Intro to MCAD

Jan Groh

TMS PNW Chapter Coordinator

June 27, 2015

Providence Portland Medical Center

Social Room

Acknowledgements

- PPMC for the space
- Nutricia for having a representative present with Neocate products
- Wendy Busse, MSc RD for traveling to speak to us
- TMS for picking up lunch for the doctors and supporting us
- All the patients who've traveled and risked anaphylaxis to attend
- All the doctors who've kindly taken the time to attend and learn
- All the hardworking doctors on the leading edge of MCAD research
- *All my fellow highly informative patients who have taught me so much and support me every day! I'm doing this WITH and FOR you!*

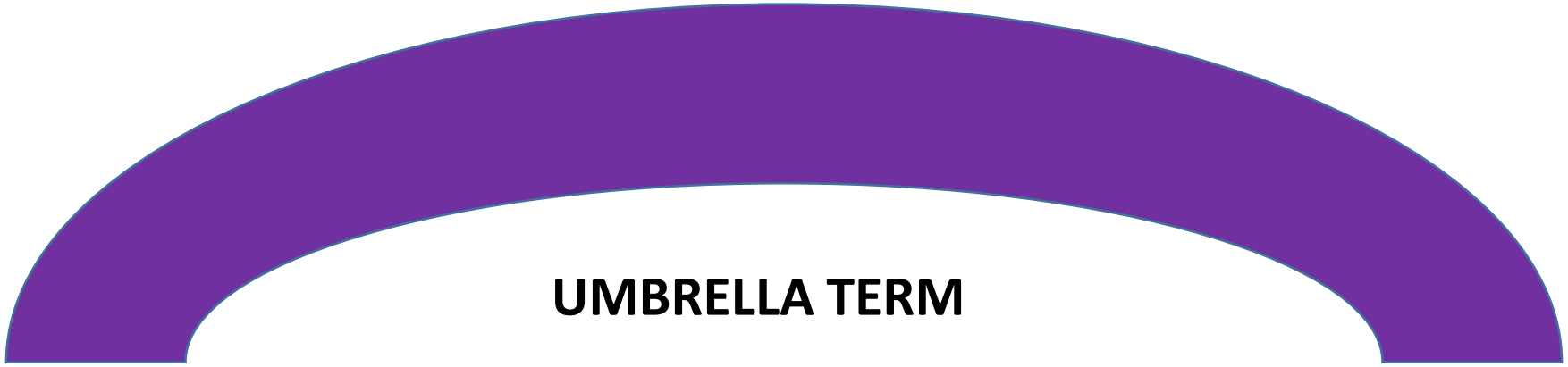
Who am I? (Jan Groh)

- HEDS, MCAS, POTS survivor finally diagnosed after 25 years in 2012 only after going from walking to wheelchair in 3 weeks in a sudden onset “cascade”. (Walking again after lots of hard work.)
- Attended 2012 TMS Conference in Bellevue, WA, and have observed thousands of patients online daily via Facebook and Inspire since 2012 with both conditions. **Http://tmsforacure.org**
- Former director of OR EDS, led successful 2013 Conference for 200 See: **http://oreds.org** to join them
- Ongoing blogger & educator on WordPress and Twitter and budding writer at **@H2OhTWIST** and **@jandroid**
- **Learn more at http://ohtwist.com**

DISCLAIMER

- I am NOT A DOCTOR! Please CONSULT YOURS for proper custom medical advice for YOUR specific case and body!
- I am not an expert, so may not be able to answer all your questions.
- This is a very high level “60,000 ft” *introductory* overview of this topic! *Please consult the TMS Medical Advisory Board for more information*.
- **See http://tmsforacure.org**

What is MCAD



UMBRELLA TERM

FOR

ALL Mast Cell Activation Diseases!

Including: **MC Leukemias (rare), most Mastocytosis, *and* MCAS**

General Consensus on use of MCAD/MCD

2011 Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options - Molderings, Afrin et al PubMed

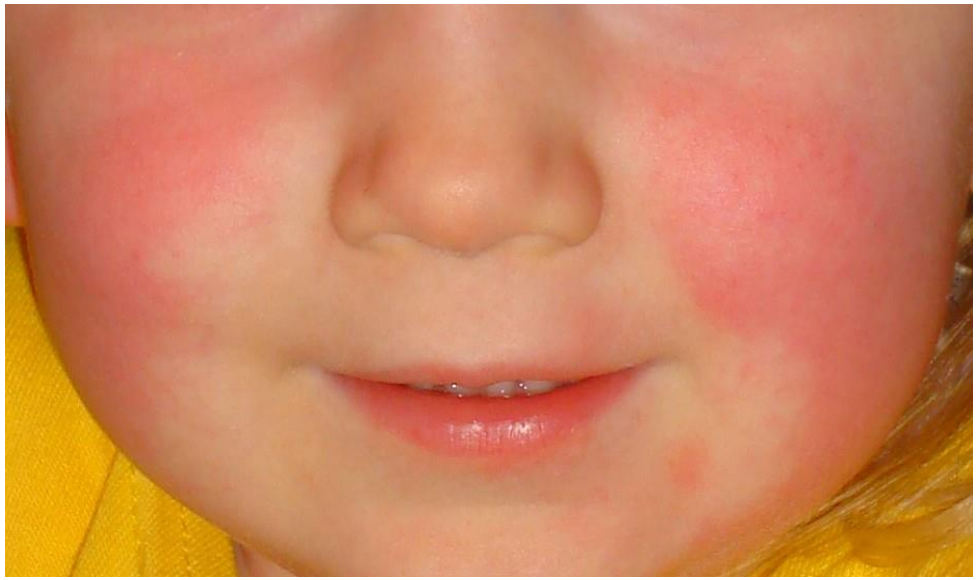
2014 Spectrum of mast cell activation disorders – Theoharides et al, Expert Review of Clinical Immunology

2014 The Presentation, Diagnosis and Treatment of Mast Cell Activation Syndrome – Afrin, L Current Allergy & Clinical Immunology Review Article

2014 Mast Cell Disorders: Mastocytosis and Mast Cell Activation Syndromes – Valerie Slee, RN BSN, Susan Jennings PhD in Special Edition of The TMS Chronicles

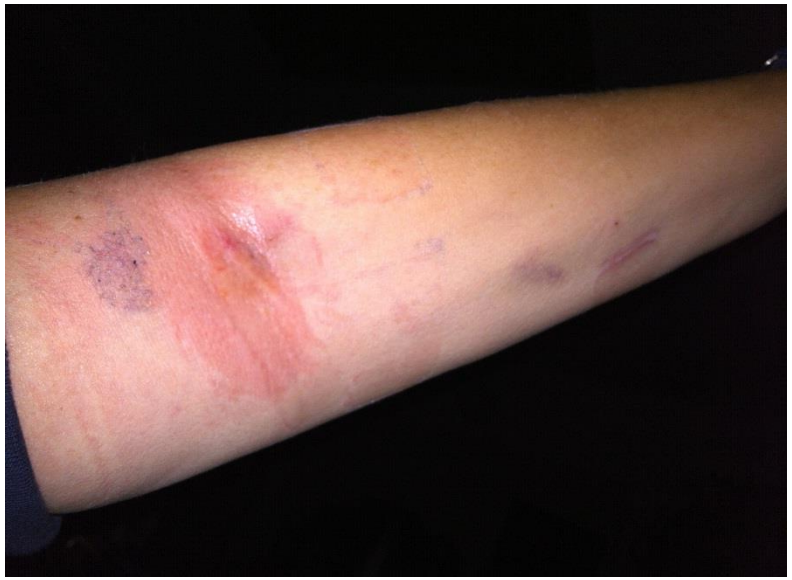
Some Common Signs of MCAD

- Easy flushing red of the “mantle” (head, neck, chest), mimics Lupus
- Chronic hives (urticaria), Urticaria Pigmentosa, dermatographia
- IBS – including constipation and/or sudden diarrhea, gas, bloating
- Frequent / sudden nausea or vomiting, react to anesthetics
- Esophageal spasms, pain, bone pain
- Asthma and itchy and runny nose & eyes & lungs
- Headaches, esp pressure from increased CSF, migraines, brain fog
- Angioedema (swelling) anywhere, esp. lips, eyes, abdomen
- Sudden variations in BP – spikes and drops, and “masto comas”
- Raciness, hyper-adrenergia, anxiety, trouble falling/staying asleep
- Lots of paradoxic (unexpected) reactions to medications, foods
- Allergy to bees & wasps, reactive to iodine contrast dye, alcohol
- Sensitive to chemicals and scents, heat, cold, vibration & *stress*

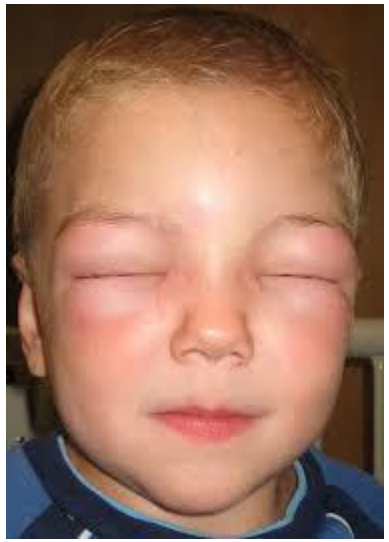


Flushed child's face

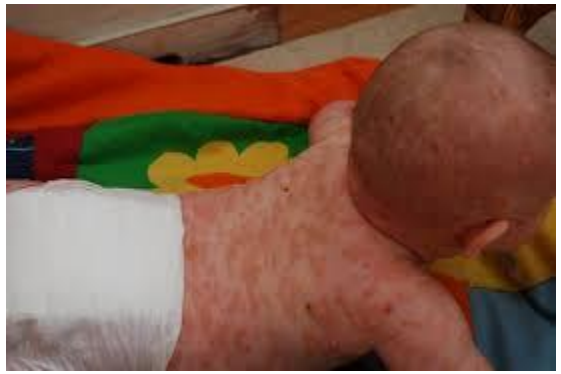
Jan's flush & hives



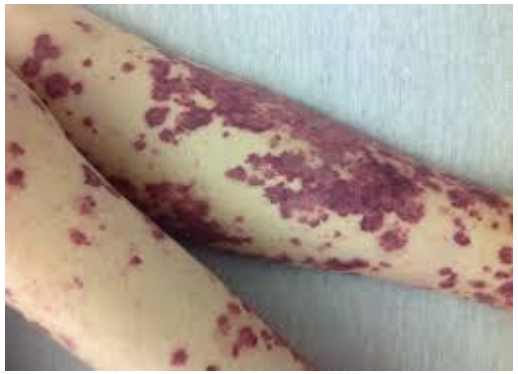
Imprints & rash from IV tape etc.



<-Angioedema (swelling) of the eyes



Urticaria pigmentosa



Purpura & petechiae

Dermatographia (skin writing)

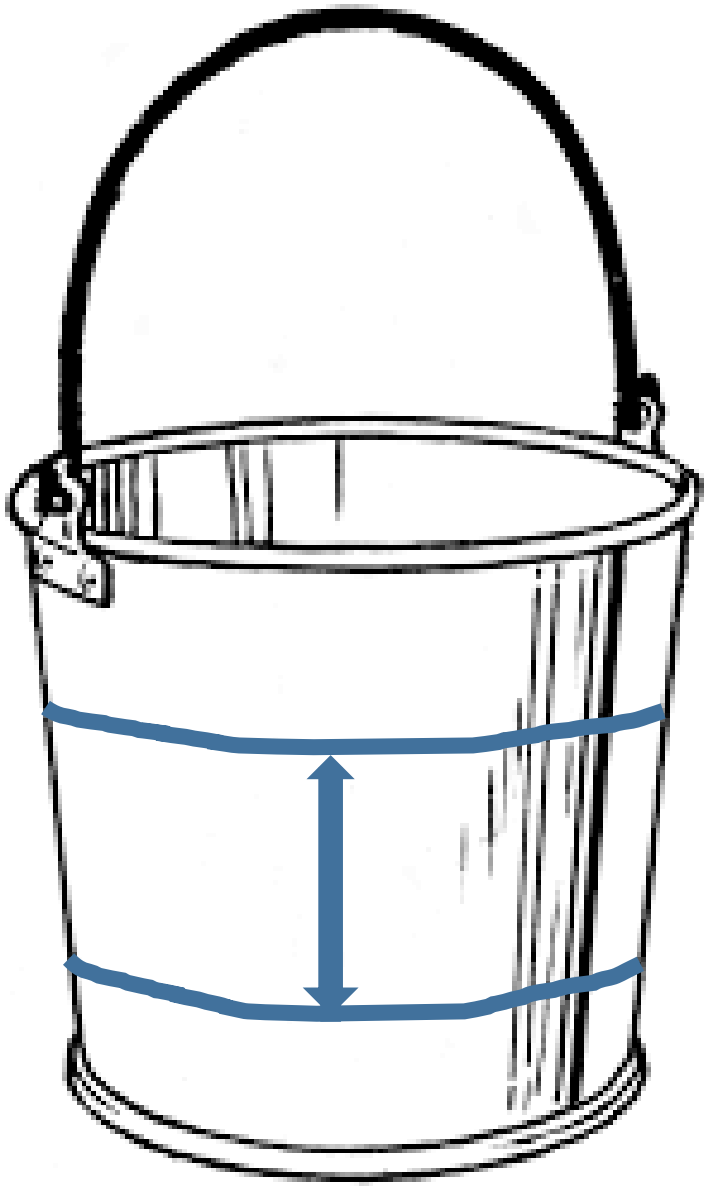
MCAD is NOT Contagious! (Not all spots are measles!)

But donating blood and organs is not advised, in case you share some bad mast cells (TMS)

It strongly resembles and *may come with* **Histamine Intolerance (HIT):**

HIT involves poor processing and degrading of histamine, lending to an excess of histamine and resulting symptoms (all shown before)

HIT usually responds to Diamine Oxidase (DAO) or similar products (including Lacotbacillus Rhamnosus possibly)



Keep your histamine bucket low!

But not too low!

You need a little histamine to survive!

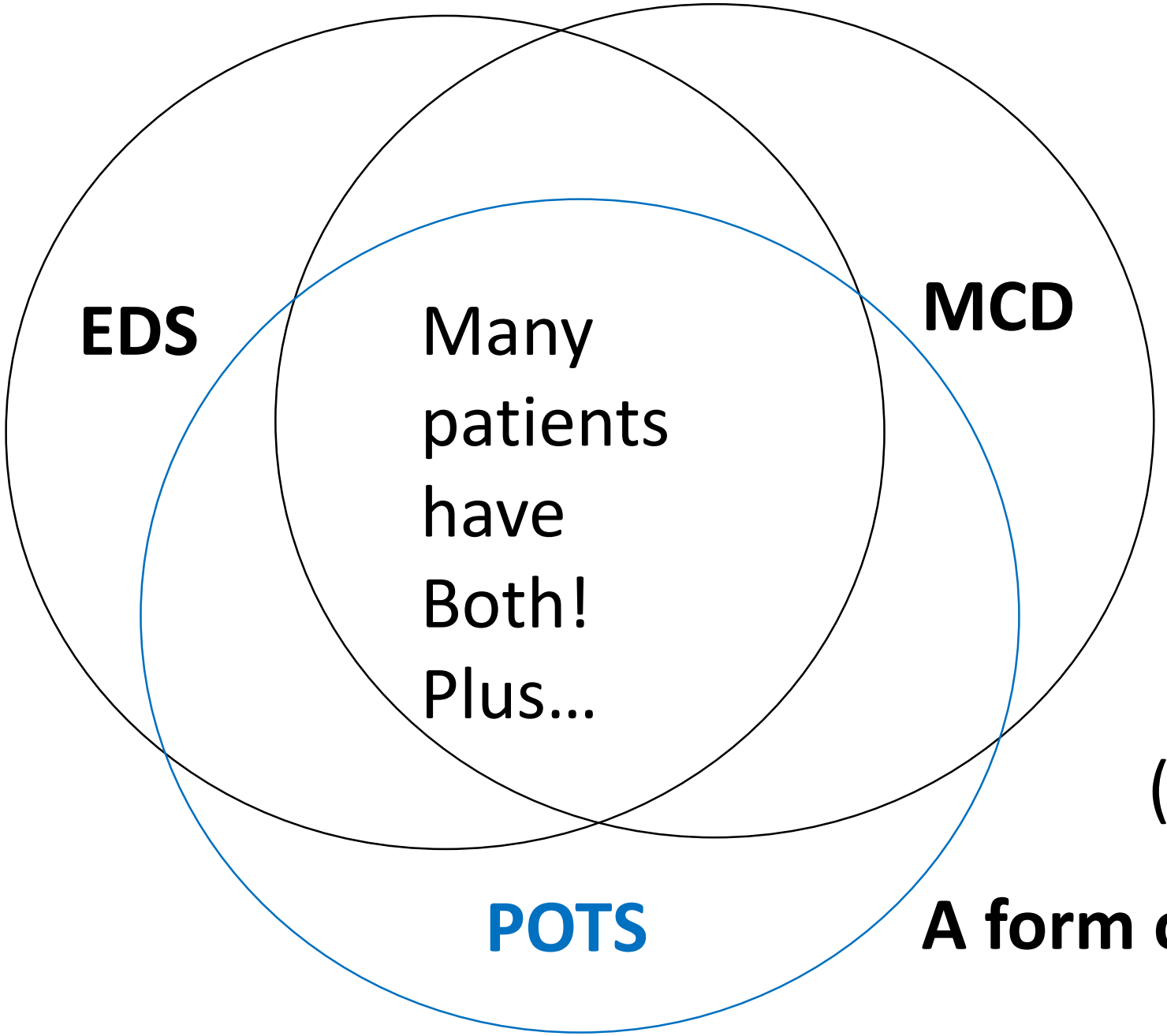
Now for a hard left turn…

Not to be confused with… (often comorbid)

Ehlers-Danlos Syndrome symptoms!

EDS = collection of genetic collagen defects causing a *systemic* connective tissue disorder lending to:

Chondromalacia (loss of cartilage), **fibromyalgia**, PAIN!
Bursitis, Tendonitis, Trigger finger, tennis elbow, claw toe
Prolapses, herniations, sprains, strains and tears
Varicose and spider veins, easy bruising, bulging veins
Fallen arches, bad teeth, TMJ, subluxations & dislocations
& *much much more!!* RARELY DIAGNOSED



And…

Autism Spectrum Disorders and/or:

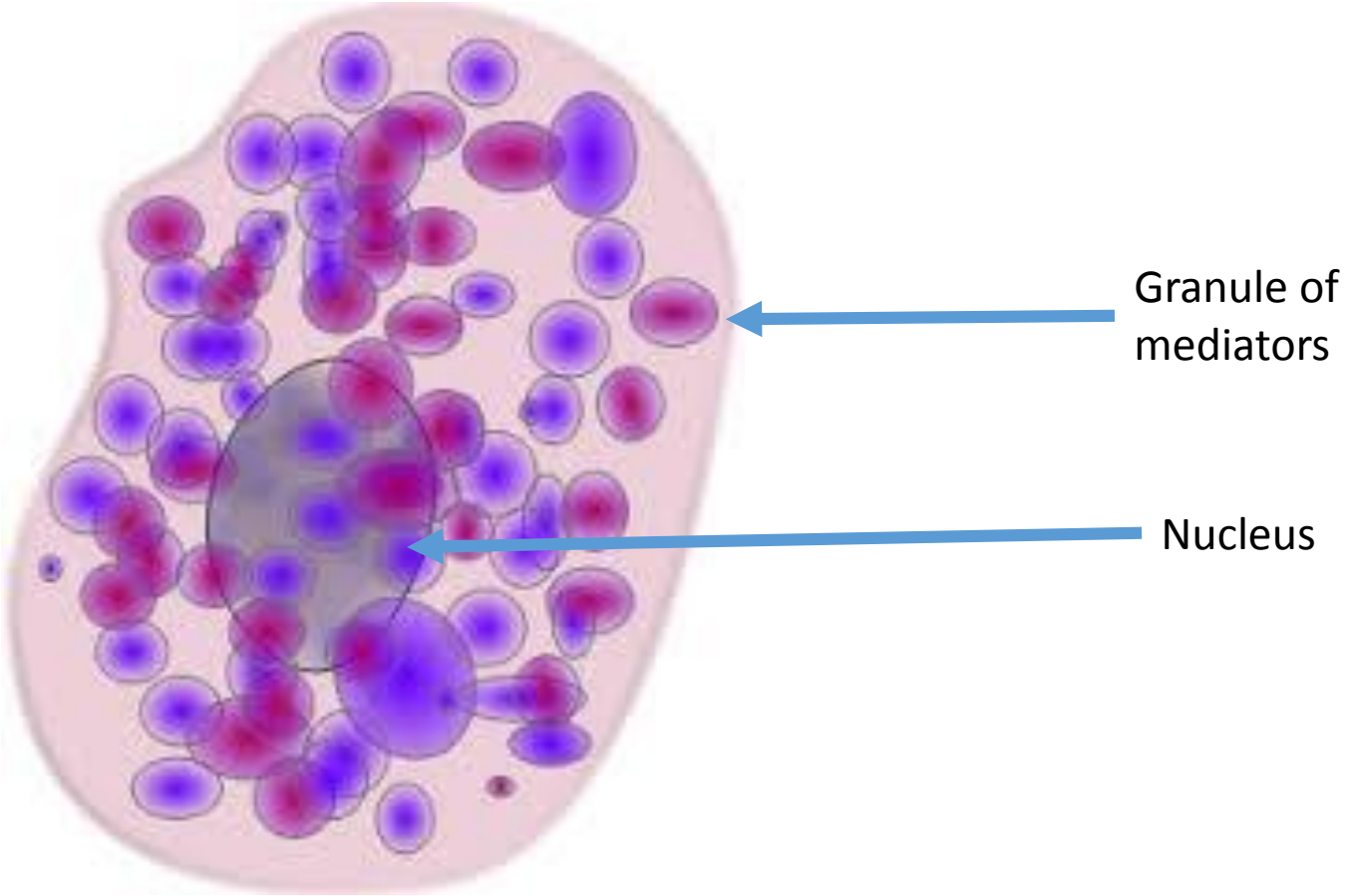
ADD/ADHD
OCD
SPD
NPD
Depression
Anxiety

(But not all!)

A form of Dysautonomia

What are Mast Cells?

- **Born in Bone Marrow**
- **Travel out of the blood throughout the body**
- **Line all external facing tissues (skin, lungs, GI)**



White blood cells forming part of our Primary Immune defenses at sites of wounds or infection

A *Few* of Our *Many* Mediators!

STORED (in the granules)	DE NOVO (produced upon triggering)
Histamine	IL-1a
Tryptase	IL-1b
Prostaglandin D2	IL-2
Cytokines	IL-3
Heparin	IL-4
Chymase	IL-33 increases activation further
Substance P (for PAIN)	B-FGF
Angiogenin	Interferon a
Corticotropin releasing hormone	Interferon b
Leptin	Leukotriene b4

Researchers report anywhere from >60 to as many as 200 may exist or form!

Some Categories of MC Activation

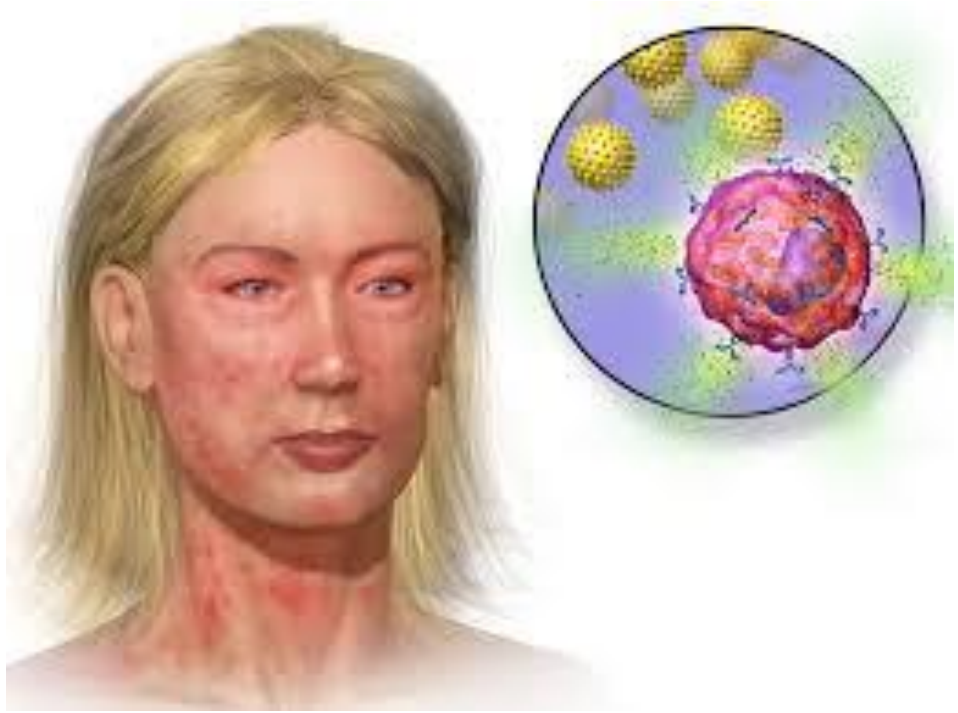
- **Allergies** – IgE mediated
- **Autoimmune** – mediated (IgG malfunction)
- **MCAD (all types)** - Multiple activators
  1. Mastocytosis = *too many mast cells*, active
  2. MCAS = normal number, but *over-active*

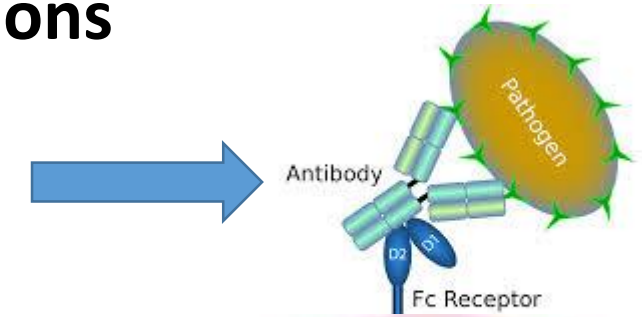
Yes, you could have any combo of the above!

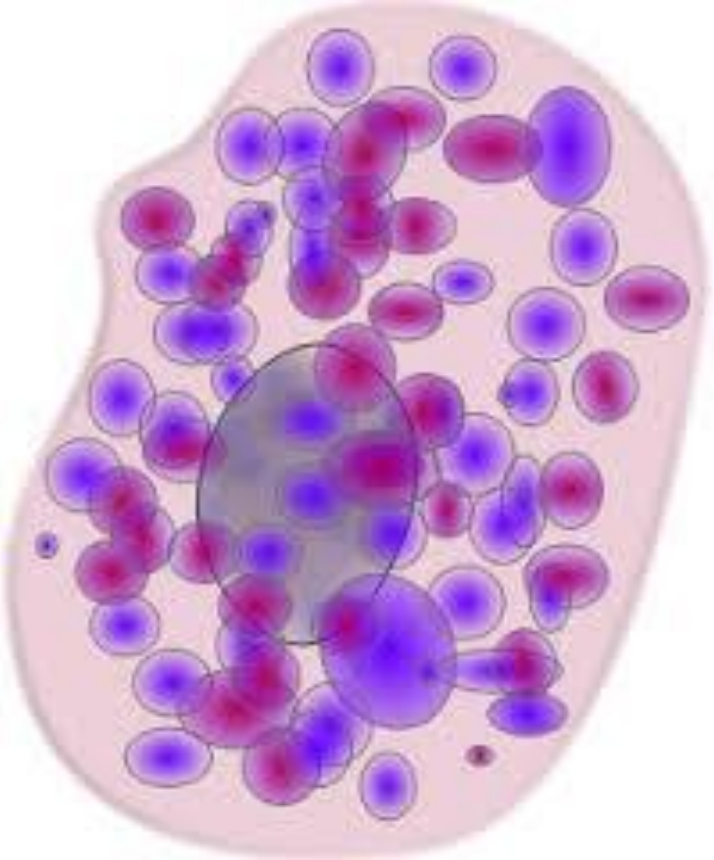
Allergies = IgE Mediated Reactions

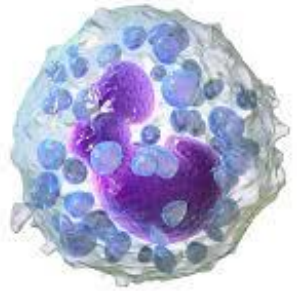
And *often* FULL ANAPHYLAXIS!

But not always!







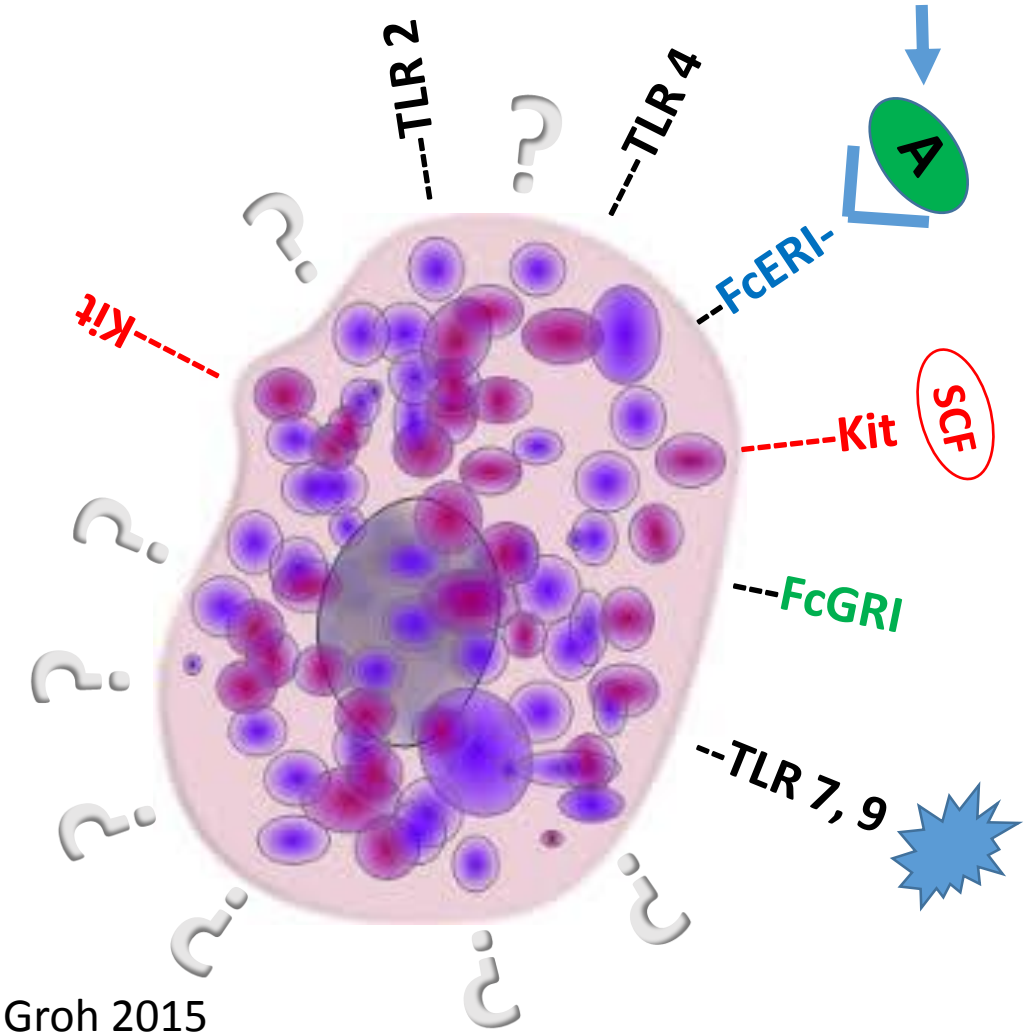


Basophil

Not to scale!!

Many MCAD Signaling Methods

***In addition* to any IgE Allergy signals**



Notably include *NON-Protein triggers*:

- Chemicals, scents
- Hormones
- *Heat, cold*
- *Exercise*
- *Stress*
- *Vibration*
- *Sunlight*

And on FIRST EXPOSURE!!

Types of MCAD (summarized)

All forms of Mastocytosis involve increased numbers of mast cells which are *usually* also over-active

>> Cutaneous forms – UP, TMEP, DCM, solitary mastocytoma, can develop into SM in some

> >Systemic Mastocytosis forms– include:

ISM (Indolent Systemic Mastocytosis) – WHO criteria for SM+, MC burden low, maybe skin lesions, no C findings, no evidence of AHNMD

- **Bone Marrow positive** - ISM but with no skin lesions

-**Smoldering SM** – ISM, typically with skin lesions, 2 or more B findings, no C findings

SM- AHNMD (SM with associated clonal hematologic non mast cell lineage disease)

ASM (Aggressive Systemic Mastocytosis) includes one or more C findings

MCL (Mast Cell Leukemia) – Meets criteria for SM. BMB shows diffuse infiltration, usually compact, by atypical, immature MCs. BM aspirate smears show 20% or more MCs.

Typical MCL: MCs comprise 10% or more of peripheral blood white cells.

Aleukemic MCL: <10% of peripheral white blood cells are MCs, usually without skin lesions.

MMAS

>>MMAS – Monoclonal Mast Cell Activation – patients meet *some* WHO SM criteria, but not all

When patients suffer like they have Mastocytosis, but are negative for any signs, you diagnose:

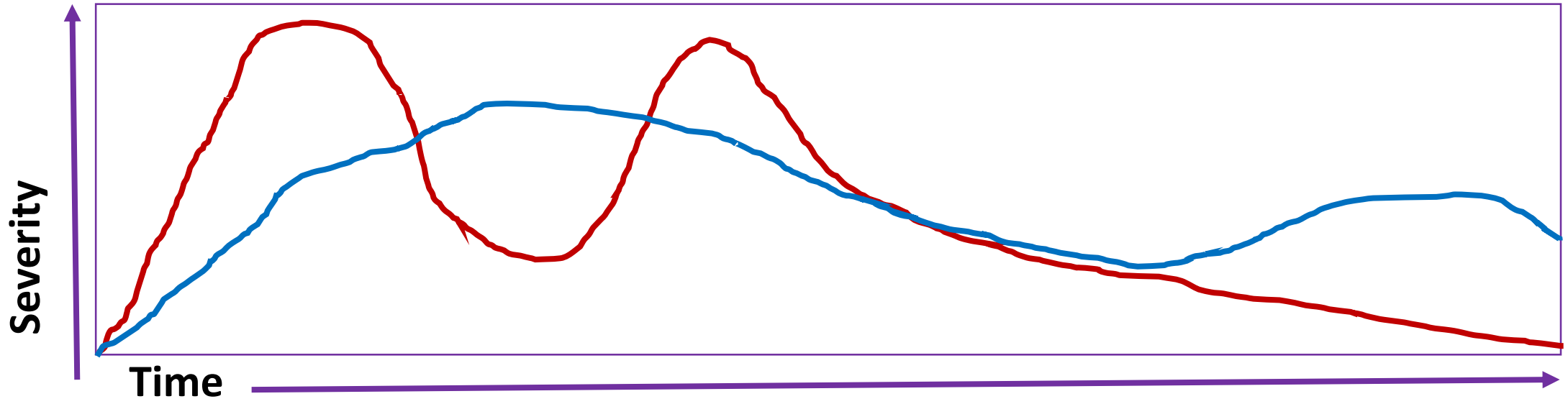
MCAS

>> MCAS (Mast Cell Activation Syndrome)– C-kit negative, no clusters evident/found, low tryptase, some mediators may elevate but not always, *but overlapping MC activation symptomatology present*.

Leakers vs Shockers

- **Shockers experience full instant degranulation leading to Stage V Anaphylaxis in minutes, often with a 2nd "biphasic" reaction hours later**

- **Leakers experience milder, slower anaphylactoid events over *hours to days,* and BP may *spike* and later drop.**



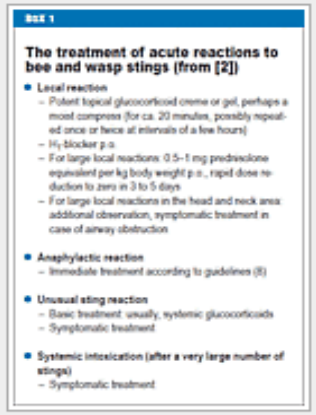
Anaphylaxis Comes in Grades

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/ sign(s) of one organ system present[i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/ sign(s) of more than one organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death
Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4. **Note:** children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.				

One example chart updated 4/5/2011

Insect Stings: Clinical Features and Management
Dtsch Arztebl Int 2012; 109(13): 238-48; DOI: 10.3238/arztebl.2012.0238

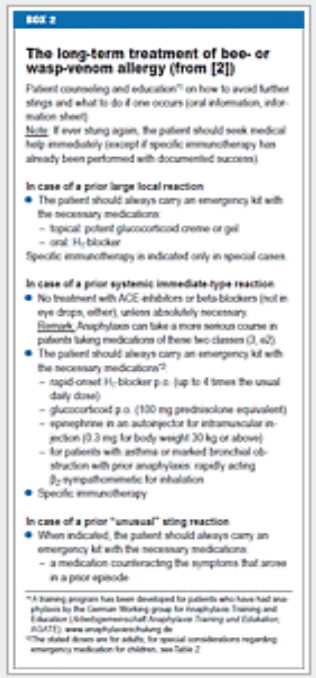
Box 1



The treatment of acute reactions to bee and wasp stings (from [2])

- **Local reaction**
  - Potent topical glucocorticoid creme or gel, perhaps a moist compress (for ca. 20 minutes, possibly repeated once or twice at intervals of a few hours)
  - H_1-blocker p.o.
  - For large local reactions: 0.5–1 mg prednisolone equivalent per kg body weight p.o., rapid dose reduction to zero in 3 to 5 days
  - For large local reactions in the head and neck area: additional observation, symptomatic treatment in case of airway obstruction
- **Anaphylactic reaction**
  - Immediate treatment according to guidelines (8)
- **Unusual sting reaction**
  - Basic treatment: usually, systemic glucocorticoids
  - Symptomatic treatment
- **Systemic intoxication (after a very large number of stings)**
  - Symptomatic treatment

Box 2



The long-term treatment of bee- or wasp-venom allergy (from [2])

Patient counseling and education[*1] on how to avoid further stings and what to do if one occurs (oral information, information sheet)
Note: If ever stung again, the patient should seek medical help immediately (except if specific immunotherapy has already been performed with documented success).

In case of a prior large local reaction
- The patient should always carry an emergency kit with the necessary medications
  - topical: potent glucocorticoid creme or gel
  - oral: H_1-blocker

Specific immunotherapy is indicated only in special cases.

In case of a prior systemic immediate-type reaction
- No treatment with ACE-inhibitors or beta-blockers (not in eye drops, either), unless absolutely necessary.
  Remark: Anaphylaxis can take a more serious course in patients taking medications of these two classes (3, e2).
- The patient should always carry an emergency kit with the necessary medications[*2]:
  - rapid-onset H_1-blocker p.o. (up to 4 times the usual daily dose)
  - glucocorticoid p.o. (100 mg prednisolone equivalent)
  - epinephrine in an autoinjector for intramuscular injection (0.3 mg for body weight 30 kg or above)
  - for patients with asthma or marked bronchial obstruction with prior anaphylaxis: rapidly acting β_2-sympathomimetic for inhalation
- Specific immunotherapy

In case of a prior "unusual" sting reaction
- When indicated, the patient should always carry an emergency kit with the necessary medications
  - a medication counteracting the symptoms that arose in a prior episode

[*1] A training program has been developed for patients who have had anaphylaxis by the German Working group for Anaphylaxis Training and Education (Arbeitsgemeinschaft Anaphylaxie Training und Edukation, AGATE): www.anaphylaxieschulung.de
[*2] The stated doses are for adults; for special considerations regarding emergency medication for children, see Table 2.

TABLE 1

Ring and Messmer grading scale for anaphylactic reactions (2)[*1]

Grade	Skin	Abdomen	Respiratory tract	Cardiovascular system
I	Itch Flushing Urticaria Angioedema	–	–	–
II	Itch Flushing Urticaria Angioedema	Nausea Cramps	Rhinorrhea Hoarseness Dyspnea	Tachycardia (rise ≥20/min) Hypotension (≥20 mm Hg drop in SBP) Arrhythmia
III	Itch Flushing Urticaria Angioedema	Vomiting Defecation	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Itch Flushing Urticaria Angioedema	Vomiting Defecation	Respiratory arrest	Circulatory arrest

[*1] Grading is always according to the worst manifestation present (no manifestation is obligatory); SBP, systolic blood pressure

We are the Canaries in the Coal Mine!

Table 2

Signs and symptoms of anaphylaxis [6,11].

Skin
- Urticaria (hives)
- Angioedema (swelling)
- Erythema (flushing)
- Pruritus (itching)

Respiratory:
- *Upper airway:*
  - Nasal congestion
  - Sneezing
  - Hoarseness
  - Cough
  - Oropharyngeal or laryngeal edema
- *Lower airway:* dyspnea
  - Bronchospasms
  - Wheezing
  - Chest tightness

Cardiovascular:
- Hypotension
- Dizziness
- Syncope
- Tachycardia

Gastrointestinal:
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea

Neurologic:
- Light-headedness
- Dizziness
- Confusion

Oral:
- Itching
- Tingling or swelling of the lips, tongue or palate

Other:
- Sense of impending doom
- Anxiety

Kim and Fischer *Allergy, Asthma & Clinical Immunology* 2011 **7**(Suppl 1):S6 doi:10.1186/1710-1492-7-S1-S6

Per the TMS:

Not all symptoms need to be present. Anaphylaxis is usually considered once 2 organ systems are involved, but some patients advance quickly after only skin involvement.

It can present as an acute cardiac or respiratory event, with hypotension as the only manifestion. (See TMS brochure).

Try to use preservative-free Epi when possible.

How to Diagnose MCAD ($64M Q)

There is NO single easy test for any form!

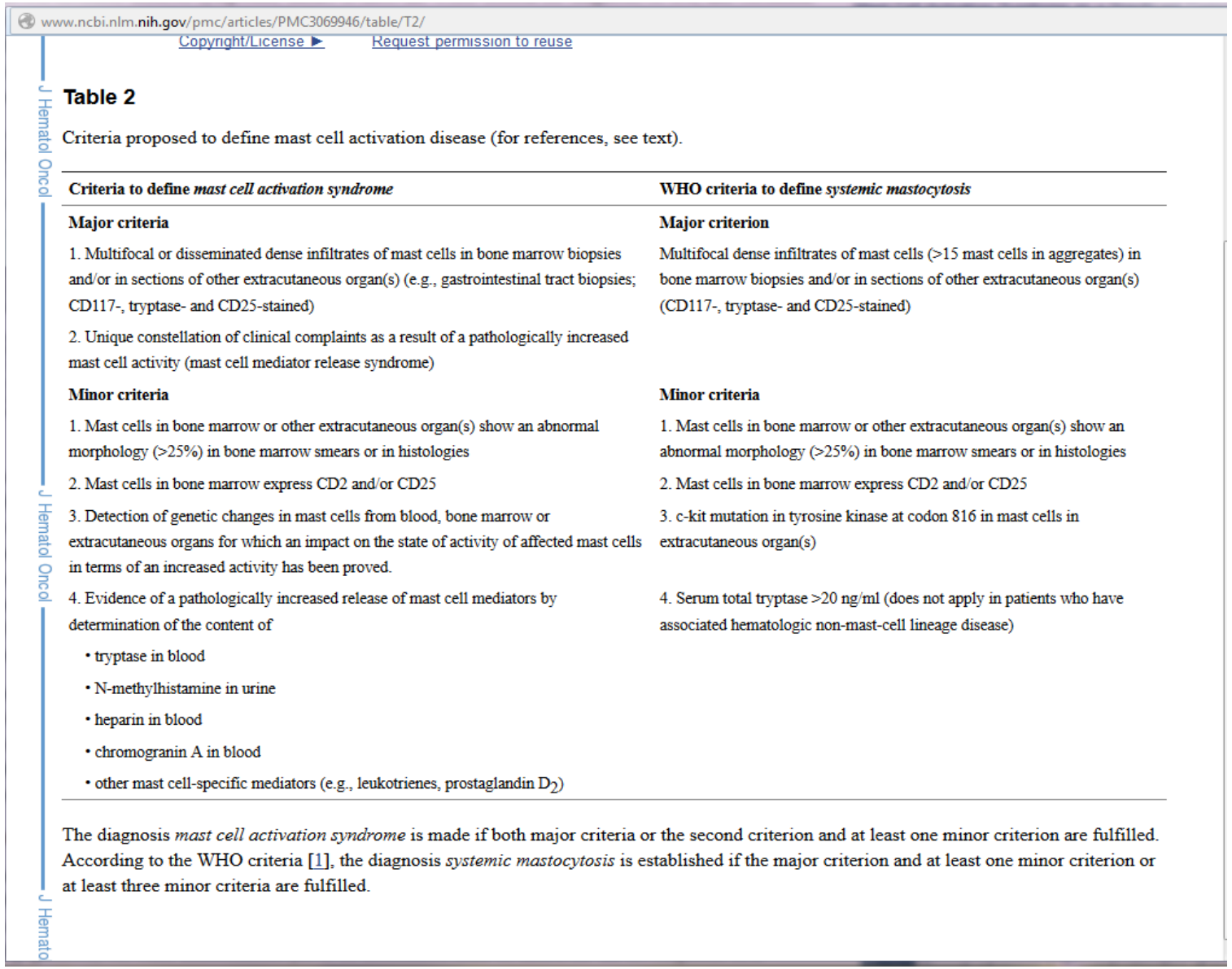
- **Rule out/treat any traditional IgG & IgE mediated allergies, carcinoid syndrome**
- **Suspect & rule out any forms of Mastocytosis before considering MCAS**
- **Easiest to suspect Cutaneous Masto if skin signs are present (e.g. UP, TMEP)**
- **Check following mediator levels at baseline and after reaction otherwise:**

Serum Tryptase level at baseline and during a flare if possible (look for 1.2 x baseline + 2 ng/ml inc)
24-hr Urine N-methylhistamine, PGD2 – *keep chilled, many dissolve in 2 minutes at room temp*

If suspect Systemic Masto, consider **C-Kit D816 mutation** test (negative result does not exclude all)
If suspect Systemic Masto, order BMB or other biopsies *if warranted* to search for MC clumps/shape
NB Cells must be stained PROPERLY to find Mast Cells, not normal histology

If all above are negative or unwarranted/unsuspected, but patient still symptomatic and responsive to H1/H2 protocol, consider presumptive diagnosis of MCAS, esp. if positive Urine Methylhistamine.

This is a VERY INCOMPLETE guide! Please consult http://tmsforacure.org for professional guidance!



www.ncbi.nlm.nih.gov/pmc/articles/PMC3069946/table/T2/

Table 2

Criteria proposed to define mast cell activation disease (for references, see text).

Criteria to define *mast cell activation syndrome*	**WHO criteria to define *systemic mastocytosis***
Major criteria	**Major criterion**
1. Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (e.g., gastrointestinal tract biopsies; CD117-, tryptase- and CD25-stained)	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (CD117-, tryptase- and CD25-stained)
2. Unique constellation of clinical complaints as a result of a pathologically increased mast cell activity (mast cell mediator release syndrome)	
Minor criteria	**Minor criteria**
1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies	1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies
2. Mast cells in bone marrow express CD2 and/or CD25	2. Mast cells in bone marrow express CD2 and/or CD25
3. Detection of genetic changes in mast cells from blood, bone marrow or extracutaneous organs for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved.	3. c-kit mutation in tyrosine kinase at codon 816 in mast cells in extracutaneous organ(s)
4. Evidence of a pathologically increased release of mast cell mediators by determination of the content of • tryptase in blood • N-methylhistamine in urine • heparin in blood • chromogranin A in blood • other mast cell-specific mediators (e.g., leukotrienes, prostaglandin D_2)	4. Serum total tryptase >20 ng/ml (does not apply in patients who have associated hematologic non-mast-cell lineage disease)

The diagnosis *mast cell activation syndrome* is made if both major criteria or the second criterion and at least one minor criterion are fulfilled. According to the WHO criteria [1], the diagnosis *systemic mastocytosis* is established if the major criterion and at least one minor criterion or at least three minor criteria are fulfilled.

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

2011 G Molderings, L Afrin et al

Journal of Hematologic Oncology

PMCID: PMC3069946

Table 2

Some Common MCAD Triggers

FOODS	NON FOODS
Tree nuts	Bees and iodine
Salicylates (tomatoes, peppers)	Anesthetics
Oxalates (green leafy veg, more)	Chemicals, fluoride & chlorine
Corn	Sunlight (not just heat)
Gluten	Heat
Left overs, esp. meat (freeze if can)	Cold
Pickles, vinegars (yeast or mold)	Stress
Dairy & cheese, esp. aged or moldy	Vibration
Alcohol	Pain

Treatment *Strategies**

Keep Histamine Bucket Low:

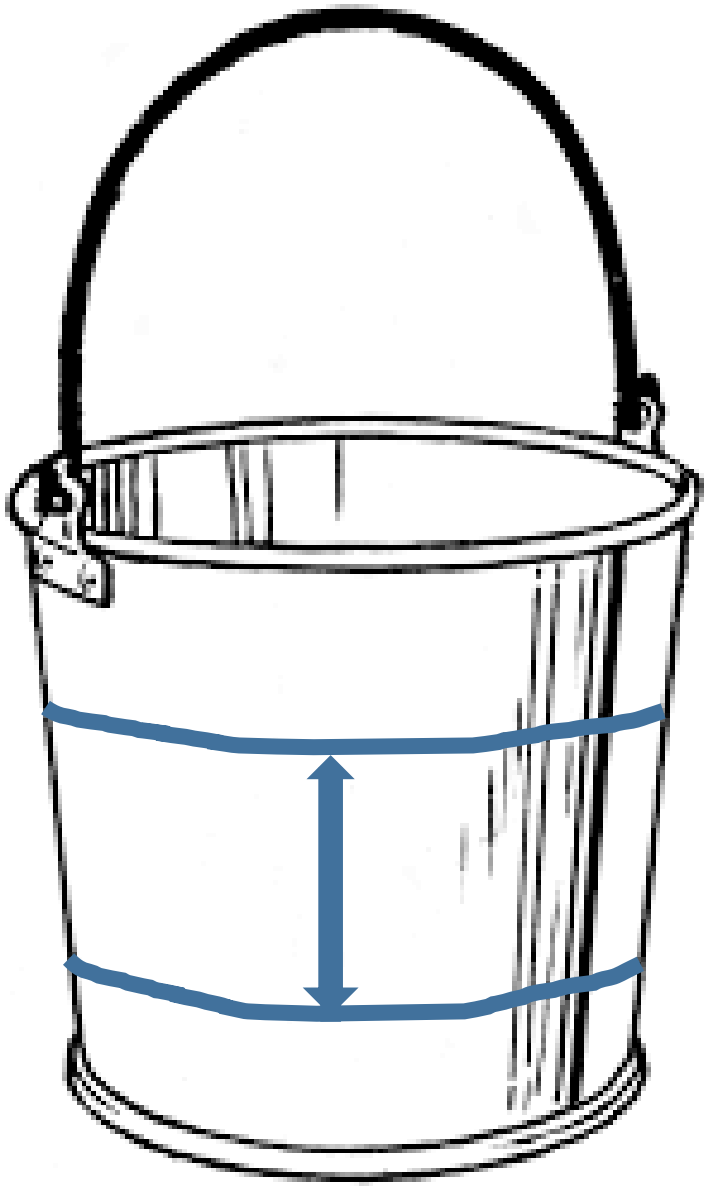
- **ID and Avoid Triggers *as able,* avoid orange/red dyes**
- **Eat nutritious low histamine *whole organic foods***
- **Detoxify your home (change cleaners, *elim mold*)**
- **Take H1/H2 Blockers (Antihistamines) Zyrtec/Zantac**
- **Try MC Stabilizers: Quercetin, Luteolin, Chromolyn Sodium, SM Patients treat proliferation as needed**
- **Rx Anti-histamines: Atarax (Hydroxyzine), Ketotifen**

**** in consultation with your doctor(s)!***

Treatment *Strategies* – cont.

Avoid and reduce stress:

- **Set good boundaries at school, work & home**
- **Try meditation, mindfulness or yoga practice**
- **Reiki, acupuncture, qi gong**
- **Exercise as tolerated, keep gently moving**
- **Good sleep hygiene (low histamine helps)**
- **Triage problems – pick top 3 to work on at any time**
- **Do something you love**
- **Think marathon, not sprint**



Keep your histamine bucket low!

Avoid:

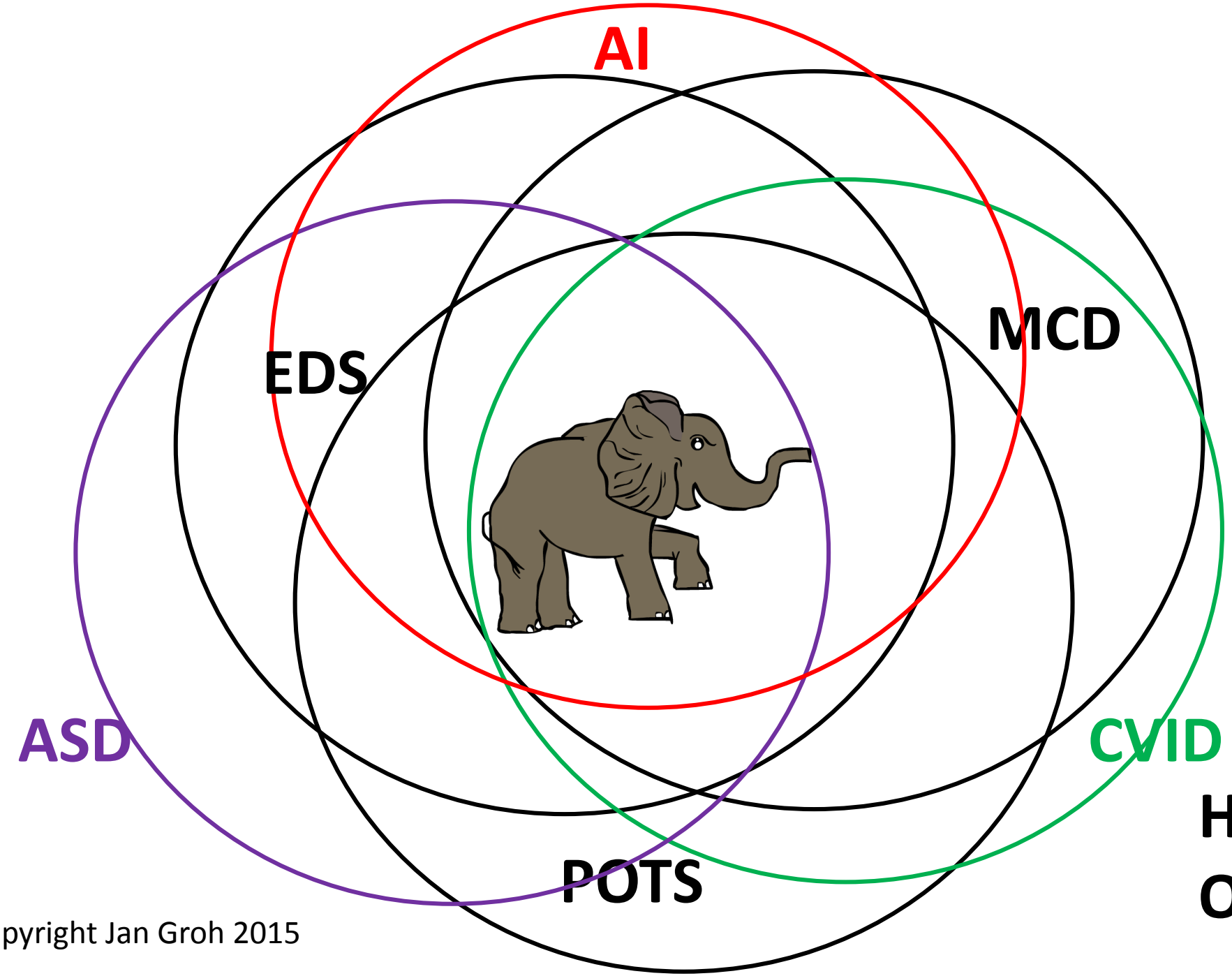
Allergens & known triggers
Stress
Temp extremes
Chemicals and scents
Leftovers
Meats and fish > 24 hrs old
Cheeses, molds, yeast, red & orange dyes

Consider trying (with your doctor's ok):

Anti-histamines (H1 & H2 blockers, Zyrtec/Zantac)
DAO – to reduce existing histamine (out process)
Quercetin, luteolin – known MC stabilizers
Chromolyn Sodium
Ketotifen (a special compounded anti-histamine)
Atarax (hydroxyzine) another Rx anti-histamine

Common MCAD Comorbidities

- Ehlers-Danlos Syndrome (CTD) & Fibromyalgia
- Dysautonomia (POTS) (HR, BP, temp, motility)
- Autism Spectrum Disorders (ADHD/OCD)
- Mixed mood disorders (depression and anxiety)
- CVID variations (primary immunodeficiencies)
- Leaky gut syndrome
- Autoimmune Disorders (all kinds and flavors, likely secondary from chronic inflammation from MCAD)



EDS
MCD
*POTS/Dys**
Autism Spec.
CVID
*Autoimmune**

**Results of?*

Hickam's Dictum
Occam's Razor

Resources

http://tmsforacure.org – The Mastocytosis Society
http://ohtwist.com – See my MCAD Resources page in menu
http://oreds.org – for local Oregon area Ehlers-Danlos Syndrome Support
http://prettyill.com – Dr. Diana Driscoll's website on EDS and MCAD
http://www.themurraywoodfoundation.org – Patricia Murray-Wood's foundation
http://www.mastattack.com – Lisa Klimas' blog (a smart patient)
http://www.iamast.com – another smart UK patient's website (Josie Evans)
http://www.mastcellmaster.com – Dr. Theoharides' site
http://www.mastcellaware.com – another informative site
http://www.Mastocytosis.ca – the Canadian Mastocytosis Society site

*Some Specialists for **Your Doctors** to Consult*

MCAD	EDS
Cem Akin MD	Claire Francomano MD
Mariana Castells MD	Brad Tinkle MD
Lawrence Afrin MD	Alan Pocinki MD
Anne Maitland MD (NY)	Heidi Collins MD (EDNF PAN)
Catherine Weiler MD	Dr. Henderson (Chiari) in MD
Theoharis Theoarides MD (research only)	Dr. Rodney Grahame (UK)
Philip B Miner Jr MD	Peter Byers MD (UW) VEDS

http://tmsforacure.org

http://ohtwist.com

http://ednf.org

http://oreds.org