with > 50 mast cells per high-power field. **c** In comparison, a duodenal biopsy from a Lynch syndrome patient without MC activation symptoms stained with CD-117 demonstrated 10 MCs per high-power field. All three images are shown at 10x/0.65 objective magnification

Weinstock, L.B., Pace, L.A., Rezaie, A. *et al.* Mast Cell Activation Syndrome: A Primer for the Gastroenterologist. *Dig Dis Sci* **66**, 965–982 (2021).

Basics of MCAS Treatment

'Beach Ball with 1000 ping pong balls inside'

https://frankiest.com.au/products/sunnylifebeachballglitter

Identify & avoid triggers

Block receptors of mediators

Inhibit mediator production

Inhibit mediator release

Molderings. Naumyn S Arch Pharm. 2016.

POTS: Postural Orthostatic Tachycardia Syndrome

1.Heart rate increased>30bpm in adults
2.Absence of orthostatic hypotension
3 Symptoms of orthostatic intolerance>6months

> J Transl Med. 2020 Aug 15;18(1):314. doi: 10.1186/s12967-020-02481-y.

Hemodynamics during the 10−minute NASA Lean Test: evidence of circulatory decompensation in a subset of ME/CFS patients

Jihyun Lee [1], Suzanne D Vernon [2], Patricia Jeys [1], Weam Ali [1], Andrea Campos [1], Derya Unutmaz [3], Brayden Yellman [1], Lucinda Bateman [1]

Affiliations + expand

PMID: 32799889 PMCID: PMC7429890 DOI: 10.1186/s12967-020-02481-y
Free PMC article

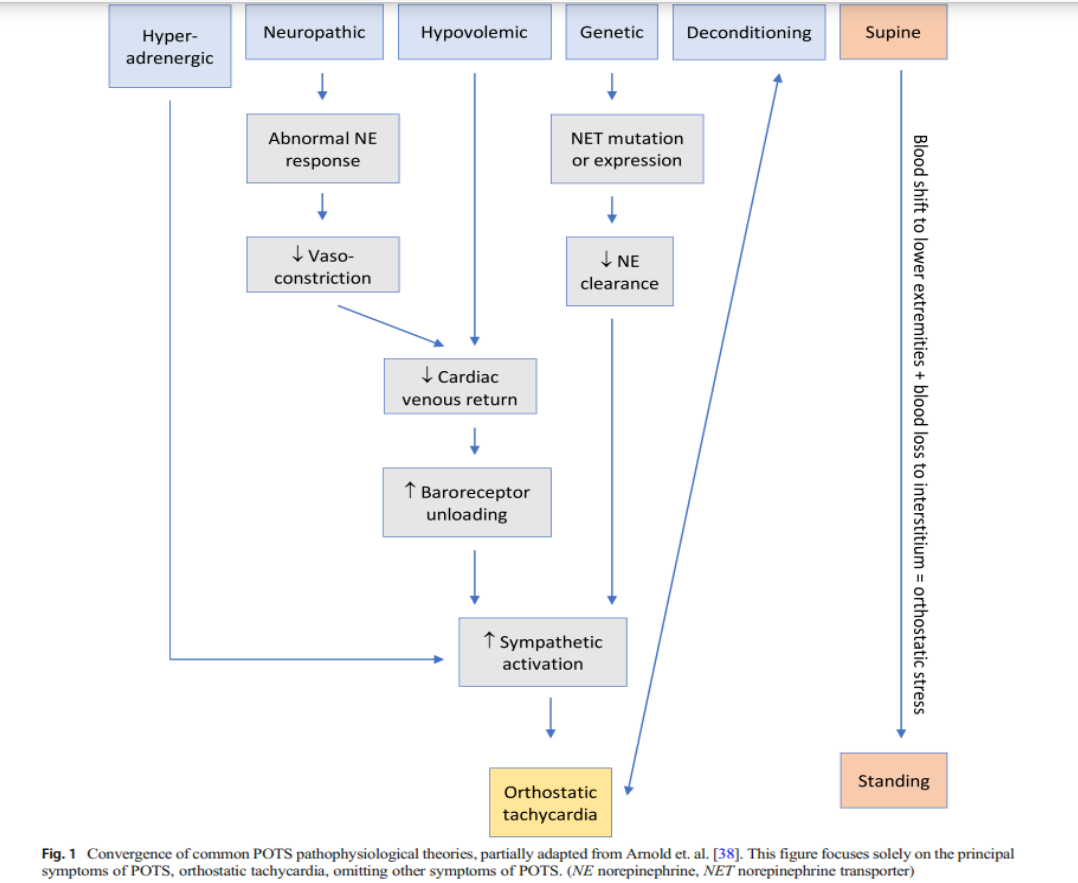
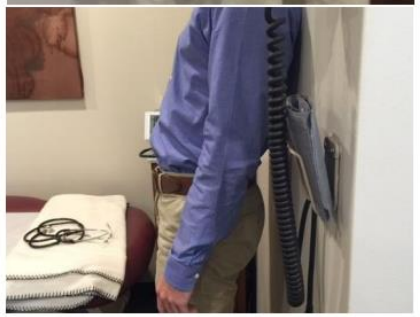


Fig. 1 Convergence of common POTS pathophysiological theories, partially adapted from Arnold et. al. [38]. This figure focuses solely on the principal symptoms of POTS, orthostatic tachycardia, omitting other symptoms of POTS. (*NE* norepinephrine, *NET* norepinephrine transporter)

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION



https://batemanhornecenter.org/

MCAS Treatment

- Identify triggers
- Treat co-morbid condition –POTS, EDS,
- Dietary Interventions – low histamine ,SIBO,
- Fructose intolerance.
- Trial of H1 antihistamines – Cetirizine, Levocetirizine Fexofenadine, Loratadine, Desloratadine
- Trial of H2 antihistamines- Famotidine, Nitazadine, Cimetidine
- Trial of leukotriene blocker - Montelukast
- Trial of Mast Cell Stabilizer - Luteolin, Quercetin, Sodium Cromoglycate, Cannabinoids
- Trial of second generation H1 blocker –Ketotifen

Molderings, G.J., Brettner, S., Homann, J. *et al.* Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J Hematol Oncol* 4, 10 (2011).

MCAS Treatment – Identify & Avoid Triggers

Foods – Low Histamine, FODMAPS
Mould
Medicines and excipients.
Personal Care products
Cleaning products
Pesticides
Atmospheric – especially humidity and EDS
Hormonal
Electrical – EMF
Vibration

Suggest keeping spreadsheet of batch number for items bought – often a change of excipients can affect some patients.

Small Intestinal Bacterial Overgrowth in Mast Cell Activation Syndrome

Leonard Weinstock, MD, Jill Brook, MS, Zahid Kaleem, MD, Lawrence Afrin, MD, Gerhart Molderings, MD
Specialists in Gastroenterology, St. Louis, Missouri, Hematology/Oncology, Mt. Kisco, New York, University Hospital Bonn, Bonn, Germany

ABSTRACT

Mast cell activation syndrome (MCAS) often presents with gastrointestinal symptoms (Sx) and patients may be misdiagnosed with functional syndromes including irritable bowel syndrome (IBS). Small intestinal bacterial overgrowth (SIBO) can be associated with IBS. We determined if SIBO was associated with MCAS.

MCAS is a common disorder of uncontrolled mast cell (MC) activation with multi-systemic inflammatory and allergic symptoms. The most common Sx are fatigue, myalgia, conjunctivitis, rhinitis, tinnitus, hives, itching, nausea, heartburn, dyspnea, near syncope, headache, chills, and edema. All organ systems can be involved.

METHODS AND AIMS

- Pts with refractory abd. pain, bloat, change bowels
- All evaluated for MCAS and SIBO
- MCAS Dx: MC activation Sx in ≥2 organs plus:
  - ≥1 elevation of MC blood and/or urinary mediators
  - clinical benefit with MC-therapy
  - and/or increased intestinal MC density
- SIBO Dx: lactulose breath test (LBT) with ≥20 ppm H2 rise within 90 min of baseline
- Methane plateau Dx: high >10 ppm, low 3 – 9 ppm
- Primary aim: LBT results in MCAS compared to controls
- Secondary aims: effect of co-morbid syndromes and medications on LBT. Effect of antibiotics on GI Sx

PATIENTS

139 MCAS subjects (116 F, 23 M, mean 47 yrs) vs.
30 controls (19 F, 11 M, mean 44 yrs).

GI Sx prior to other MCAS Sx in 66% pts.

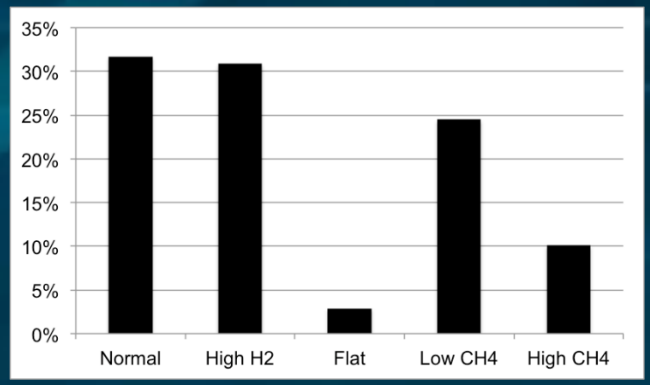
Abdominal pain (87%), bloating (74%), constipation (66%), diarrhea (63%), nausea (61%), heartburn (54%), and dysphagia (30%).

Rome IV criteria for IBS-mixed (40%), IBS-constipation (22%), and IBS-diarrhea (19%).

RESULTS

- SIBO in 31% vs. Controls 10% (p=0.023)
- Higher methane levels were associated with IBS-constipation compared to H2 positive subjects: 43% vs. 9% (p=0.02)
- Antibiotics prescribed in 74 subjects: 68% marked improvement in GI Sx
- SIBO was not associated with postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, PPI or statin Rx, or thyroid supplementation.

LBT PATTERNS IN 139 MCAS PTS



CONCLUSIONS

- Abnormal lactulose breath tests are common in MCAS patients.
- SIBO pattern is statistically more common than controls.

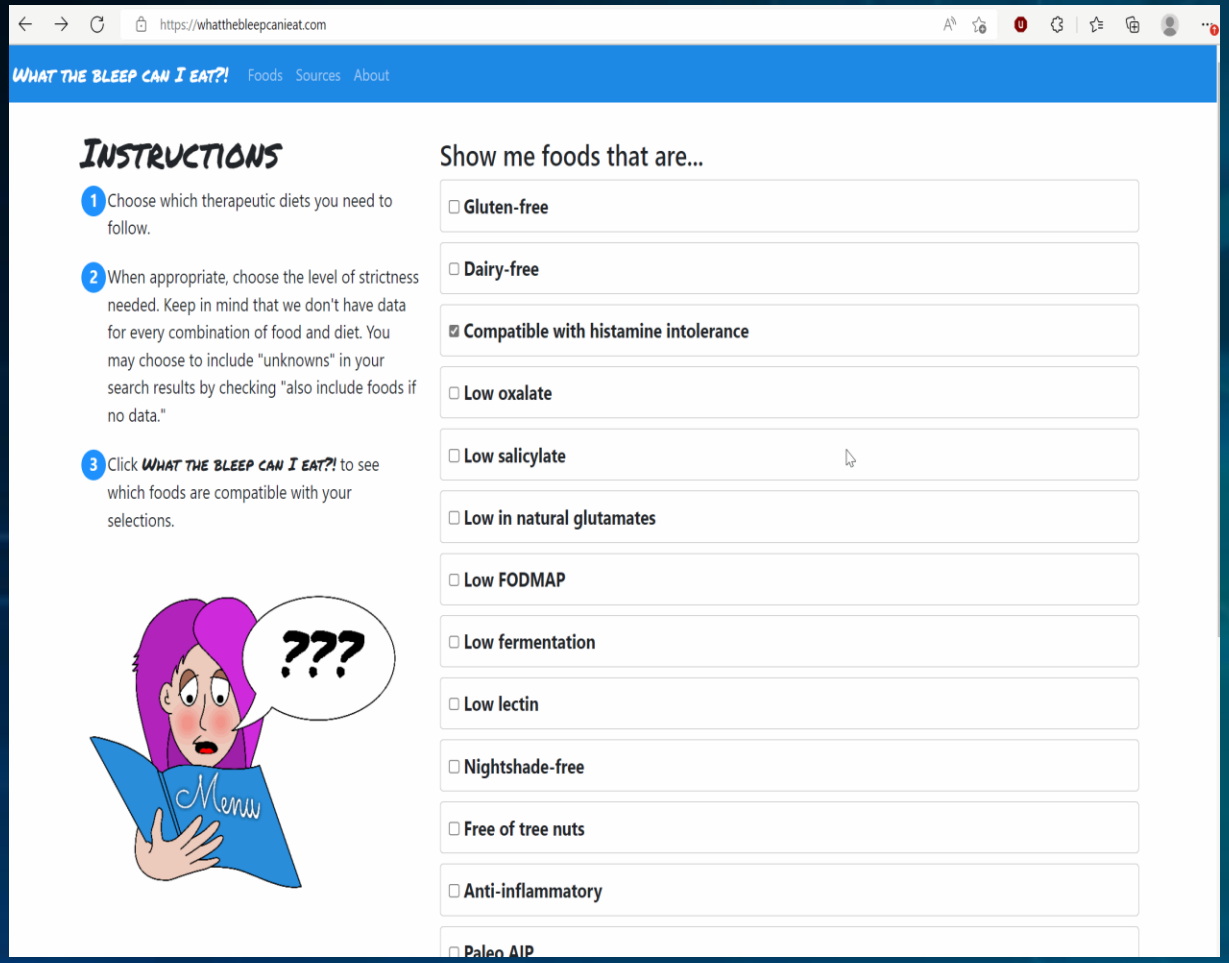
THEORIES

MCAS could cause SIBO due to altered motility caused by local release of MC mediators next to nerves or muscles, alterations of the GI immune system, or MC damage to interstitial cells of Cajal as in achalasia.

(Achalasia reference: Liu. Neurogast Mot. 2019)

What the BLEEP can I eat?

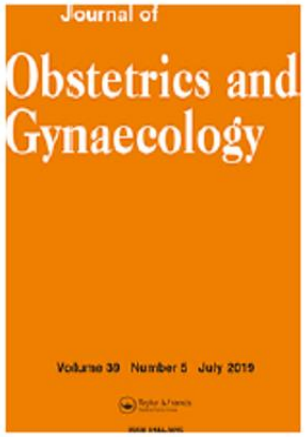
www.whatthebleepcanieat.com



Antihistamine medications

Group	Generation	Drug on the market	Brand	Strength	Characteristic
H1 Antagonists	1st	Diphenhydramine	Snuzaid, Unisom, Paedamin Antihistamine	50MG	Drowsiness
		Doxylamine	Restavit, Dozile	25MG	
		Alimemazine (Trimeprazine)	Vakkergan	1.5MG/ML	
		Promethazine	Avomine, Phenergan, Allersooth	10MG or 25MG	
		Brompheniramine	Dimetapp	2MG/5ML	
		Dexchlorpheniramine	Polaramine	2MG	
		Cyprheptadine	Periactin	4MG	
	2nd	Loratidine	Claratyne	10MG	Non drowsy
		Desloratidine	Aerius	5MG	
		Cetrizine	Zyrtec	10MG	
		Azelastine	Azep Nasal Spray	0.1%W/V	
		Fexodenadine	Telfast	30MG, 60MG, 120MG, 180MG	
H2 Antagonists		Nizatidine	Nizac	300MG	
		Cimetidine	Magicul	400MG	
		Famotidine	Pamacid	20MG, 40MG	

MCAS - Gynaecology



Taylor & Francis
Taylor & Francis Group

Journal of Obstetrics and Gynaecology

ISSN: 0144-3615 (Print) 1364-6893 (Online) Journal homepage: https://www.tandfonline.com/loi/ijog20

Successful mast-cell-targeted treatment of chronic dyspareunia, vaginitis, and dysfunctional uterine bleeding

Lawrence B. Afrin, Tania T. Dempsey, Lila S. Rosenthal & Shanda R. Dorff

25mg Diphenhydramine in 50ml normal saline douche per vagina at night.

Mast Cell Activation Syndrome - Treatments

- **Leukotriene inhibitors –** montelukast (10mg-20mg BD)
- **Ketotifen:** Typical dose 1mg . Can escalate to maximal efficacy. Max dose 4-6 mg BD-TDS. For sensitive patients can start 0.25g once or BD. May induce fatigue.
- **Sodium Cromoglycate:** oral form 100mg – 200mg. Can be made into cream or douche. Consider Slow release form for GIT issues. 20 min prior to meals
- **Olopatadine** 0.6 % nasal drops good for vasomotor rhinitis.

Edwards AM, Hagberg H. Oral and inhaled sodium cromoglicate in the management of systemic mastocytosis: a case report. *J Med Case Rep*. 2010;4:193. Published 2010 Jun 26.

Sokol KC, Amar NK, Starkey J, Grant JA. Ketotifen in the management of chronic urticaria: resurrection of an old drug. Ann Allergy Asthma Immunol. 2013 Dec;111(6):433-6

NICE. Asthma: diagnosis, monitoring and chronic asthma management [Internet]. NICE guidance. 2017. Available from: www.nice.org.uk/guidance/ng80

Afrin. Never Bet Against Occum.

Riccioni G, et al. Advances in therapy with antileukotriene drugs. Ann Clin Lab Sci. 2004 Autumn;34(4):379-87

Smith PK, Collins J. Olopatadine 0.6% nasal spray protects from vasomotor challenge in patients with severe vasomotor rhinitis. Am J Rhinol Allergy. 2011 Jul-Aug;25(4)

Mast Cell Activation Syndrome - Treatments cont.

- **Benzodiazepines** – Diazepam 2-5mg qd-bid. Midazolam helpful for perioperative management.
- **Low dose Naltrexone** – (1.5-6mg/d,)
- **COX2 blocking**. Celecoxib (100-300mg BID) typically well tolerated.


Novel treatment (new drug/intervention; established drug/procedure in new situation)

OPEN ACCESS

Case report

Low-dose naltrexone as a treatment for chronic fatigue syndrome

Monica Jane Bolton [1], Bryan Paul Chapman, [2] Harm Van Marwijk [3]

Haenisch B, Huber M, Wilhelm T, Steffens M, Molderings GJ. Investigation into mechanisms mediating the inhibitory effect of 1,4-benzodiazepines on mast cells by geneexpression profiling. Life Sci. 2013;92(6-7):345-51.

Bolton MJ, Chapman BP, Van Marwijk H. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Rep. 2020;13(1):e232502. Published 2020 Jan 6.

Weinstock, et al. Successful treatment of postural orthostatic tachycardia and mast cell activation syndrome using naltrexone, immunoglobulin and antibiotic treatment. BMJ Care Rep. 2018 Jan 11;2018 pii: bcr-2017-221405.

Younger, et al. The use of LDN as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014. 33:451-9.

Molderings GJ, Haenisch B, Brettner S, et al. Pharmacological treatment options for mast cell activation disease. *Naunyn Schmiedebergs Arch Pharmacol*. 2016;389(7):671-694. doi:10.1007/s00210-016-1247-1

MCAS Intravenous Protocol

- The volume of fluid selected as either saline or lactated Ringer's solution related to the work and experience already known and published for POTS patients. 0.5 to 2 L NS. (often the POTS patients need 2L at least but smaller patients and patients with concern for IIH, I reduce the volume to 1.5L.)

- +/- Ondansatron 4mg IV

- Preservative-free **Diphenhydramine** (25 or 50mg) placed in infusion bag. Infuse slowly over 15 minutes – never push wait 15 min. Diphenhydramine blocks histamine at the H1 receptor. Dosage of 25 to 50 mg is low toxicity risk for adverse events. The medication's half life is about 6 hours. Towards the end of the infusion patients feel lethargic lasting around the half life of the medication.

- **Diazepam** 5mg wait 15 min. Experimental work has revealed that 1,4 benzodiazepines class drugs work at the GABA receptor on the mast cell to stabilize against degranulation Due to the addiction or dependency of this class of medication, there is justifiable concern in relation to dependency however at the low dose of 5mg and the infrequency of weekly or monthly doses, the concern surrounding this should be reduced. Diazepam half-life is up to 60 hours.

- **Ketorolac / Toradol** 25-30mg and (no wait). The cyclooxygenase inhibitors has been shown to stabilize mast cells thereby reducing mast cell degranulation, tryptase release resulting in a clinical effect on mast cell-mediated symptoms including mast-cell induced migraine Caution is needed with NSAID sensitive patients so modifications to the protocol, including omission might be needed in those cases There is a low risk of toxicity or adverse events at the low infusion dose of 25 to 30mg either weekly or monthly.

- **Famotidine 20mg.** Famotidine directly blocks histamine action at the H2 receptors. While H2 receptions are found throughout the whole body, H2 receptors are known to be localized in the GI tract. Blocking can therefore prevent mast cell-mediated inflammation within the stomach and small bowel. Generally within MCAS patients H2 blockade tends to have a positive effect. IV delivery isn't necessarily superior to oral delivery however with some MCAS patients unable to tolerate oral medications, the IV administration may be the only option. Generally Famotidine is very well-tolerated. Famotidine's half life is about 3 hours.

MCAS IV Protocol References

Afrin LB, Dempsey TT, Rosenthal LS, Dorff SR. Successful mast-cell-targeted treatmentof chronic dyspareunia, vaginitis, and dysfunctional uterine bleeding. J Obstet Gynaecol.2019;39(5):664-9.

. Leonardi A, Busato F, Fregona I, Plebani M, Secchi AG. Anti-inflammatory andantiallergic effects of ketorolac tromethamine in the conjunctival provocation model. Br JOphthalmol. 2000;84(11):1228-32.

Ghanizada H, Al-Karagholi MA, Arngrim N, Morch-Rasmussen M, Metcalf-Clausen M,Larsson HBW, et al. Investigation of sumatriptan and ketorolac trometamol in the humanexperimental model of headache. J Headache Pain. 2020;21(1):19.

Levy D. Migraine pain, meningeal inflammation, and mast cells. Curr Pain HeadacheRep. 2009;13(3):237-40.

. Steinke JW, Huyett, P., Borish, L. Activation of Mast Cells by NSAIDs ReleasesArachidonic Acid Metabolites Independent of Histamine via a non-PPARγ Signaling Pathway. JAllergy Clin Immun. 2010;125(2):AB179.

. Zhong J, Hu N, Du Y, Li L. Comment on the successful treatment by Duenas-Laita et alof chronic drug-resistant urticaria with alprazolam. J Allergy Clin Immunol. 2010;125(5):1172;author reply -3.

3Duenas-Laita A, Ruiz-Munoz P, Armentia A, Pinacho F, Martin-Armentia B. Successfultreatment of chronic drug-resistant urticaria with alprazolam. J Allergy Clin Immunol.2009;123(2):504-5.

Alfter K vKI, Haenisch B, Frieling T, Hülsdonk A, Haars U,. New aspects of liverabnormalities as part of the systemic mast cell activation syndrome. Liver. 2009;29:181-6.

Molderings GJ BM, Raithel M, Wilken V, Hartmann K, Brockow K,. SystemischeMastozytose als Grund für chronische gastrointestinale Beschwerden. Dtsch Arztebl.2005;102:A1744-9.

Haenisch B, Huber M, Wilhelm T, Steffens M, Molderings GJ. Investigation into mechanisms mediating the inhibitory effect of 1,4-benzodiazepines on mast cells by geneexpression profiling. Life Sci. 2013;92(6-7):345-51.

39. Bertaccini G, Coruzzi G. Extragastric H2-receptors. J Clin Gastroenterol. 1983;5 Suppl1:57-70.

Mast Cell Activation Treatments - Supplements

- Vitamin C – slow-release formulation, 500-1000mg
- Vitamin D – 5000 Daily
- Palmitoylethanolamide PEA (400mg BD-TDS)
- Luteolin – 100mg – 300mg up to TDS
- Quercetin 250mg – TDS

Petra, et al. Spectrum of Mast Cell Activation Disorders. Expert Rev Clin Immunol, 2014. 10(6)729-39.
Theoharides, et al. Brain "fog", inflammation and obesity. Neuropyschiatric disorders improved by Luteolin.
Weng Quercetin is more effective then cromolyn in blocking human mast cell cytokine release. PLoS One. 2012;7(3):e33805
Frontiers in neuroscience; 2015: 9:225

Histamine Production by Gut Microbiota

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GUT MICROBIOTA

Histamine production by the gut microbiota induces visceral hyperalgesia through histamine 4 receptor signaling in mice

Giada De Palma[1]†, Chiko Shimbori[1]†, David E. Reed[2]†, Yang Yu[2], Virginia Rabbia[1], Jun Lu[1], Nestor Jimenez-Vargas[2], Jessica Sessenwein[2], Cintya Lopez-Lopez[2], Marc Pigrau[1], Josue Jaramillo-Polanco[2], Yong Zhang[2], Lauren Baerg[1], Ahmad Manzar[1], Julien Pujo[1], Xiaopeng Bai[1], Maria Ines Pinto-Sanchez[1], Alberto Caminero, Karen Madsen[3], Michael G. Surette[1], Michael Beyak[2], Alan E. Lomax[2], Elena F. Verdu[1], Stephen M. Collins[1], Stephen J. Vanner[2]‡, Premysl Bercik[1]*‡

The gut microbiota has been implicated in chronic pain disorders, including irritable bowel syndrome (IBS), yet specific pathophysiological mechanisms remain unclear. We showed that decreasing intake of fermentable carbohydrates improved abdominal pain in patients with IBS, and this was accompanied by changes in the gut microbiota and decreased urinary histamine concentrations. Here, we used germ-free mice colonized with fecal microbiota from patients with IBS to investigate the role of gut bacteria and the neuroactive mediator histamine in visceral hypersensitivity. Germ-free mice colonized with the fecal microbiota of patients with IBS who had high but not low urinary histamine developed visceral hyperalgesia and mast cell activation. When these mice were fed a diet with reduced fermentable carbohydrates, the animals showed a decrease in visceral hypersensitivity and mast cell accumulation in the colon. We observed that the fecal microbiota from patients with IBS with high but not low urinary histamine produced large amounts of histamine in vitro. We identified *Klebsiella aerogenes*, carrying a histidine decarboxylase gene variant, as a major producer of this histamine. This bacterial strain was highly abundant in the fecal microbiota of three independent cohorts of patients with IBS compared with healthy individuals. Pharmacological blockade of the histamine 4 receptor in vivo inhibited visceral hypersensitivity and decreased mast cell accumulation in the colon of germ-free mice colonized with the high histamine-producing IBS fecal microbiota. These results suggest that therapeutic strategies directed against bacterial histamine could help treat visceral hyperalgesia in a subset of patients with IBS with chronic abdominal pain.

metabolites

MDPI

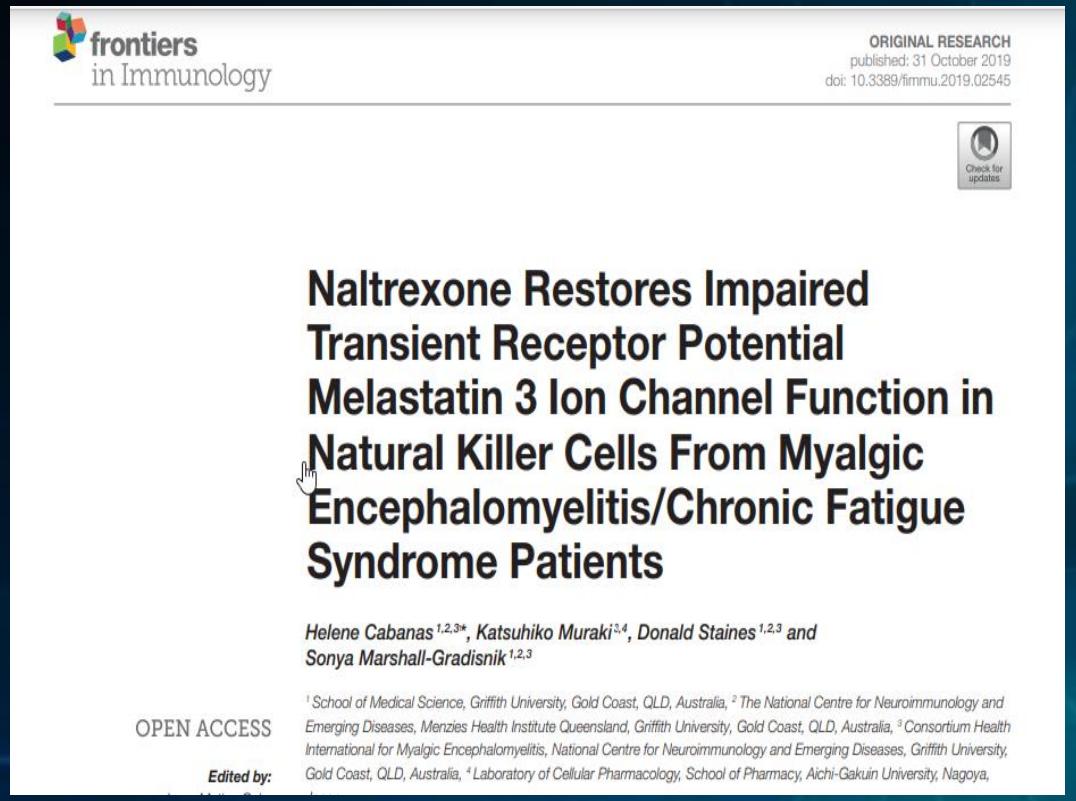
Review

Histamine: A Mediator of Intestinal Disorders—A Review

Sylwia Smolinska [1,*], Ewa Winiarska [1], Anna Globinska [2] and Marek Jutel [1,3]

The species of bacteria with the highest histidine decarboxylase activity are Morganella morganii, Eschericha coli, Hafnia alvei, Proteus vulgaris, Proteus milabilis, Enterobacter aerogenes, Raoultella planticola, Raoultella ornithinolytica, Citrobacter freundii, Pseudomonas fluorescens, and Photobacterium damselae [21]. Some bacteria have the ability to

Low Dose Naltrexone



frontiers in Immunology

ORIGINAL RESEARCH
published: 31 October 2019
doi: 10.3389/fimmu.2019.02545

Check for updates

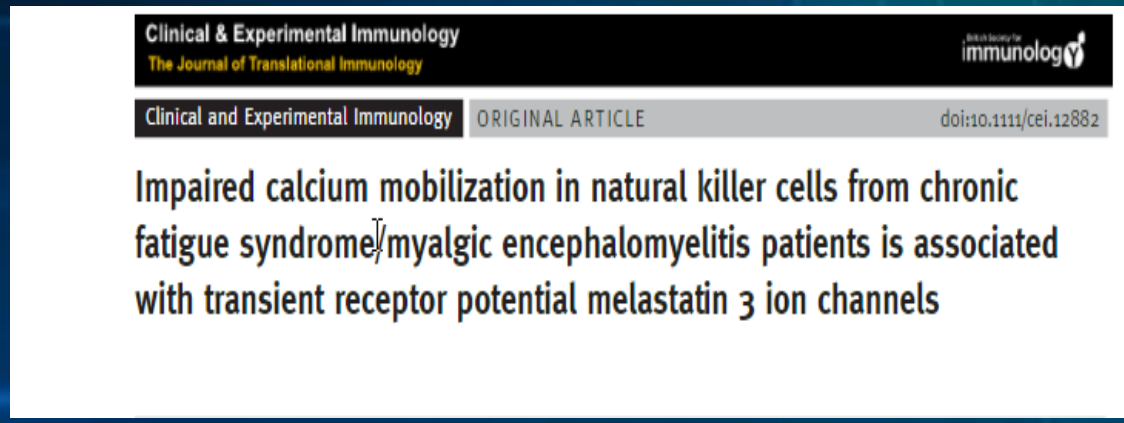
Naltrexone Restores Impaired Transient Receptor Potential Melastatin 3 Ion Channel Function in Natural Killer Cells From Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients

Helene Cabanas[1,2,3]*, *Katsuhiko Muraki*[3,4], *Donald Staines*[1,2,3] and *Sonya Marshall-Gradisnik*[1,2,3]

[1] School of Medical Science, Griffith University, Gold Coast, QLD, Australia, [2] The National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia, [3] Consortium Health International for Myalgic Encephalomyelitis, National Centre for Neuroimmunology and Emerging Diseases, Griffith University, Gold Coast, QLD, Australia, [4] Laboratory of Cellular Pharmacology, School of Pharmacy, Aichi-Gakuin University, Nagoya,

OPEN ACCESS

Edited by:



Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology | ORIGINAL ARTICLE | doi:10.1111/cei.12882

Impaired calcium mobilization in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients is associated with transient receptor potential melastatin 3 ion channels

Novel treatment (new drug/intervention; established drug/procedure in new situation)

OPEN ACCESS

Case report

Low-dose naltrexone as a treatment for chronic fatigue syndrome

Monica Jane Bolton [1], Bryan Paul Chapman,[2] Harm Van Marwijk[3]

1.6-6mg/day.

MCAS Summary

1. History
2. Identify and treat triggers
3. Introduce one treatment at a time
4. Back to basics

   - Sleep, food, exercise, relationships ie: decrease stress
5. Diagnosis of exclusion

Mast Cell Activation Syndrome

"Ask not what your profession (and patients) can do for you; ask what you can do for your profession and your patients. ;-)" Afrin September 2020