

# Living with Mast Cell Activation Syndrome

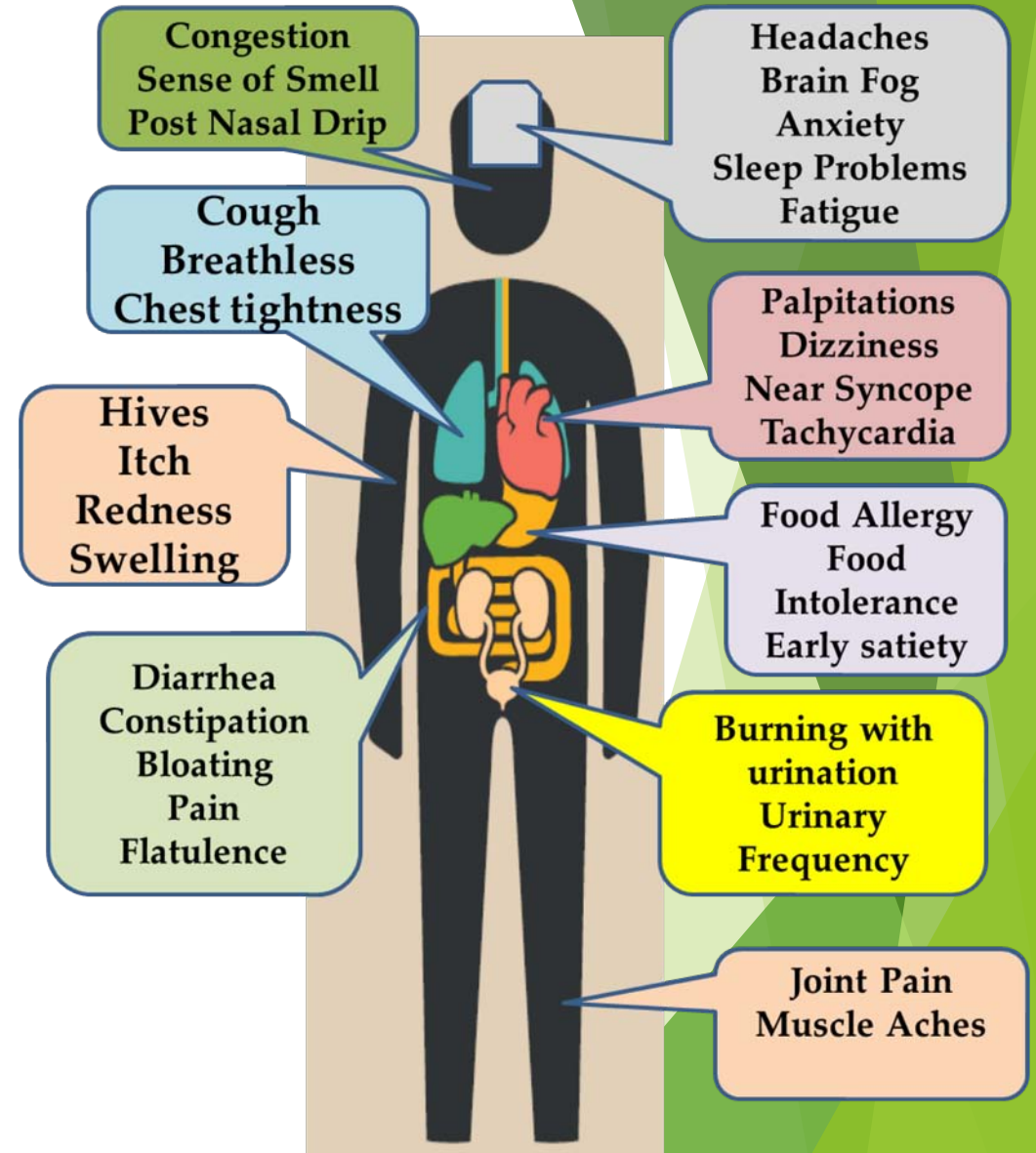
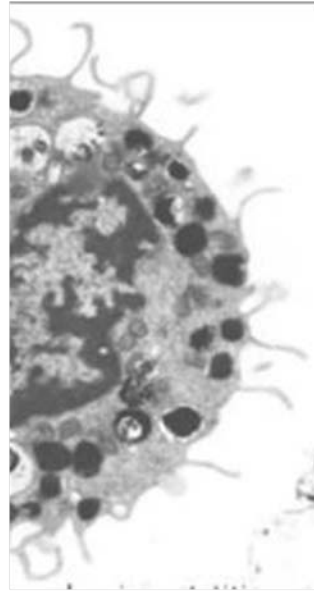
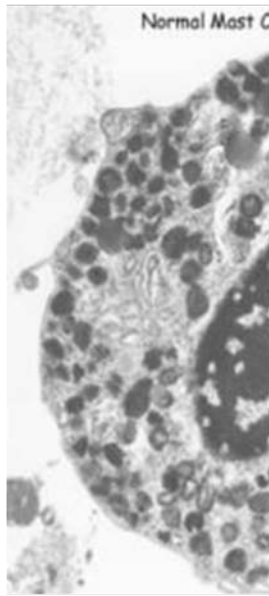
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Icahn School of  
Medicine at Mt Sinai,  
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# Got MCAS?



# Mast Cell mediated disorders are common

- ▶ 1 out of 2 of us are coping with some chronic immune mediated disorder.

- 'allergies' (rhinitis), sinus infections, hives (urticaria), food allergy/intolerance, skin swelling (angioedema), eczema (atopic dermatitis and contact dermatitis), asthma issues, and the prototype of immediate hypersensitivity syndromes, anaphylaxis



Rashes



Anaphylaxis Signs and Symptoms





# Why the rise in hypersensitivity disorders? Our genes in this environment!

The human race has come to dominate its environment so completely that any analysis of the increase or appearance of a disease has to take changes in our lifestyle into account. In the case of allergic disease [hypersensitivity disorders] changes in our environment, diet, water quality, and personal behavior over the last 150 years have played a dominant role in the specificity of these diseases, as well as in prevalence and severity...

it is clear that the consequences of hygiene, indoor entertainment, and changes in diet or physical activity have never been predicted.

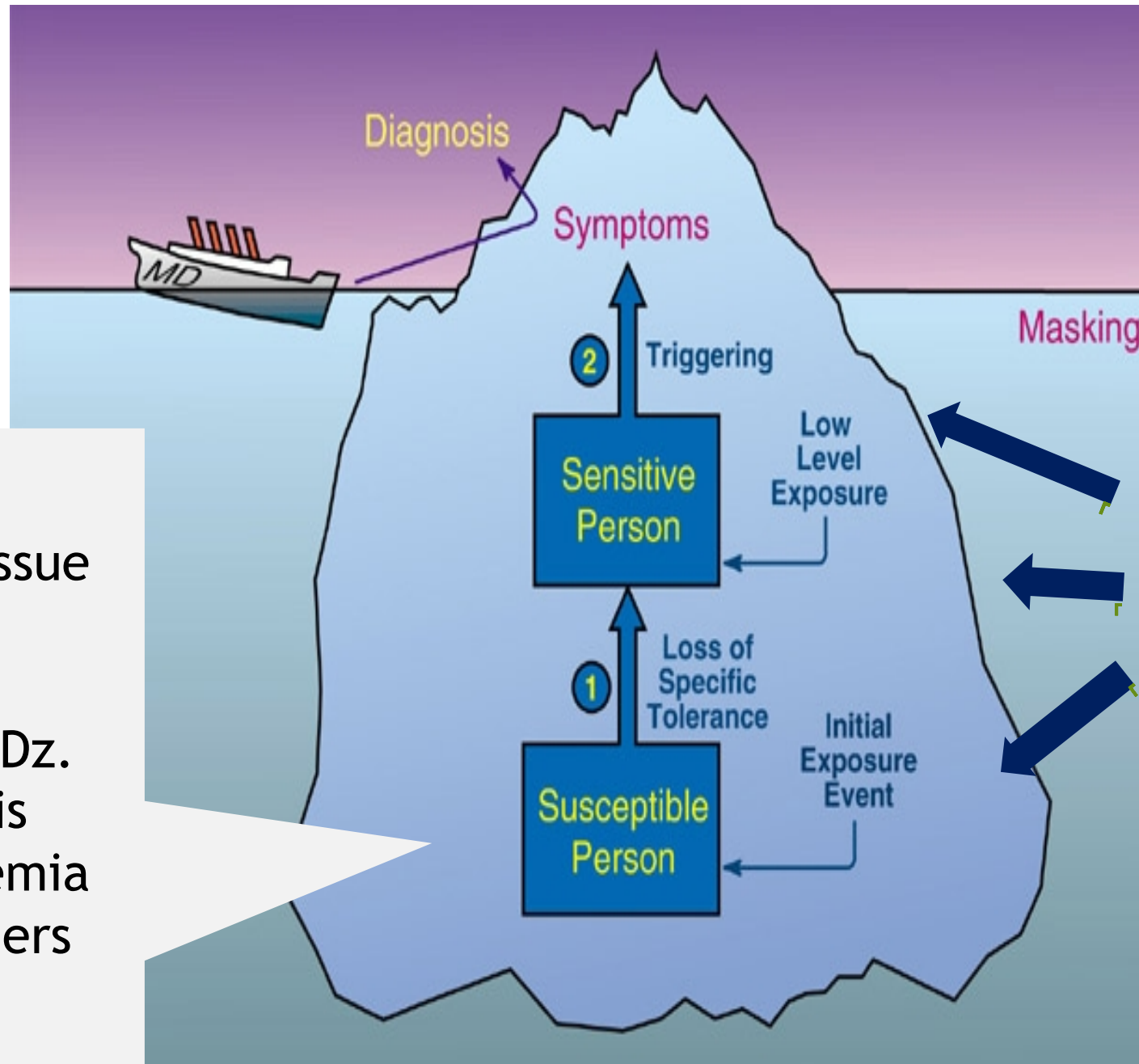


Thomas A. E. Platts-Mills, MD, PhD, FRS,

The allergy epidemics: 1870-2010; J Allergy Clin Immunol 2015;136:3-13.

# Why?

Connective Tissue Disorder  
PIDD  
Autoimmune Dz.  
Mastocytosis  
Hypertryptasemia  
Atopic Disorders



Trauma  
Stress  
Infection  
Chemical exposure  
-manufactured  
-mold, mycotoxins (naturally occurring)

## But most patients with MCAD suffer for years...

It is very common for one hypersensitivity condition to progress/morph into another, be provoked by more triggers. Consider the “allergic march”:

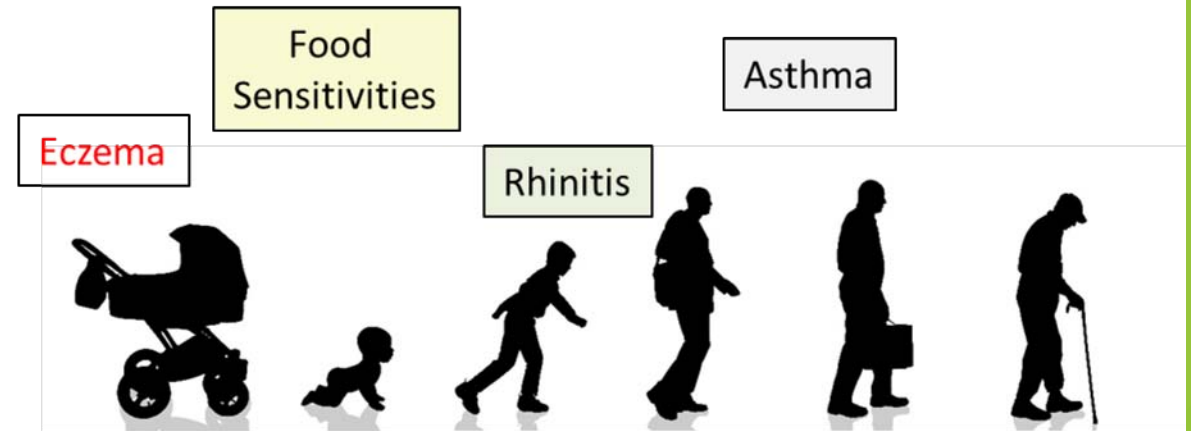
Yet most children and adults, with reactions to substances in foods and medications, in the air, or in lotions/creams applied to our skin, report not

- feeling better with available treatments, and
- suffering with other illnesses that travel with these chronic hypersensitivity disorders.



## Mast cell activation syndrome is easily treated, if it's recognized

Patients with mast cell activation syndrome (MCAS) frequently go for years without an accurate diagnosis... Harding, Reuters Health-New York, 2011



Urticaria/Angioedema: can occur at any age and can last for weeks or years for some

**Sleep Disorders:**  
**Tossing and turning all night due to hay fever?**  
- Daily mail, 2017

**Why Seasonal Allergies Cause 'Brain Fog' -- Here's What The Science Says**  
Forbes, 2018

**Sad in the spring? Allergy-mood link is real**  
cnn.com, 2011

**If you can't  
measure  
it,  
it doesn't  
exist.**

## Delayed diagnosis - PTSD in addition to MCAD

Fate of those having symptoms for years but deemed  
“Nothing the matter with them”,  
labeled as a “Malingering”, “Somatic”, “Conversion Disorder”

Medically speaking, they are not serious cases as  
regards prospective death, but they are often  
extremely serious as regards prospective life.

Their symptoms will rarely prove fatal, but their  
lives will be long and miserable, and they may end  
by nearly exhausting their families and friends.

The Care of the Patient,  
Francis Peabody, MD JAMA 1927



# Is this a Mast cell activation disorder (MCAD)?

My skin gets itchy and my asthma acts up every change of season.

Even if seafood is cooked in another room, Jamie gets a headache and her throat starts to close.

My sister breaks out in hives and feels faint if she jumps out of the pool.

With some foods, Katie becomes red in the face and has to run to the bathroom

During ragweed season, my son gets stuffy. He also cannot eat fresh melons and bananas,

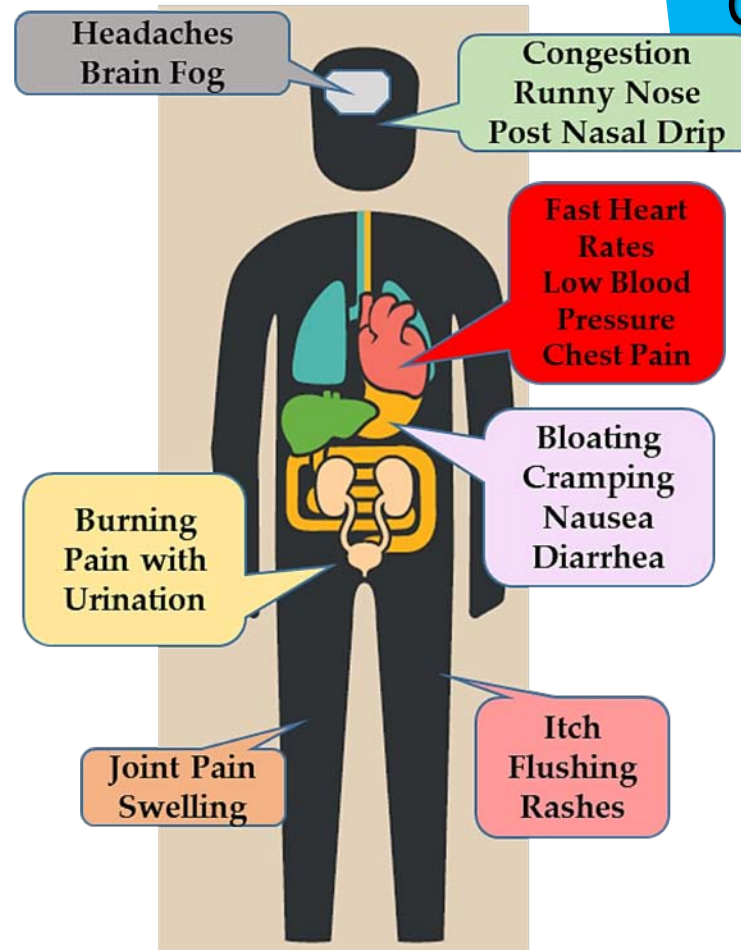
All my tests were normal but I get bloated, "gassy" and my joints hurt if I eat bread.

# MCAD? Possibly.

The diagnosis of Mast Cell Activation syndrome (MCAS) should be considered, when

- (1) symptoms are recurrent (keep coming and going);
- (2) laboratory tests detect an increase in mediators (chemical messengers) released by mast cells or find atypical, clustered mast cells in tissue biopsies from affected organs (skin, gut, bone marrow);
- (3) the signs of symptoms of these reactions get better with treatments that block mast cell activation or the action of chemicals that get released by activated mast cells.

Valent, 2013



Criteria #1

Criteria #2



Criteria #3





# Living with Mast Cell Activation Syndrome

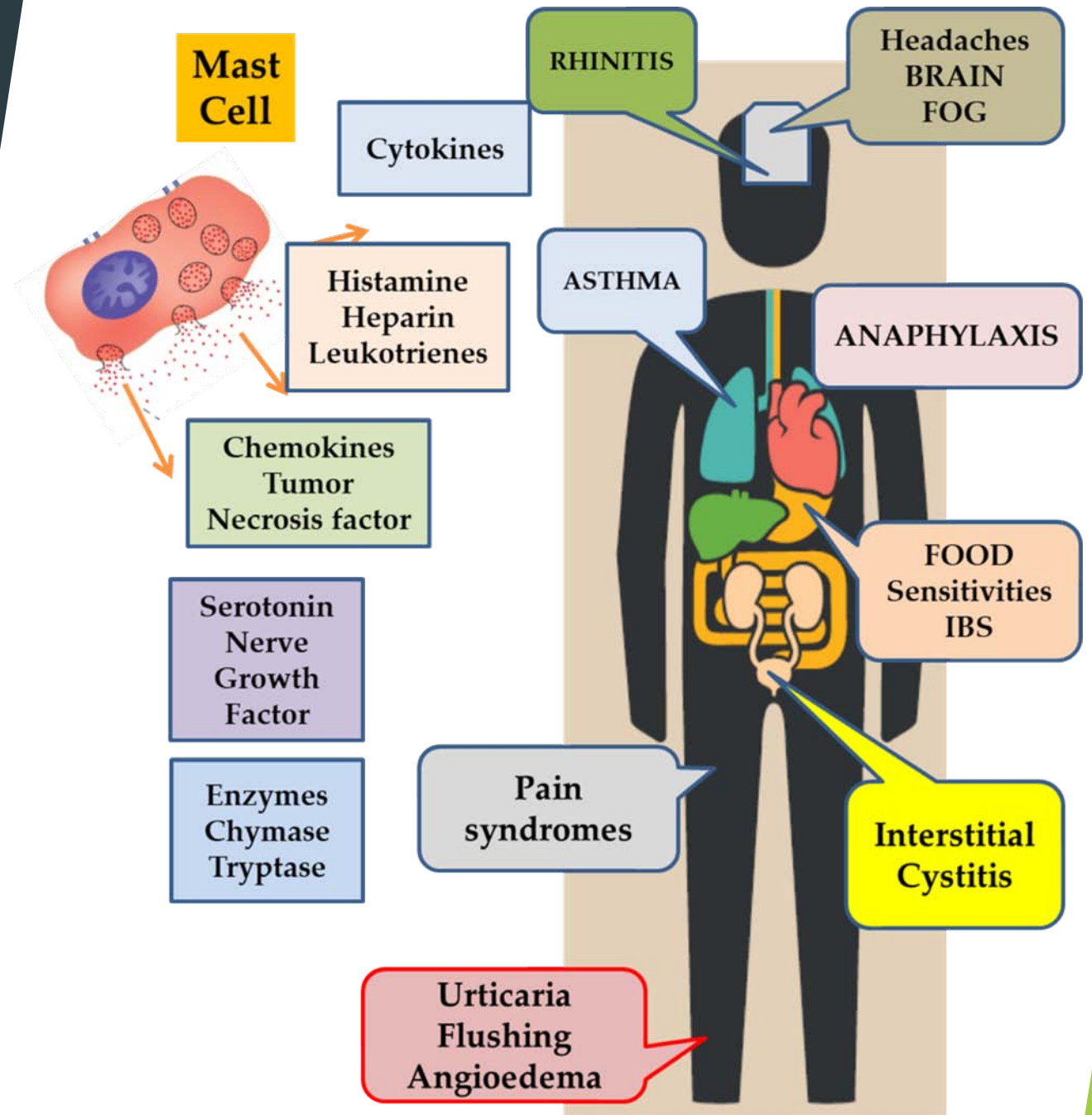
**TEAM WORK!**



# Got MCAS?

The human race has come to dominate its environment so completely that any analysis of the increase or appearance of a disease has to take changes in our lifestyle into account. In the case of allergic disease changes in our environment, diet, water quality, and personal behavior over the last 150 years have played a dominant role in the specificity of these diseases, as well as in prevalence and severity.

Platts Mills, J Allergy Clin Immunol, 2017



To help navigate a new path through the maze of specialists, testing and treatments, here is a guide to Mast Cell Activation Disorders.



- ✓ Coordinated Care between you, Your Primary Care Provider and Team of Medical Specialists

- ✓ New Set of Questions
- ✓ Suggested Tests
- ✓ Recommended treatment plans

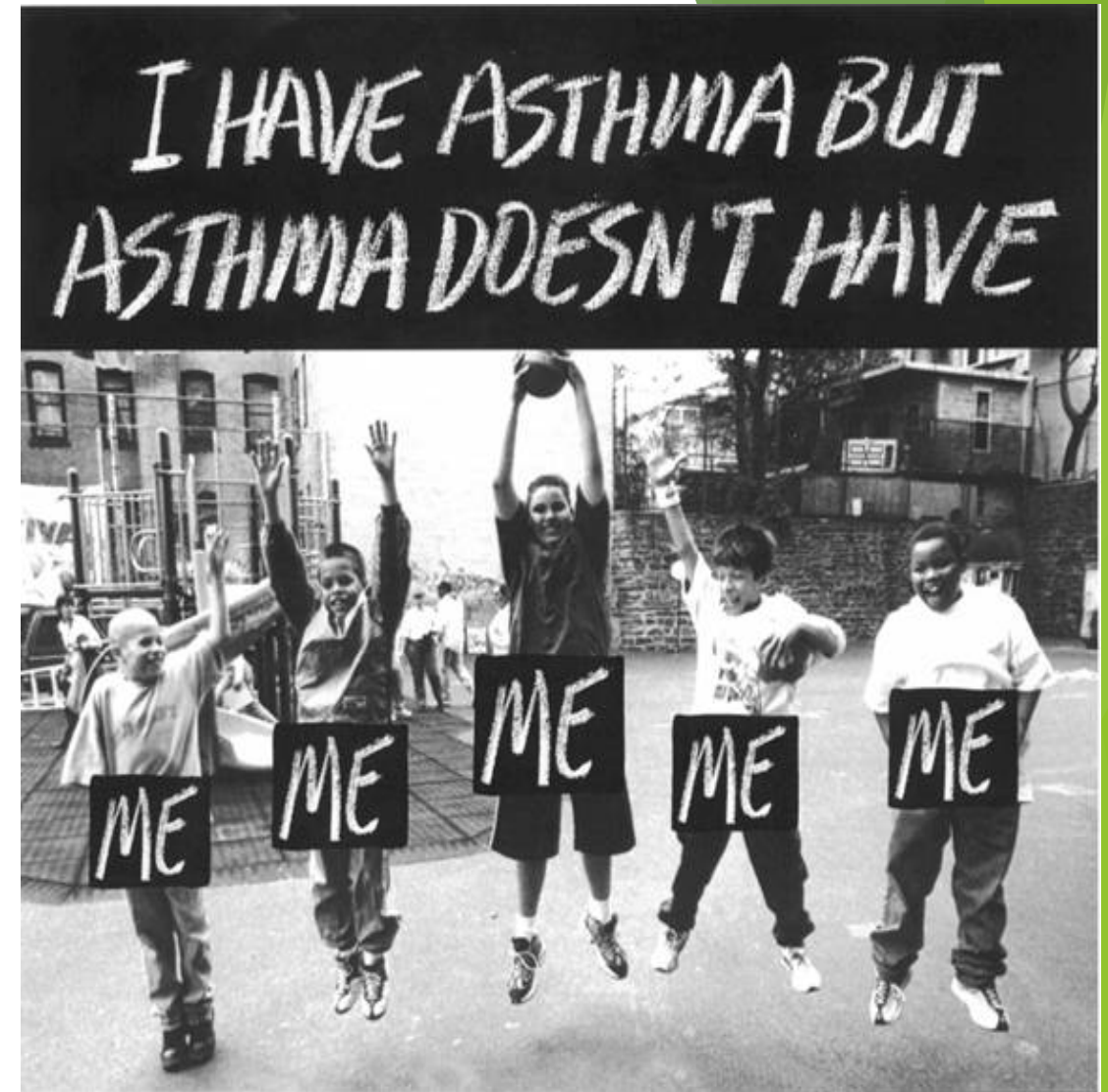


Find your way

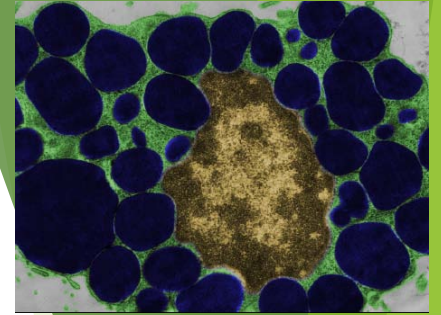


# To Feel and Live Better - S.T.E.P. Up to Your Next Check Up!

- ✓ Screen
  - ▶ Symptoms?
  - ▶ Risk Factors?
  - ▶ Previous treatments?
- ✓ Tests -
  - ▶ MCAD
  - ▶ MCAD co-morbid illnesses
- ✓ Educate yourself
  - ▶ Triggers
  - ▶ Recognition of MCAS symptoms
- ✓ Plan



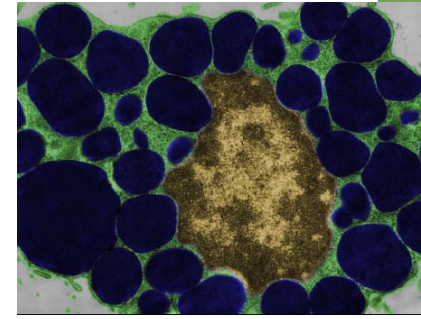
# Practitioner-Patient Partnership Guidelines -> Mast Cell Activation Syndrome (MCAS) Control



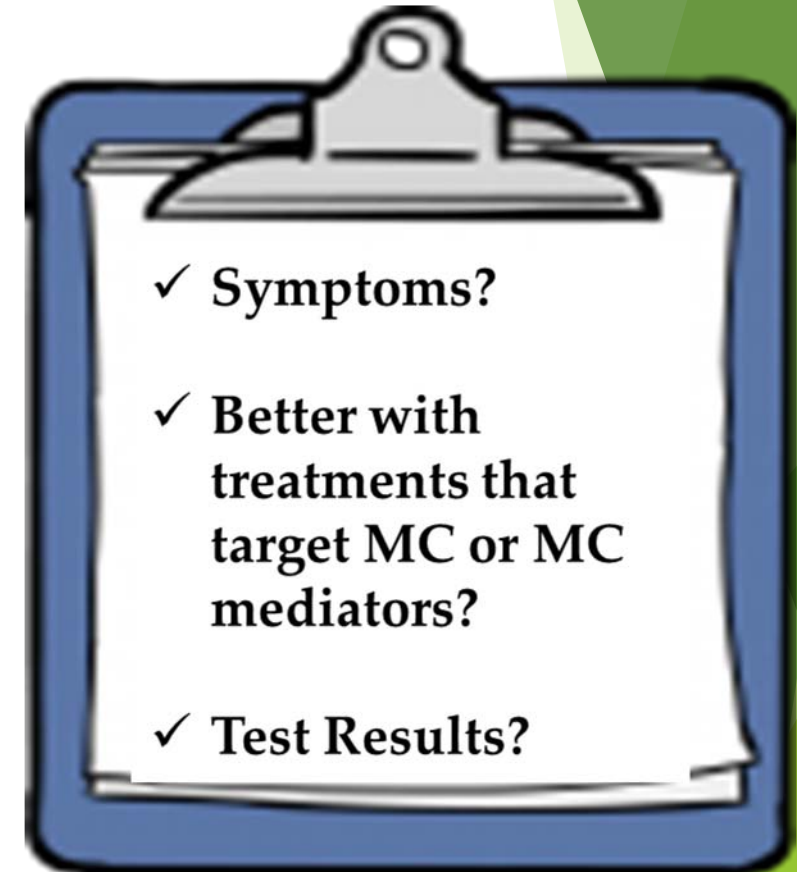
- ▶ Prevent chronic and disabling symptoms
- ▶ Maintain normal function
- ▶ Provide optimal pharmacotherapy
- ▶ Maintain Normal Activity Levels
- ▶ Prevent Recurrent Exacerbations and Minimize the need for Emergency Department visits & hospitalizations
- ▶ Meet patients' and families' expectations with asthma care

# Mast Cell Activation Disorders (including MCAS)

Valent, Allergy 2013



When symptoms are recurrent, are accompanied by an increase in mast cell-derived mediators in biological fluids, and are responsive to treatment with mast cell-stabilizing or mediator-targeting drugs, the diagnosis of mast cell activation syndrome (MCAS) is appropriate.



# Proposed Diagnostic Criteria: Mast Cell Activation Disorders

(1)

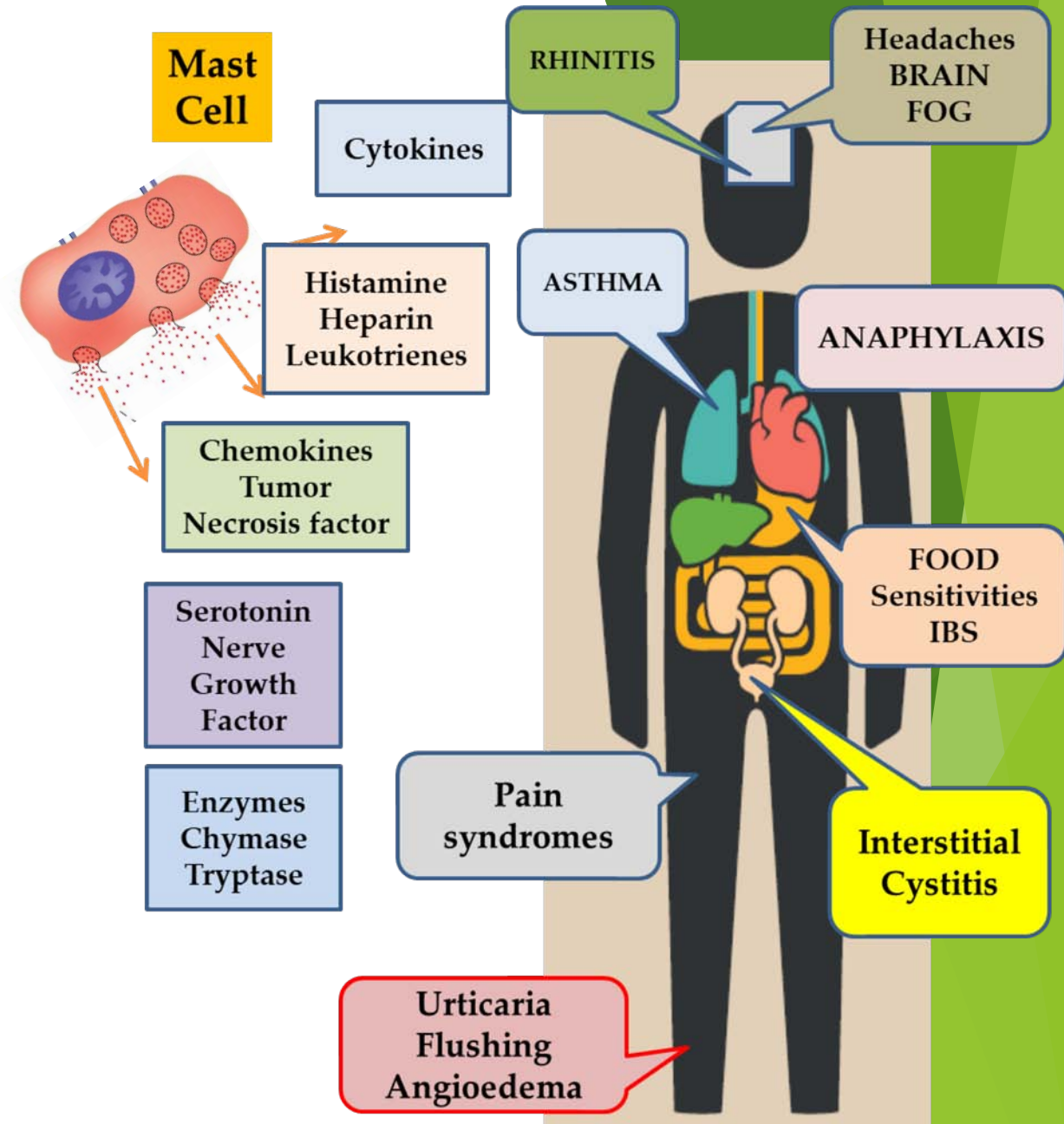
Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems

(2)

Response to therapy - decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers

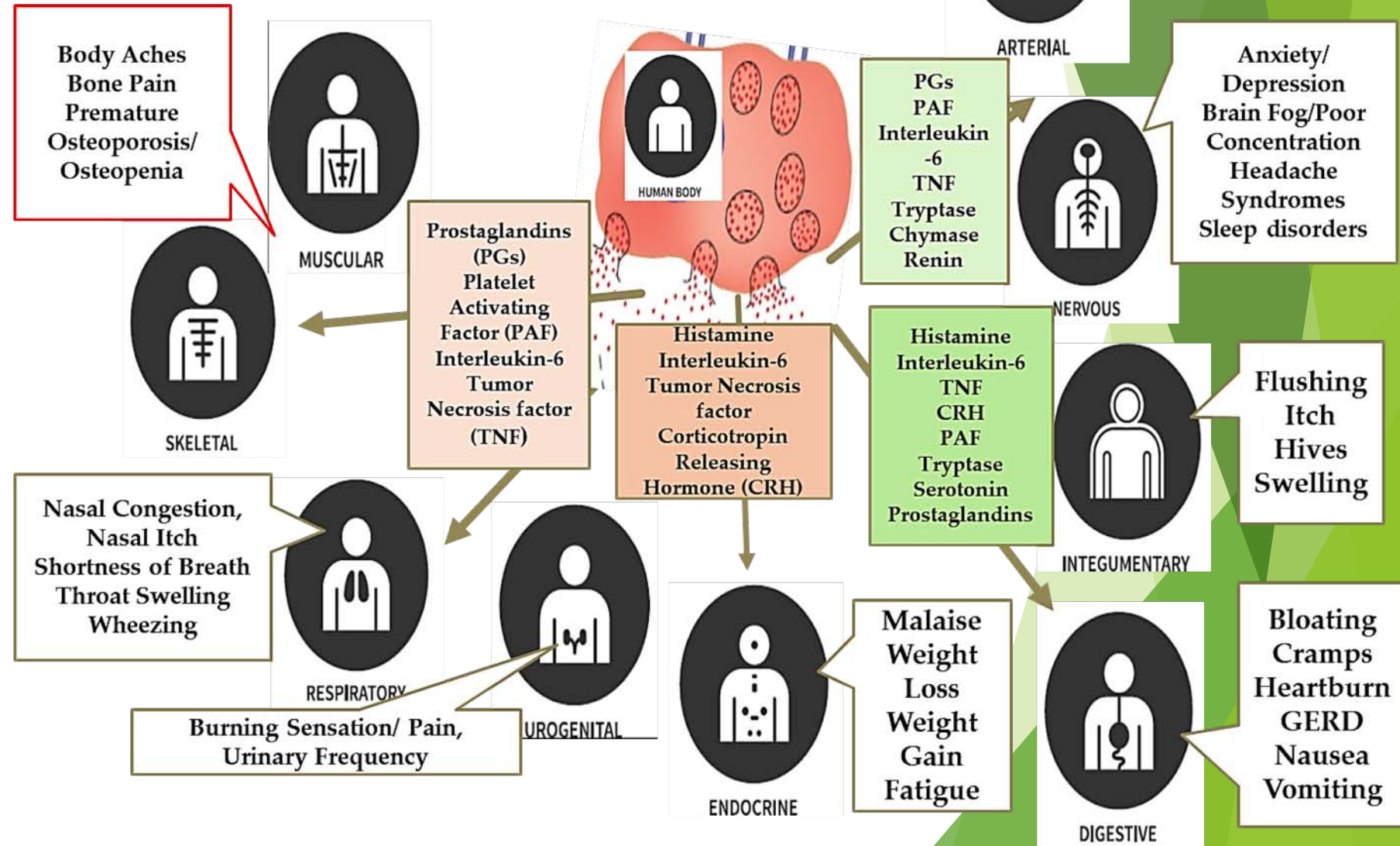
(3)

Evidence of an increase in validated urinary or serum markers of MC activation; increased burden of tissue mast cells (CD117) or chronically activated mast cells (CD117+ and CD25+/CD2+/CD30+)



Mast Cells are situated in every organ system and have various sensors to detect different “dangers.”

- ▶ The kind of trigger and the site of encounter will determine which chemical mediators are released, and consequently, the MCAD associated symptoms.



(2)  
Measuring  
Mast Cell  
Activation  
Markers,  
Inflammatory  
Mediators

**Immediate Release**

Granule contents:  
Histamine,  $\text{TNF-}\alpha$ ,  
Proteases, Heparin

Urine  
PGD<sub>2</sub>,  
11-beta PGF<sub>2</sub>

**Over Minutes**

Lipid mediators:  
Prostaglandins  
Leukotrienes

Serum Tryptase

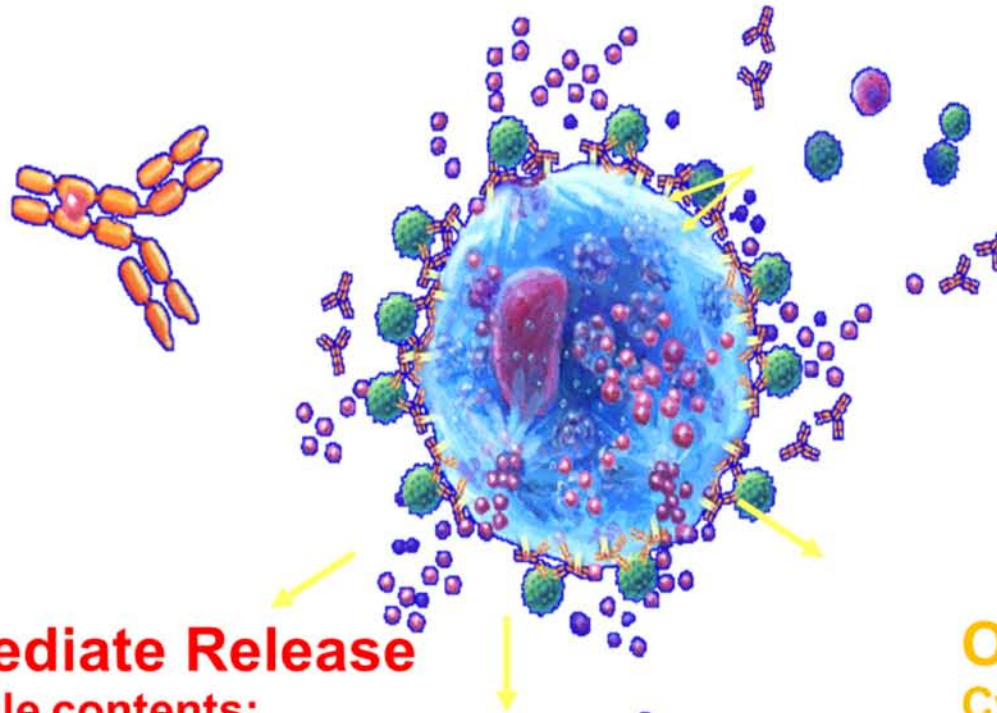
**Over Hours**

Cytokine  
production:  
IL-4, IL-6, IL-13

Serum, Urine  
Histamine

Pathology-  
spindle MC, MC  
aggregates

CD2,  
CD25  
Expression

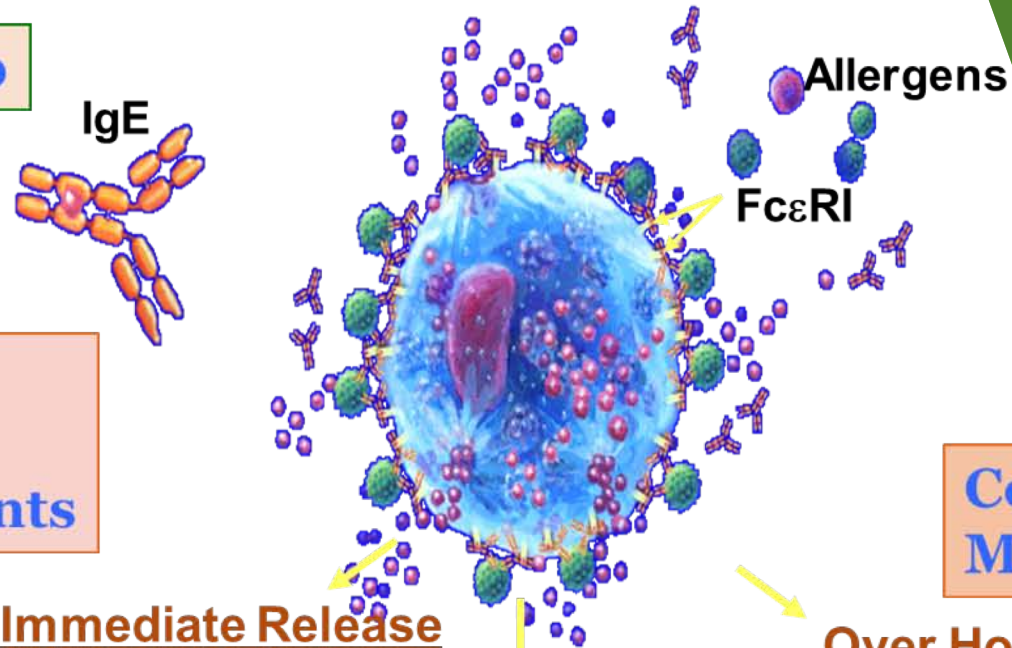


### (3) Response to Treatment:

Targeting  
MC/MC  
Inflammatory  
Mediators

Anti-IGE mAb

Histamine  
Blockade  
Tricyclic Agents



#### Immediate Release

Granule contents:

Histamine, TNF- $\alpha$ ,

Proteases, Heparin

Sneezing  
Nasal  
congestion  
Itchy, runny  
nose  
Watery eyes

#### Over Minutes

Lipid mediators:

Prostaglandins

Leukotrienes

Wheezing  
Bronchoconstriction

#### Over Hours

Cytokine production:

Specifically IL-4, IL-13

Mucus production  
Eosinophil recruitment

Traditional  
Chinese  
(TCM)  
Herbal  
Medicine  
Acupuncture

Corticosteroids  
MC stabilizers

Leukotriene  
Blockade

## **Airway Reactions (ENT/Lungs)**

Throat tightening, Throat Swelling  
Nasal congestion, Rhinorrhea  
Wheezing, Dyspnea, Chest Tightness

## **Brain**

Sense of uneasiness,  
Angst/Anxiety  
Headache, Dizziness  
Confusion, Tunnel Vision

## **Gastrointestinal tract**

Nausea, Cramping  
Abdominal Pain  
Vomiting, Diarrhea

## **Heart, Blood Pressure**

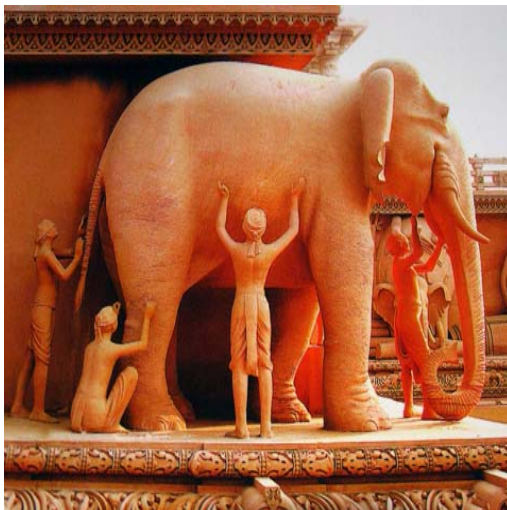
Fainting, Chest Pain  
Fast Heart Rate,  
Palpitations (pounding)  
Weak pulse, Dizziness

## **Genito- Urinary tract**

Uterine  
Cramping  
Swelling -labia

## **Pain: Joint, Muscle, Nerve**

**Skin** Hives (Urticaria), Itch  
Flushing, Swelling  
(Angioedema)

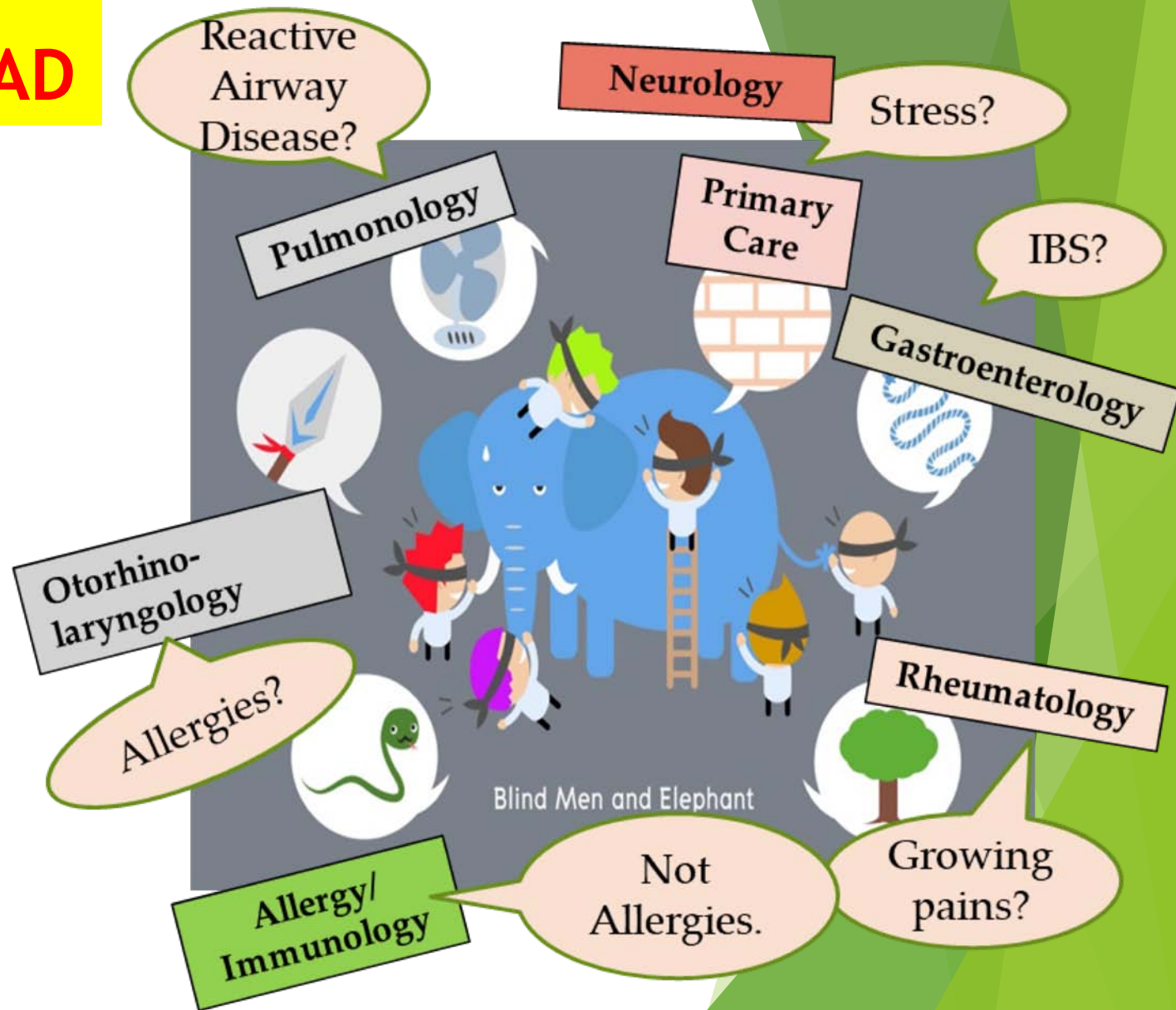


# Roadblock #1

## Delay in diagnosis of MCAD

(Mast Cell) disorders now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting only in confusion.

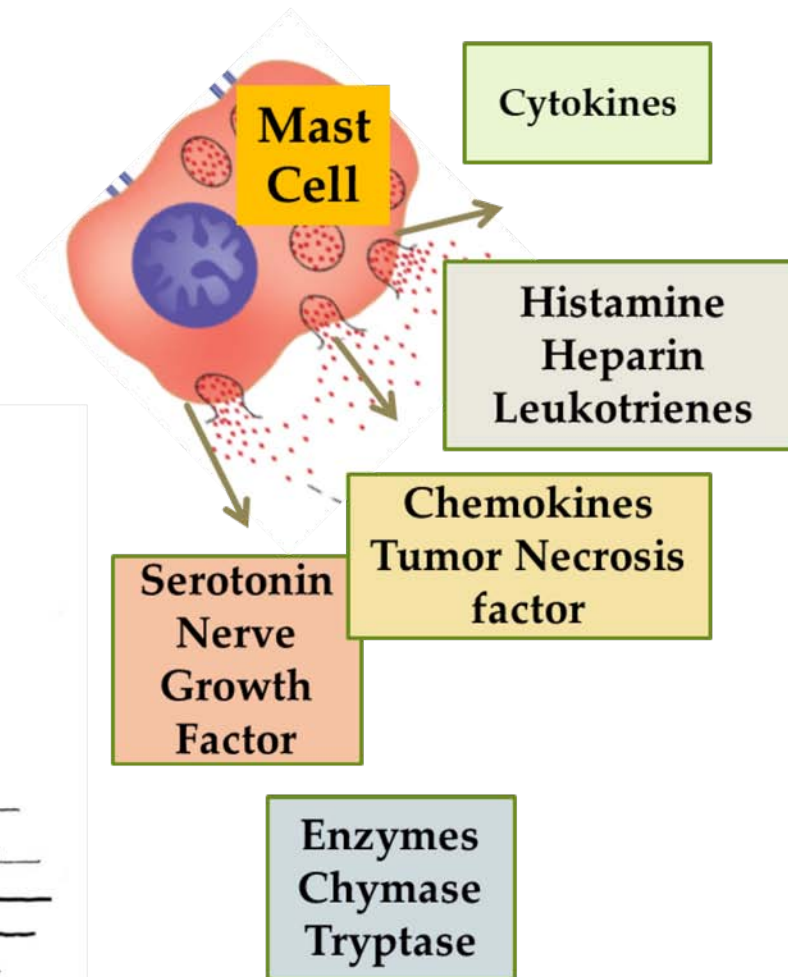
Allergy: the unmet need,  
Royal College of Physicians, 2006



## Roadblock #2

### Delay in diagnosis of MCAD

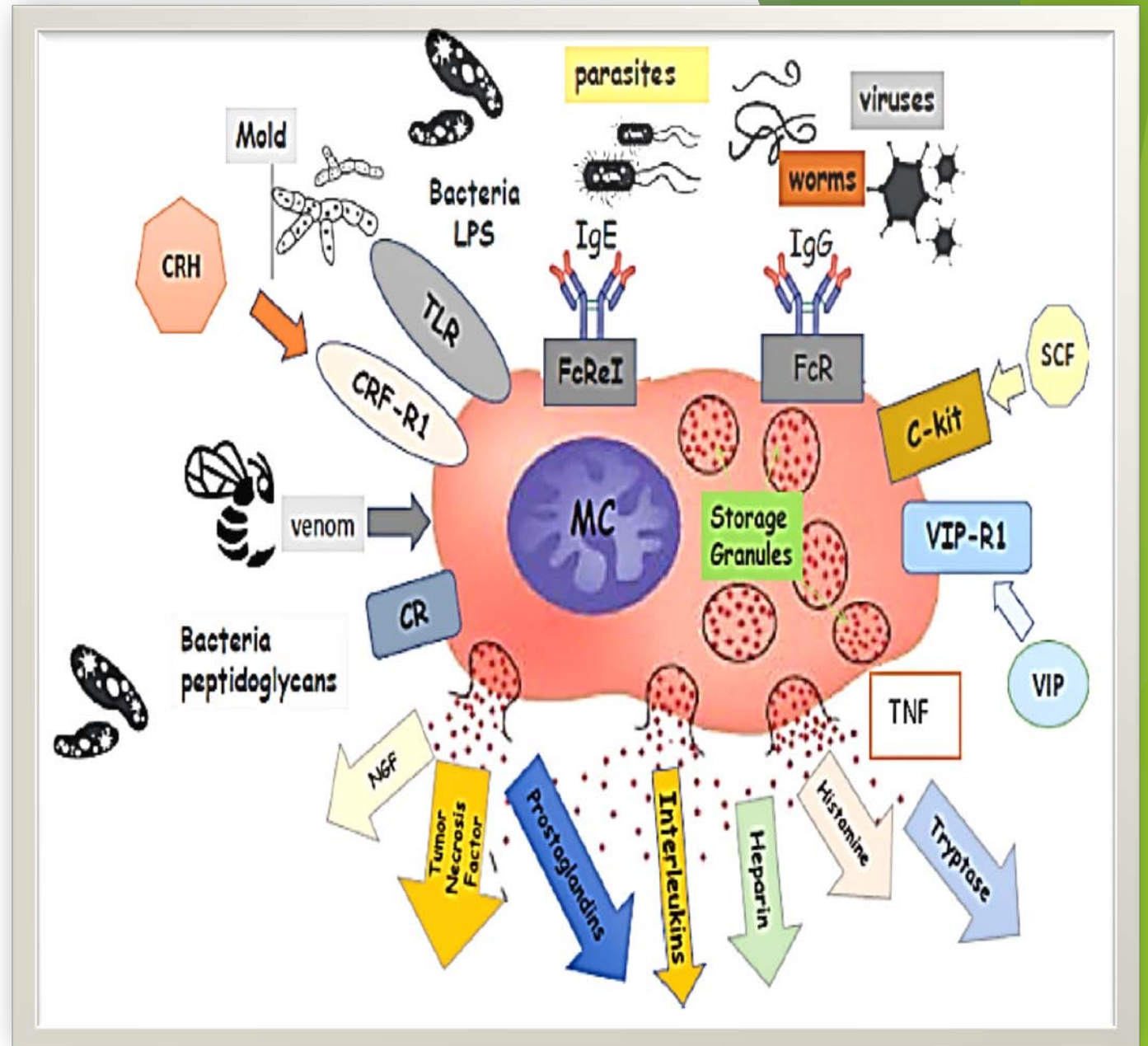
- ▶ Few commercial tests available to detect MCA
- ▶ Not all mediators are MC specific (only tryptase)
- ▶ Failure to inform pathologists to stain for mast cells (anti-CD117 or anti-tryptase Antibodies)
- ▶ Not enough data on number or morphology of mast cells = worrisome for MCAD?



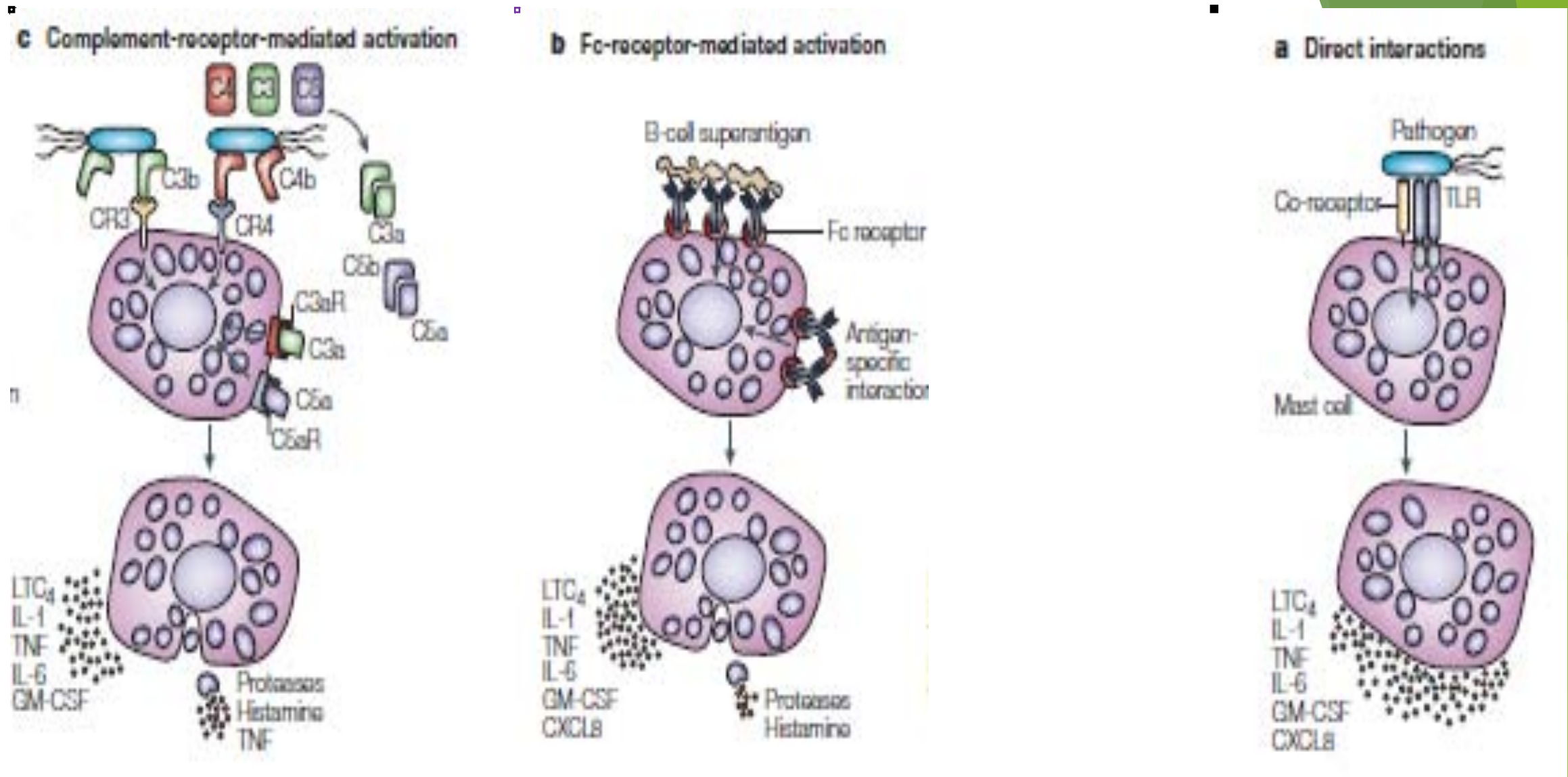
# Mast Cell Activation triggers?

- While the cause(s) of MCAS isn't clear...  
"we have some clues that it might be something to do with the signaling that goes on at the mast cell surface."

- Hamilton, Reuters - Brigham and Women's Hospital, Boston, 2011



# Not all Sensor triggered MC signaling is the same!



## MCAD/MCAS Treatment: Targeting MCs or MC derived Inflammatory Mediators

Corticosteroids  
MC stabilizers  
Cytokine Antagonists

Anti-IGE mAb

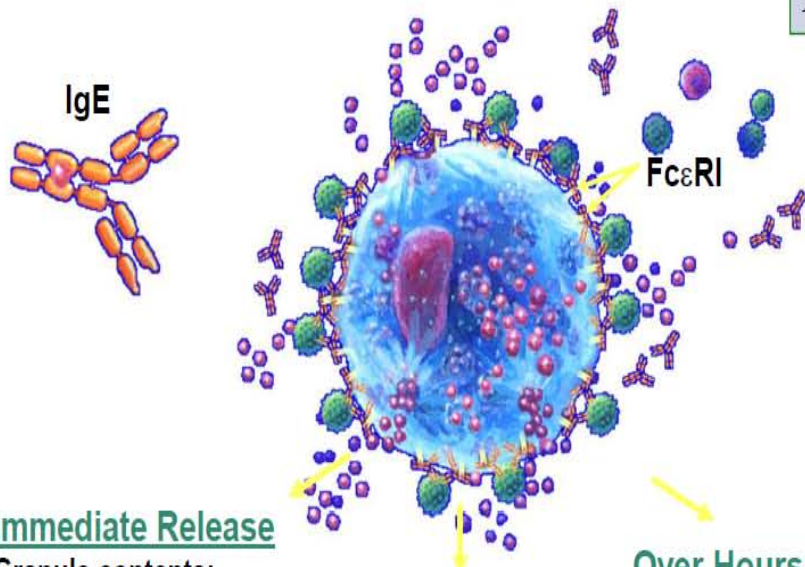
Histamine  
Blockade  
Tricyclic Agents

Leukotriene Blockade  
Cyclooxygenase Inhibitors

### Nutraceuticals

DAO supplement  
Vitamin C  
Quercetin  
Stinging Nettle  
Butterbur

Traditional  
Chinese (TCM)  
Herbal Medicine  
Acupuncture



### Immediate Release

Granule contents:  
Histamine,  $\text{TNF-}\alpha$ ,  
Proteases, Heparin

### Over Minutes

Lipid mediators:  
Prostaglandins  
Leukotrienes

### Over Hours

Cytokine production:  
Specifically IL-4, IL-13

## Roadblock #3:

**Delay in diagnosis  
of MCAD**  
**Mast Cell Suppression ->  
Symptoms -  
No Better or Worse with  
Histamine Blockers??**



(1)

Something wrong with the medications? Fillers, preservatives

“ACTIVE INGREDIENTS”  
Diphenhydramine  
Phenylephrine



**Drug Facts**

**Active Ingredients (In each 5 mL)**

Diphenhydramine HCl 12.5 mg.....Antihistamine/  
Cough suppressant

Phenylephrine HCl 5 mg.....Nasal decongestant

controls cough due to minor throat and irritation and relieves nasal congestion as with a cold  
relieves the following symptoms due to other upper respiratory allergies:  
■ runny nose ■ itchy, watery eyes  
■ sore throat

■ with any other product containing diphenhydramine, even one used on the skin  
■ if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have  
■ heart disease ■ diabetes ■ high blood pressure  
■ thyroid disease ■ glaucoma  
■ trouble urinating due to an enlarged prostate gland  
■ a breathing problem such as emphysema or chronic bronchitis  
■ persistent or chronic cough such as occurs with smoking, asthma or emphysema  
■ cough that occurs with too much phlegm (mucus)

Ask a doctor or pharmacist before use if  
■ you are taking sedatives or tranquilizers.

When using this product  
■ do not use more than directed  
■ excitability may occur, especially in children  
■ marked drowsiness may occur  
■ alcohol, sedatives and tranquilizers may increase drowsiness  
■ avoid alcoholic drinks  
■ be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if  
■ nervousness, dizziness or sleeplessness occur  
■ symptoms do not get better within 7 days or occur with fever  
■ cough lasts more than 7 days, comes back, or occurs with fever, rash or persistent headache. These could be signs of a serious condition.

**Drug Facts (continued)**

If pregnant or breast feeding, ask a health professional before use.  
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

**Directions**

- do not take more than directed
- do not take more than 6 doses in any 24-hour period
- measure only with dosing cup provided
- do not use dosing cup with other products
- dose as follows or as directed by a doctor
- mL = milliliter

Age (year)	Dose (mL)
adults and children 12 years of age and over	10 mL every 4 hours
children 6 to under 12 years of age	5 mL every 4 hours
children 4 to under 6 years of age	do not use unless directed by a doctor
children under 4 years of age	do not use

**Other Information**

- each 5 mL contains: sodium 10 mg
- tamper evident: do not use if neckband on bottle cap is broken or missing
- dosing cup provided
- store between 15-30°C (59-86°F)
- Keep carton for full directions for use

**Inactive Ingredients** anhydrous citric acid, anhydrous trisodium citrate, carboxymethylcellulose sodium, edetate disodium, FD&C Blue #1, FD&C Red #40, flavors, glycerin, propyl gallate, propylene glycol, purified water, sodium benzoate, sorbitol, sucralose

**Questions?**  
You may also report side effects to this phone number.

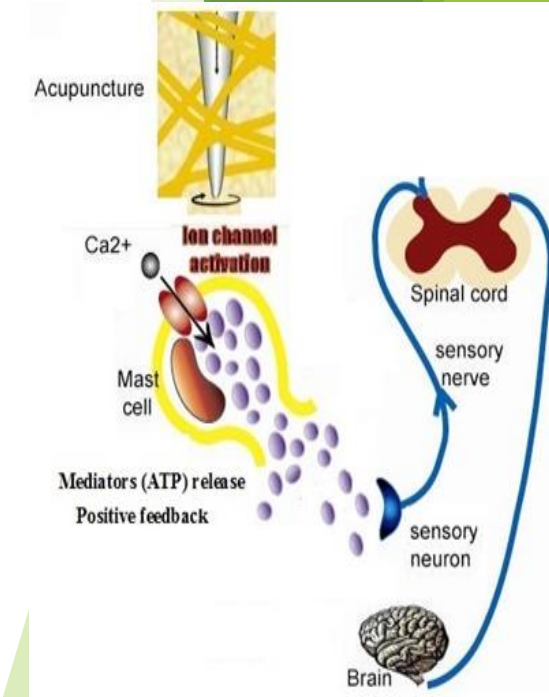
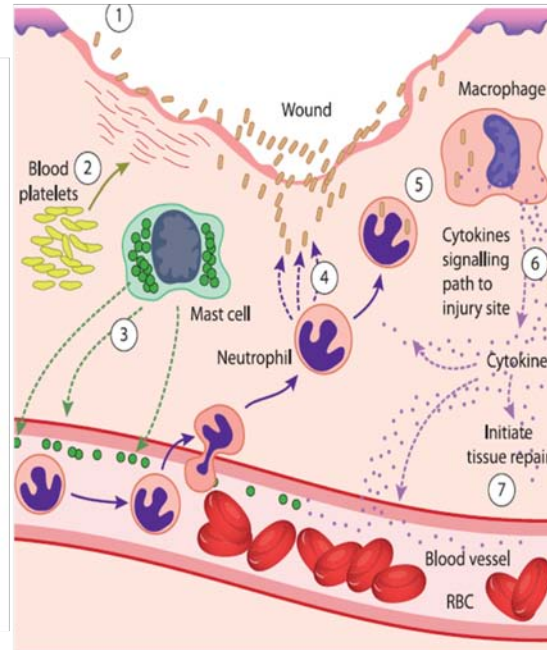
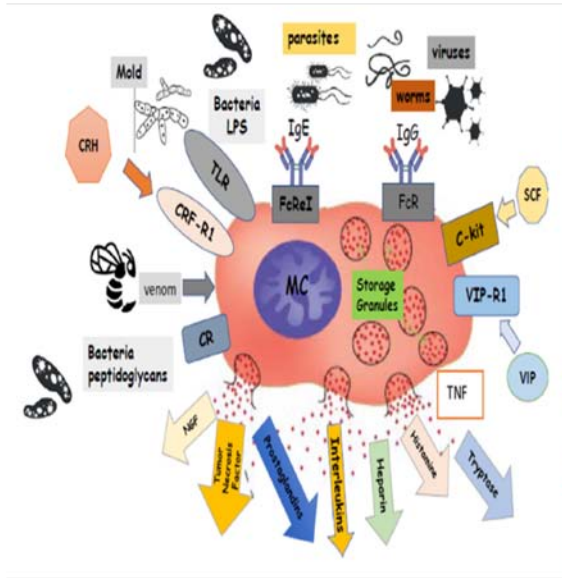


“INACTIVE INGREDIENTS”  
Anhydrous chloric acid, Anhydrous trisodium Citrate, Carboxymethylcellulose, Edetate disodium, FD&C Blue #1, FD&C Red#40, “flavors”, glycerin, propyl gallate, propylene glycol, purified water, sodium benzoate, sorbitol, sucralose

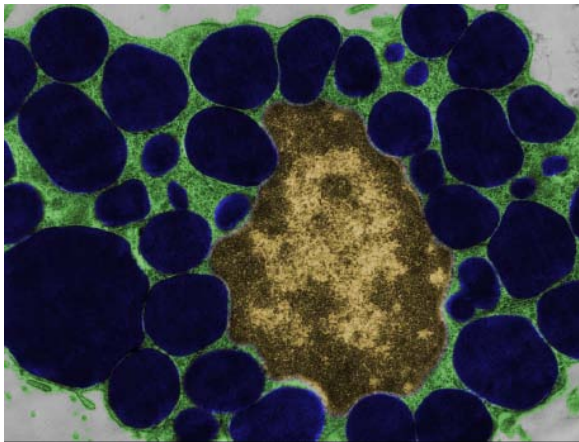
## (2) Are signs and symptoms of MC activation (MCA) an early warning signs of another disorder?



### Mast Cells: Border Defense and Tissue Repair



# Mast Cell Activation Disorders



Or is it?

- ✓ IgE-mediated reactions from foods, drugs, or other allergens
- ✓ Autoimmune urticaria: thyroid autoantibodies and IgE receptor autoantibodies)
- Chronic infections: viral infections- hepatitis B and C, EBV, herpes simplex virus; Helicobacter pylori infections; and helminthic parasitic infections
- Antibody and Complement component deficiencies
- Serum sickness or other immune-complex mediated processes
- Autoimmune/Connective tissue diseases, systemic lupus erythematosus and rheumatoid arthritis
- thyroid disease (both hypothyroidism and hyperthyroidism)
- neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders)

# Lessons from Urticaria

## Chronic Urticaria (CU) Care:



- Histamine Blockers
- Leukotriene Blockers
- Cromones



# Mast Cell activation (MCA) can driven by other co-morbid illnesses: MCAD/MCAS Endotypes

- Allergic (IGE mediated) Disorders
- MC activation associated with chronic inflammatory/neoplastic disorders
  - Autoimmune Disorders
    - Chronic Autoimmune Urticaria
    - Rheumatology - syndromes
    - Autoimmune Neuropathies
  - Immune deficiency Syndromes
- Physical Urticarias

Idiopathic  
Anaphylaxis

Disorders associated with  
mast cell activation

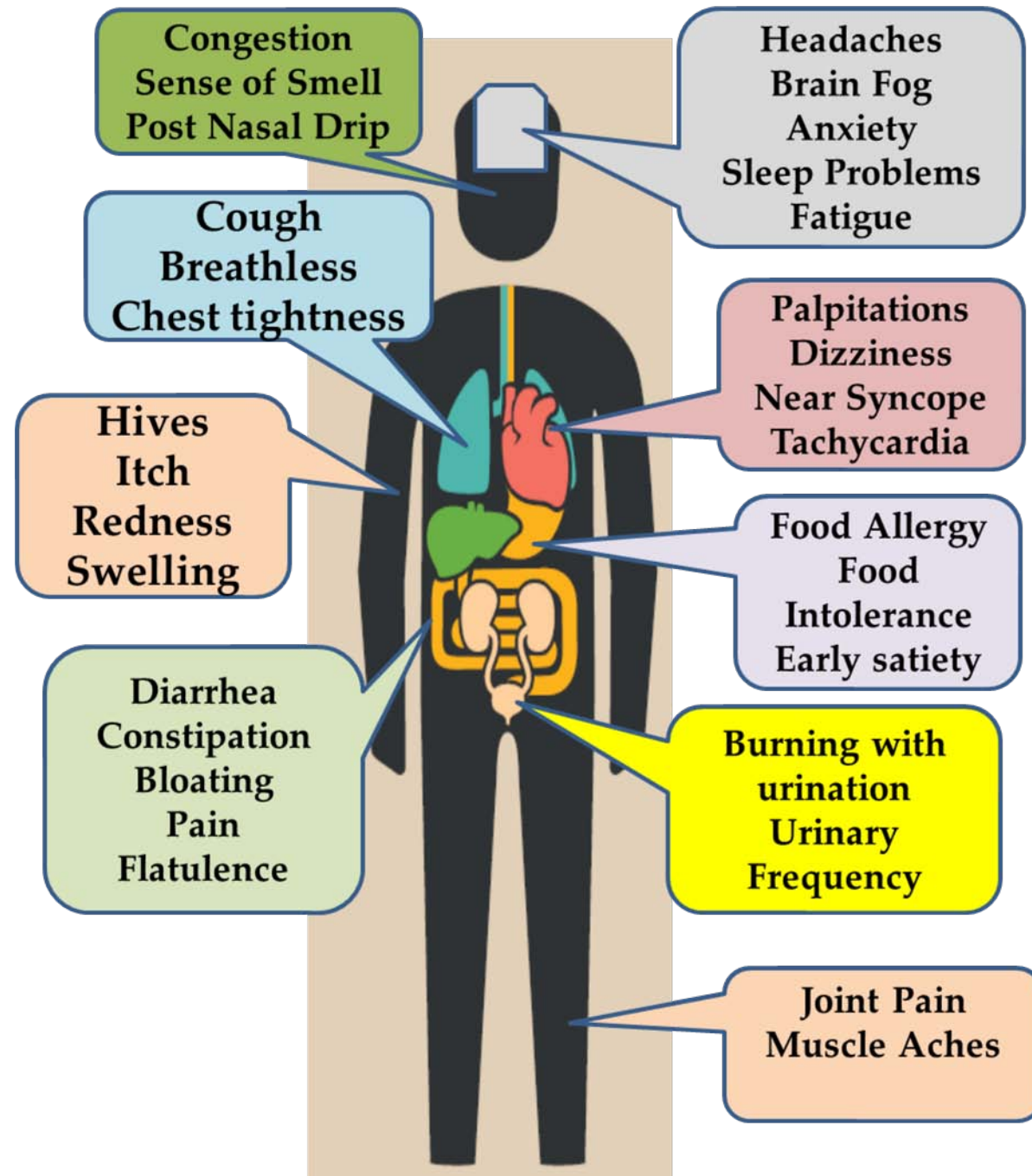
MCAS

IA

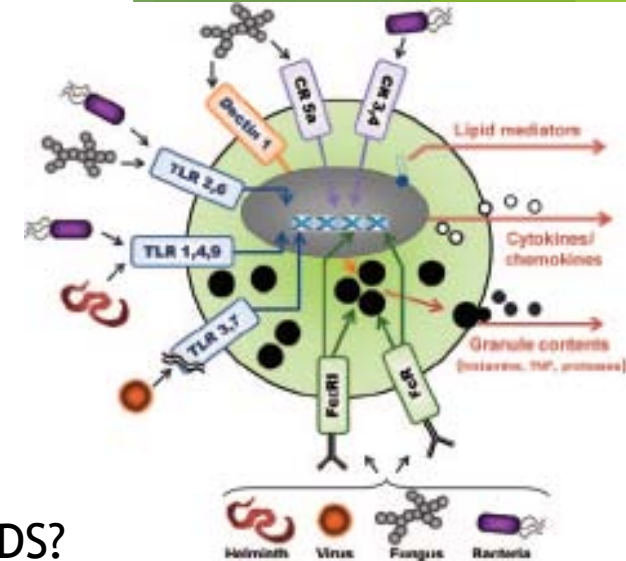
Clonal mast cell  
disorders

Hyper-  
tryptasemia

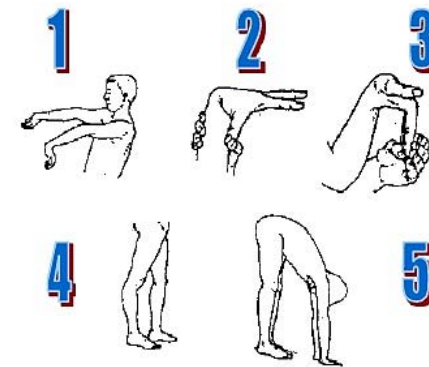
Mastocytosis  
Monoclonal  
MCAS



#1 Got MCAS?  
If so, which form?



#2 Got EDS?  
If so, which form?



Total = 9 possible points

**Allergen  
testing**  
Celiac Panel  
EGD/  
Colonoscopy

- ▶ Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk\*, egg\*, soy\*)
- ▶ Medications
- ▶ Airborne Allergens
- ▶ Insect stings or bites
- ▶ Autoimmune Disorders
- ▶ Infections
- ▶ Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

**Allergen  
testing**

**Rheumatology  
Panel**  
ANA, RF, ANCA,  
Thyroid Abs  
Neuonal Abs  
PIDD evaluation

**PIDD  
evaluation**  
Primary  
Immune  
Deficiency  
Disorder

**EDS Screen?  
Neuropathy?**

# Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century Peter

Arkwright & Andrew R. Gennery Ann. N.Y. Acad. Sci. 1238: 7-14.

The 10 warning signs of primary immunodeficiency are being promoted as a screening tool for use by both the general public and physicians.

A recent study, however, shows that except for family history, need for intravenous antibiotics and failure to thrive, the 10 warning signs are not a useful screen of primary immunodeficiency diseases (PIDs).

The 10 warning signs do not take into account the fact that PIDs now include diseases that present with

- sporadic infections,
- autoimmunity,
- autoinflammation, and
- malignancy.

## 10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1



Four or more new ear infections within one year.

2



Two or more serious sinus infections within one year.

3



Two or more months on antibiotics with little effect.

4



Two or more pneumonias within one year.

5



Failure of an infant to gain weight or grow normally.

6



Recurrent, deep skin or organ abscesses.

7



Persistent thrush in mouth or fungal infection on skin.

8



Need for intravenous antibiotics to clear infections.

9



Two or more deep-seated infections including septicemia.

10



A family history of PI.

Presented as a public service by:



Jeffrey Modell Foundation



Centers for Disease Control and Prevention



National Institutes of Health



National Institute of Allergy and Infectious Diseases



National Institute of Diabetes and Digestive and Kidney Diseases



National Institute of Mental Health



National Institute of Neurological Disorders and Stroke



National Institute of Nursing Research



National Institute of Public Health



National Institute of Social, Behavioral, and Economic Sciences



National Institute of Translational Research



National Institute of Women's Health



National Institute of Zoonotic and Foodborne Diseases



Baxter



CSL Behring



GRIFOLS



octapharma



PPTA



Talecris

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. © 2010 Jeffrey Modell Foundation

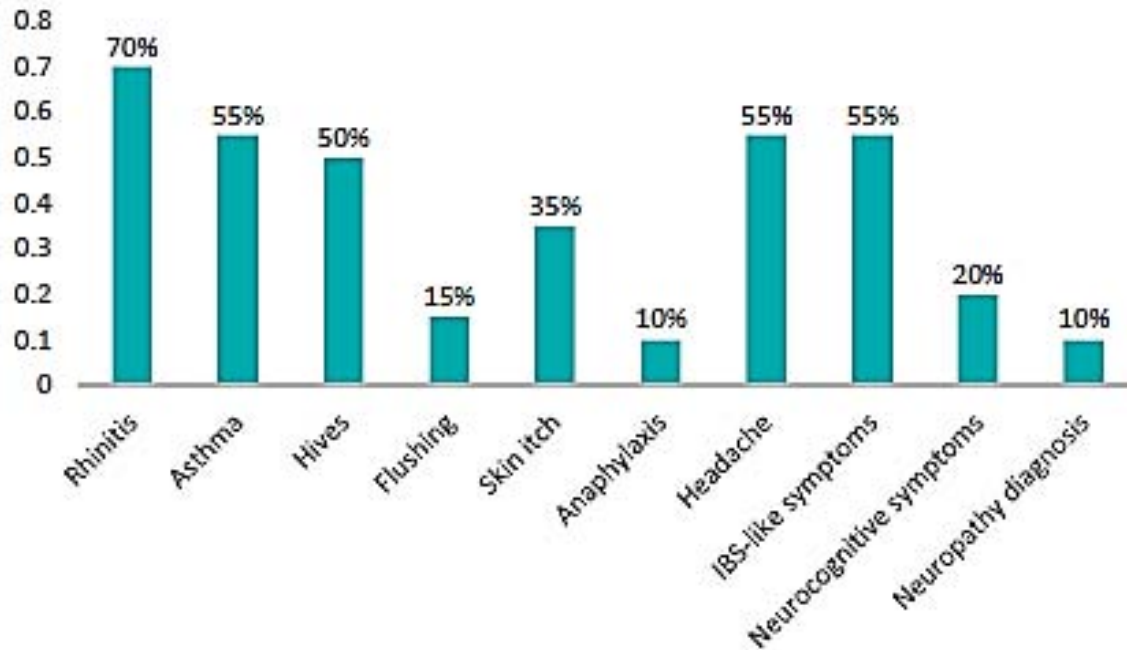
For information or referrals, contact the Jeffrey Modell Foundation: 866-INFO-4-PI | [info4pi.org](http://info4pi.org)

# New Paradox: MCAS and Primary Immune Deficiency (PID)

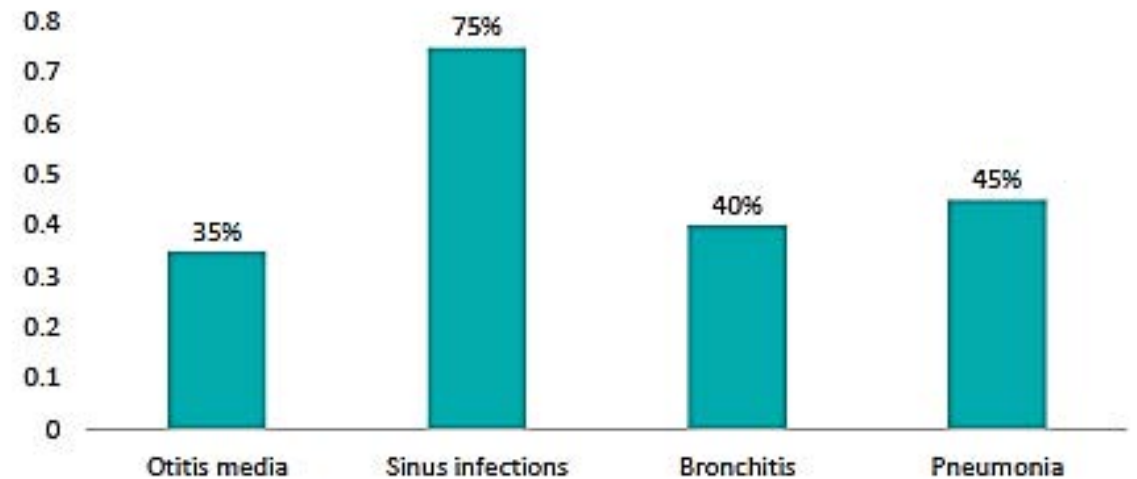
## Mast Cell Activation Syndrome In The Setting Of Idiopathic CD4 Lymphopenia

Roizen, Peruffo & Maitland, AAAAI 2018

Frequency of patient's Mast cell activation symptoms



Annual recurrent infections among patients with MCA symptoms



## Mast Cell Activation as a Presentation of Primary Immunodeficiencies

Roizen & Maitland, AAAAI 2018

# Treatment of MCAS:

Targeting the co-morbid disorders driving MC Activation



## Allergens

- Avoidance measures (Diet, Environment)
- Medications: histamine blockade
- Desensitization (Immunotherapy)
- Omalizumab
- Anti-interleukin mAb

## Infections \*\*\*

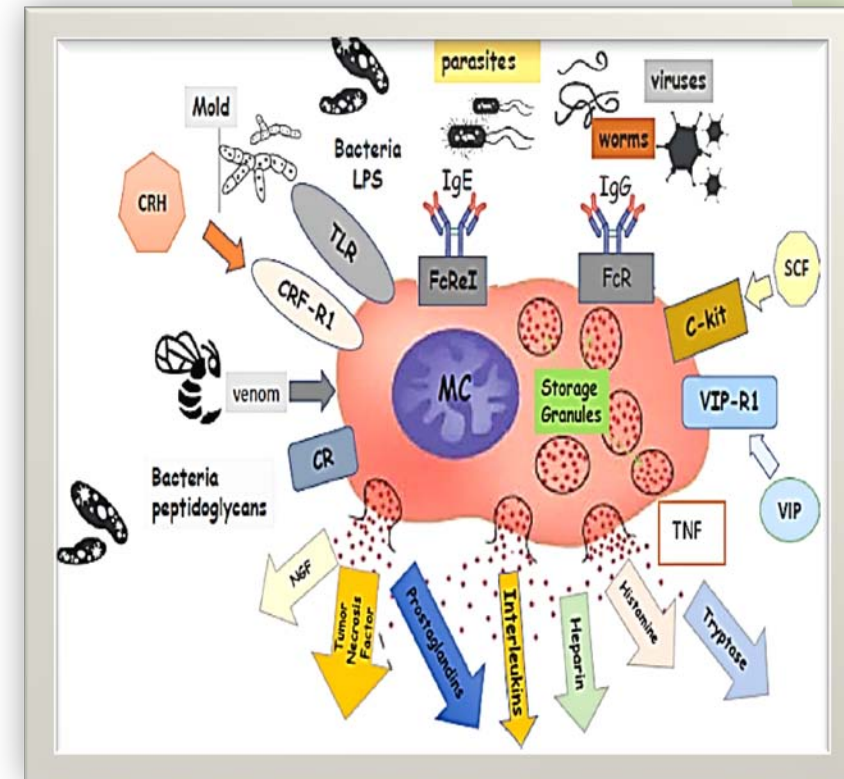
- infection vs exposure/sensitization
- Hepatitis, Lyme, Borrellia, EBV, HSV

## Primary Immune Deficiency

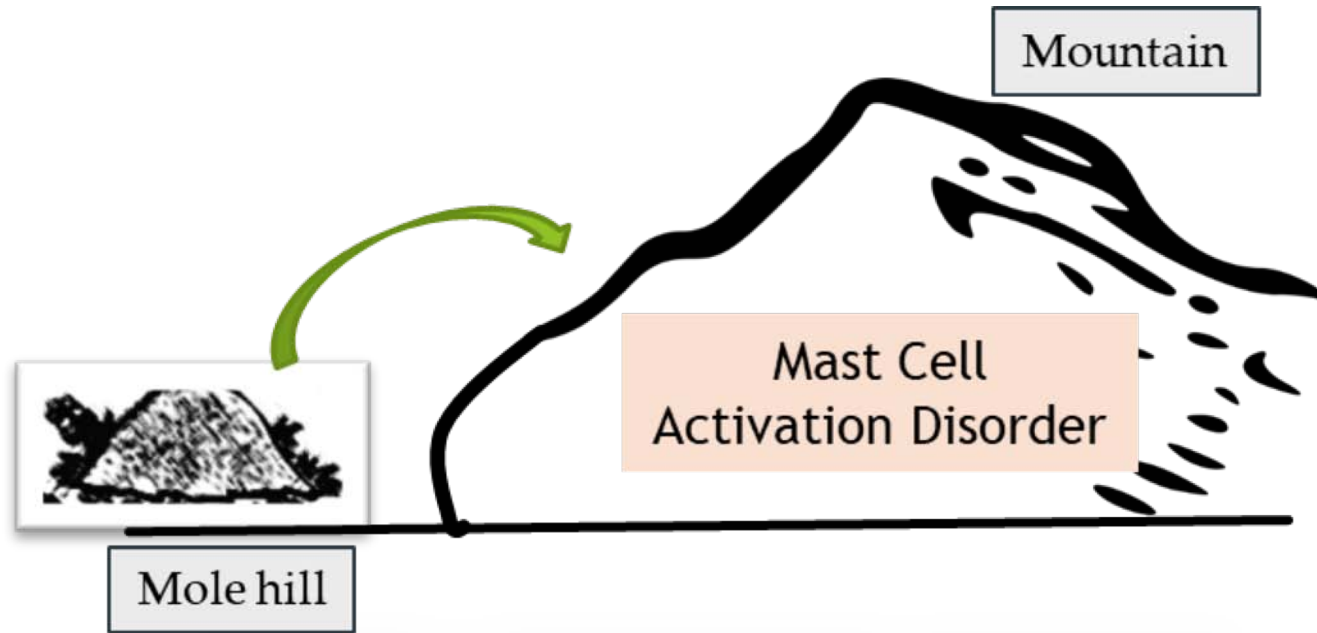
- Prophylactic Antibiotics
- Immune Globulin

## Autoimmune Disorders

- Anti-inflammatory Agents
- Immune Globulin



Is that “mole hill” of symptom (hives, bloating, headache) an early sign of a mountain of health troubles?



## Mountains out of Mole Hills

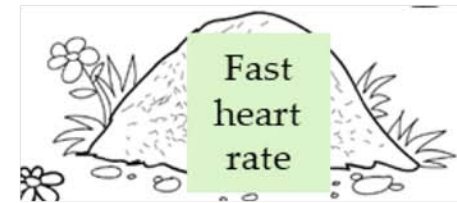
I frequently meet patients who are so overwhelmed by the fatigue, headaches or gastrointestinal distress, that he or she did not recall the large local reactions to insect bites, failed to take notice of the itch that is worse at night, or the trouble breathing when climbing stairs. These are all clues to reach a better working diagnosis!



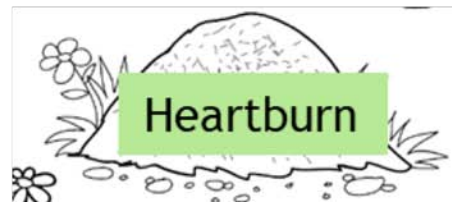
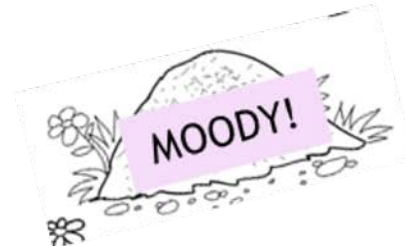
When telling your story do remember to write down those nuisance, “molehills” signs and symptoms.



Do **X**t make a mountain out of a molehill



Do **X**t exaggerate a minor problem



All these individual symptoms may seem like a mole hill, rather than a mountain.

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But if the symptoms keep re-occurring, these molehills maybe a mountain of other or impending health problems

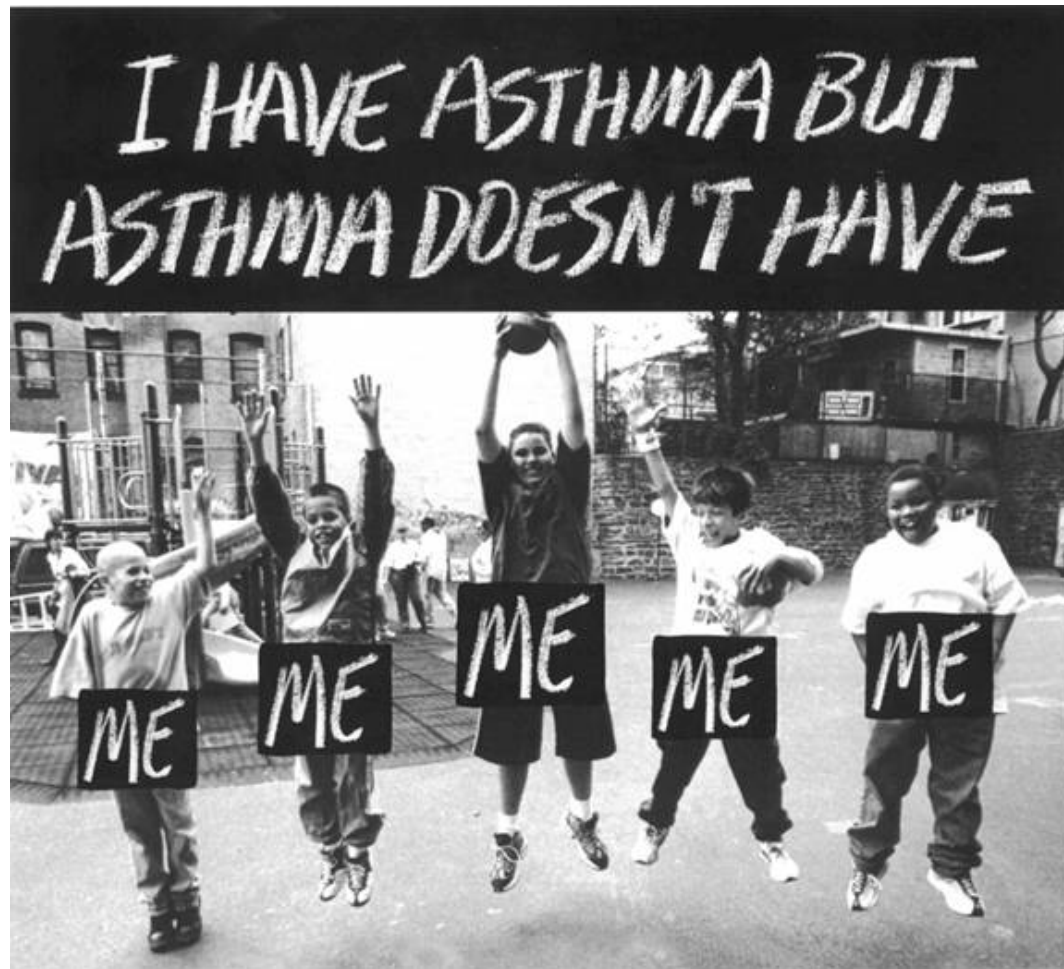
When recalling your mountain of MCAD symptoms, do not forget the Molehills!

# Stress Reduction & Regain Tolerance

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





## Steps to feeling better

- ▶ Screen
- ▶ Testing
- ▶ Education
- ▶ Prevention

So that you are eating, sleeping, playing, working, with signs and symptoms of Mast Cell Activation Syndrome under control

# Gratitude!

- Patients and their families
- Colleagues
- Chiari Sryingomyelia Foundation
- Ehlers Danlos Society
- The Mastocytosis Society

