MCAS, Mastocytosis, or Something Else

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NIH Disclaimer

- **Off Label Disclosures: None**

- **No Conflict of Interests**

Objectives

1. Define mast cell activation and create a differential diagnosis
2. Differentiate between clonal and non-clonal mast cell disease
3. Apply clinical and laboratory parameters for a therapeutic approach

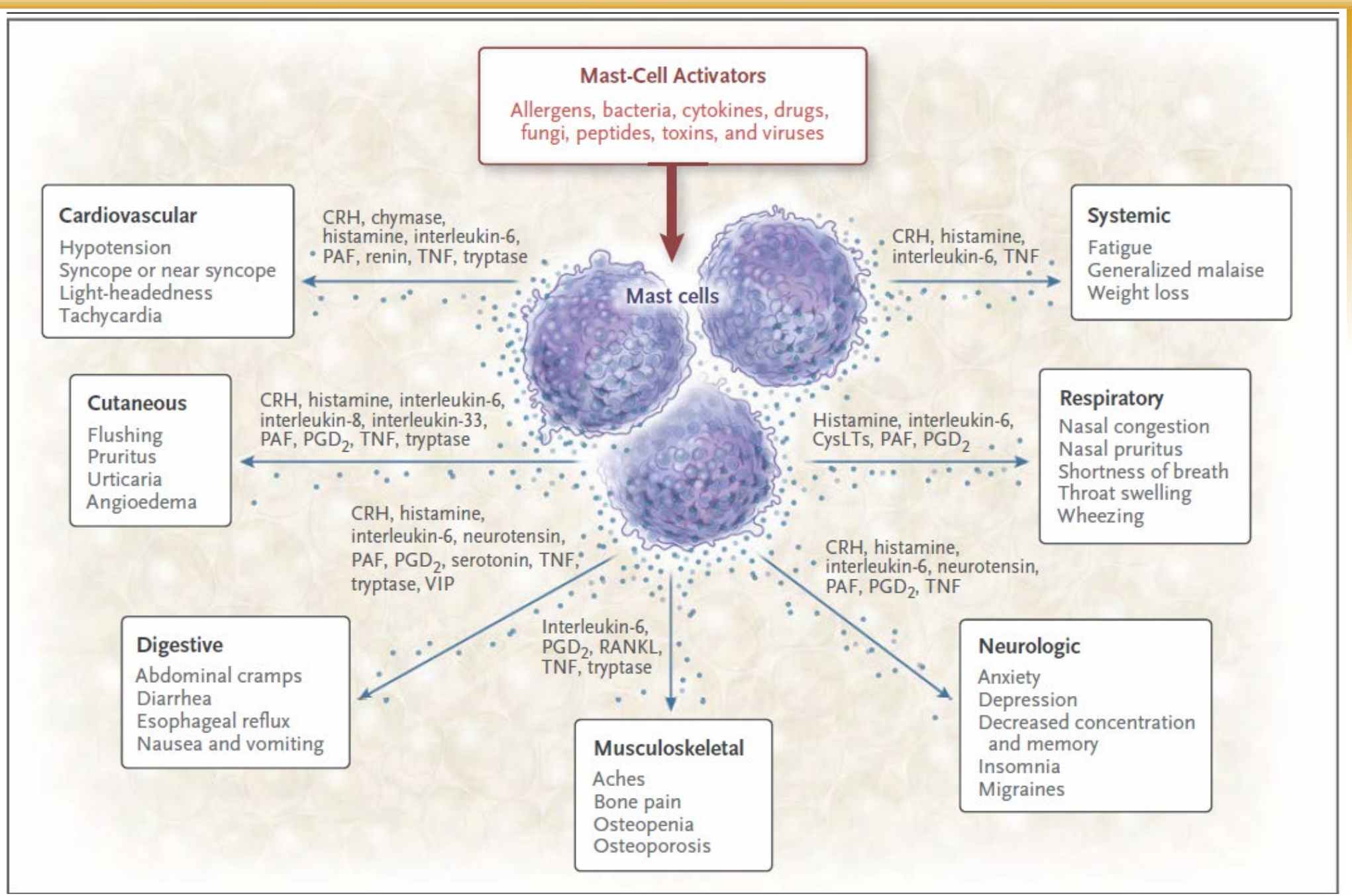
Overview

- Mast cells and mediators
- Mast cell disorders and differential diagnosis
- Primary mast cell disorders (clonal)
- Secondary mast cell disorder
- Idiopathic mast cell disorders
  - Anaphylaxis
- Hereditary alpha-tryptasemia syndrome

The Mast Cell

- Their primary role is to initiate an appropriate program of inflammation and repair in response to tissue damage initiated by a variety of diverse stimuli.
- Roles in maintenance of tissue homeostasis
- Their “misguided” activation by allergens contributes to the development of allergic symptoms.
- With ongoing tissue insult, their sustained release of numerous proinflammatory mediators, proteases and cytokines within specific tissue structures contributes to the pathophysiology of various chronic diseases

Peter Bradding, Hirohisa Saito, Middleton's Allergy: Principles and Practice, Ninth Edition, 2020



T. Theoharides et al *NEJM* 2015

Mast Cell Disorders (MCAS)

Classification of mast cell disorders
Primary mast cell disorders
Mastocytosis (systemic and cutaneous)
Monoclonal mast cell activation syndrome
Secondary mast cell disorders
Allergic disorders
Physical urticarias
Mast cell activation associated with chronic inflammatory or neoplastic disorders
Idiopathic mast cell disorders
Idiopathic anaphylaxis
Idiopathic urticaria (also called chronic spontaneous urticaria)
Idiopathic histaminergic angioedema
Idiopathic mast cell activation syndrome

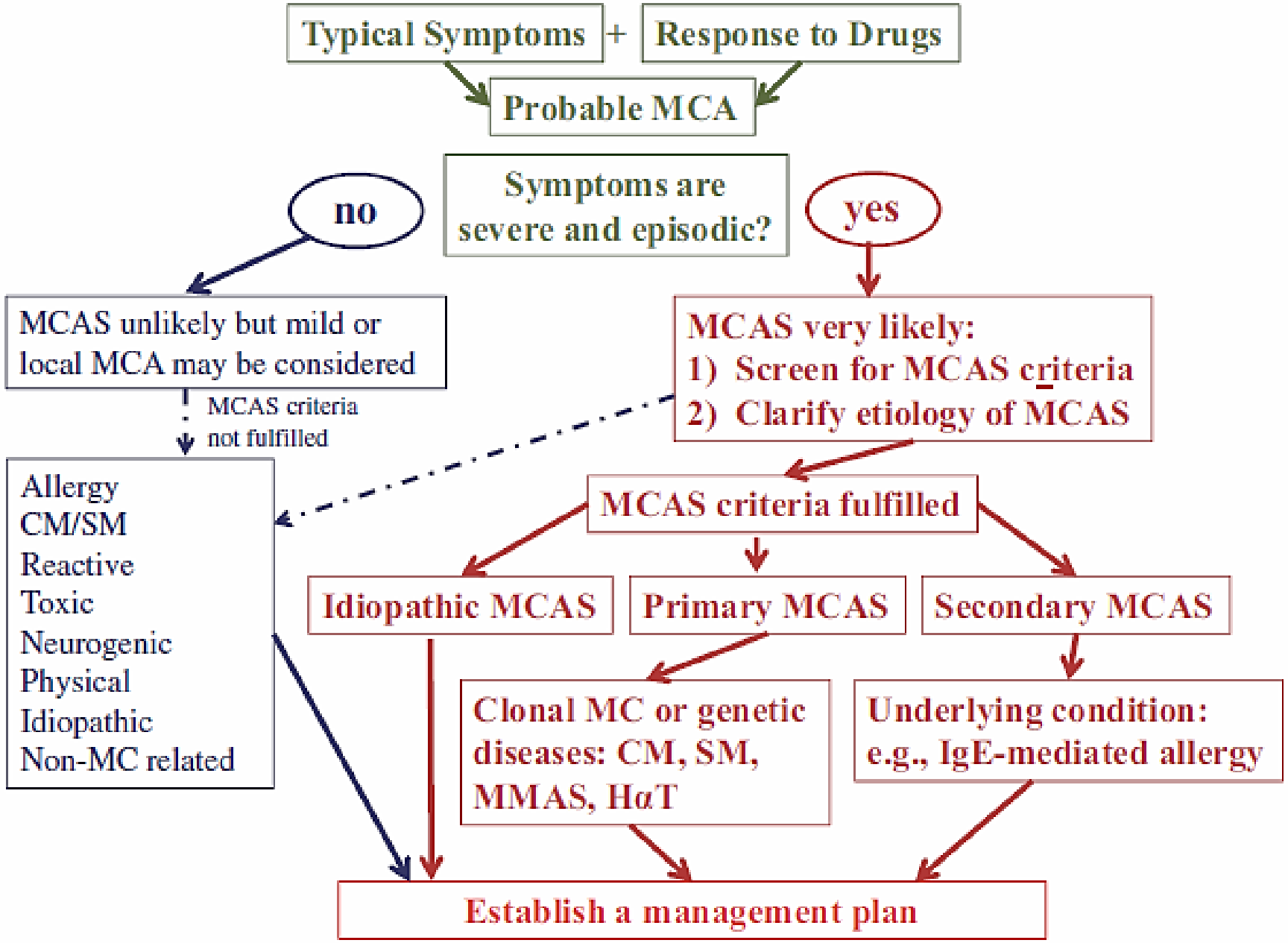
Classic Preformed and Newly Generated Human Mast Cell Autacoid Mediators and Proteases With Examples of Their Biologic Effects	
Mediator	Activity
Histamine (stored)	Bronchoconstriction; tissue edema; ↑ vascular permeability; ↑ mucus secretion; ↑ fibroblast proliferation; ↑ collagen synthesis; ↑ endothelial cell proliferation, dendritic cell differentiation and activation
Heparin (stored)	Anticoagulant; mediator storage matrix; sequesters growth factors; fibroblast activation; endothelial cell migration
Tryptase (stored)	Degrades respiratory allergens and cross-linked IgE; generates C3a and bradykinin; degrades neuropeptides; TGF-β activation; increases basal heart rate and ASM contractility; ↑ fibroblast proliferation and collagen synthesis; epithelial ICAM-1 expression and CXCL8 release; potentiation of mast cell histamine release; neutrophil recruitment
Chymase (stored)	↑ Mucus secretion; ECM degradation, type I procollagen processing; converts angiotensin I to angiotensin II; ↓ T cell adhesion to ASM; activates IL-1β, degrades IL-4, releases membrane-bound SCF
PGD_2 (synthesized)	Bronchoconstriction; tissue edema; ↑ mucus secretion; dendritic cell activation; chemotaxis of eosinophils, Th2 cells, and basophils via the CRTH2 (CD294) receptor
LTC_4/LTD_4 (synthesized)	Bronchoconstriction; tissue edema; ↑ mucus secretion; enhances IL-13-dependent airway smooth muscle proliferation; dendritic cell maturation and recruitment; eosinophil IL-4 secretion; mast cell IL-5, IL-8, and TNF-α secretion; tissue fibrosis

Criteria for the Diagnosis of Idiopathic Mast Cell Activation Syndrome

- Episodic symptoms consistent with mast cell mediator release affecting two or more organ systems (e.g. skin, gastrointestinal, cardiovascular, respiratory).
- Allergic diseases have been ruled out, as well as all diseases in DDx of presenting signs and symptoms (includes mastocytosis).
- Response to anti-mediator therapy.
- Evidence of an elevation above resting levels of a surrogate marker of mast cell activation (esp. serum tryptase) during an exacerbation.

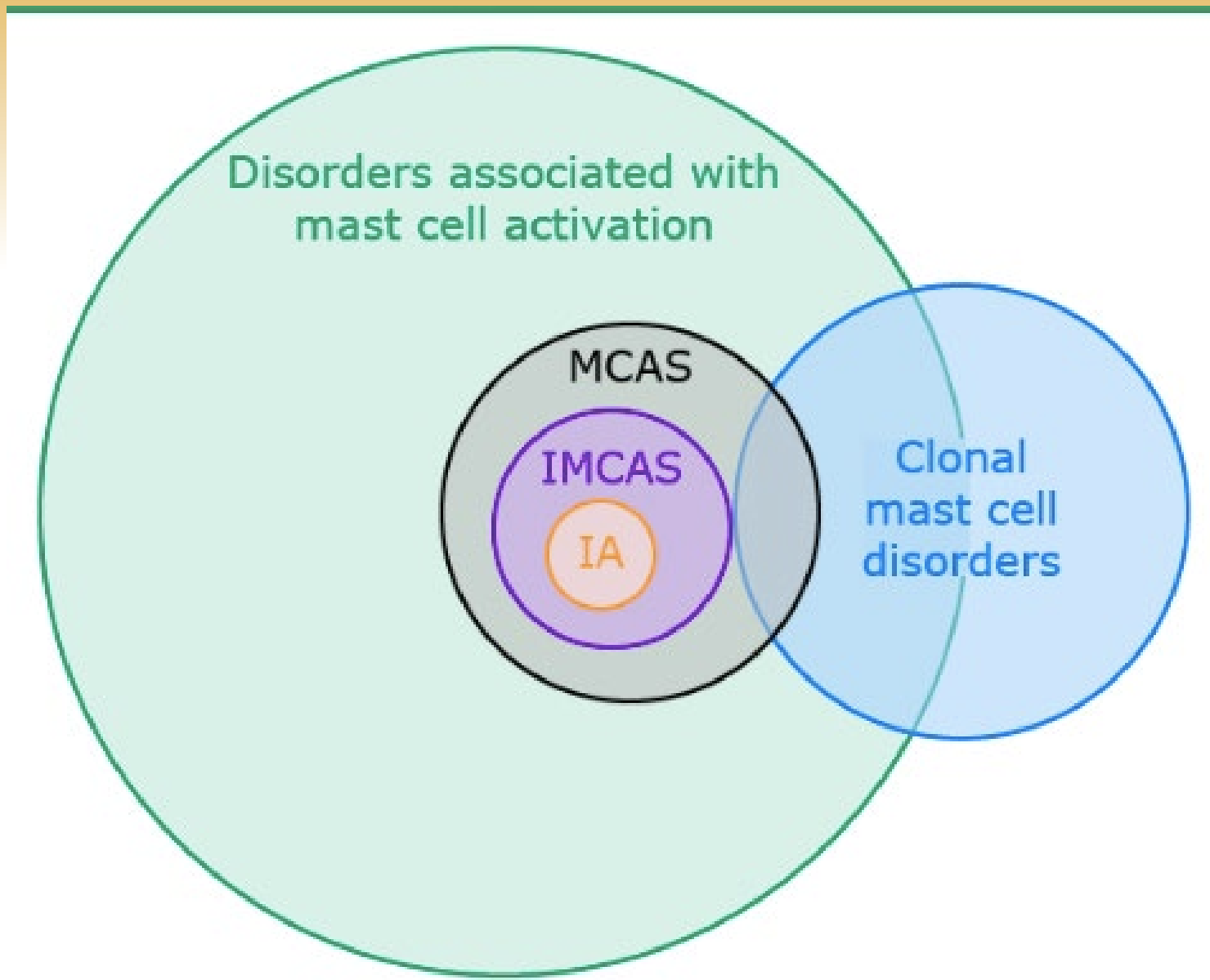
Akin, Valent and Metcalfe *JACI* 2010

Diagnostic Algorithm for suspected MCAS



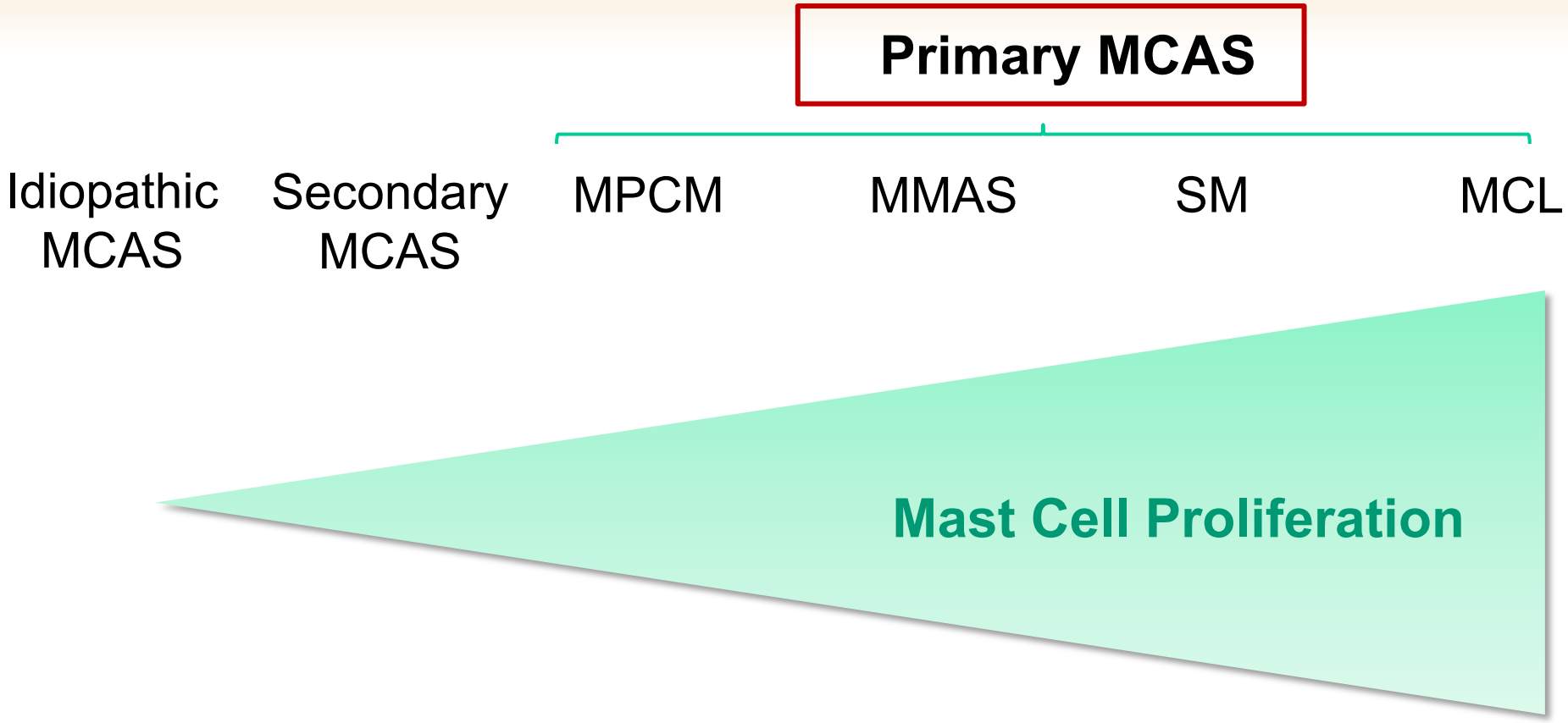
Arock M et al *Leuk Lymph* 2019

MCAS



Akin C. JACI 2017

Spectrum of Mast Cell Disorders



Primary Mast Cell Disorder

- In the 2016 revision of the World Health Organization (WHO) classification of myeloid neoplasms
- Mastocytosis is no longer considered a subgroup of myeloproliferative neoplasms (MPNs) and is considered a distinct disease category.
- It results from a clonal proliferation of morphologically and immunophenotypically abnormal mast cells (MCs) that accumulate in one or more organ systems.

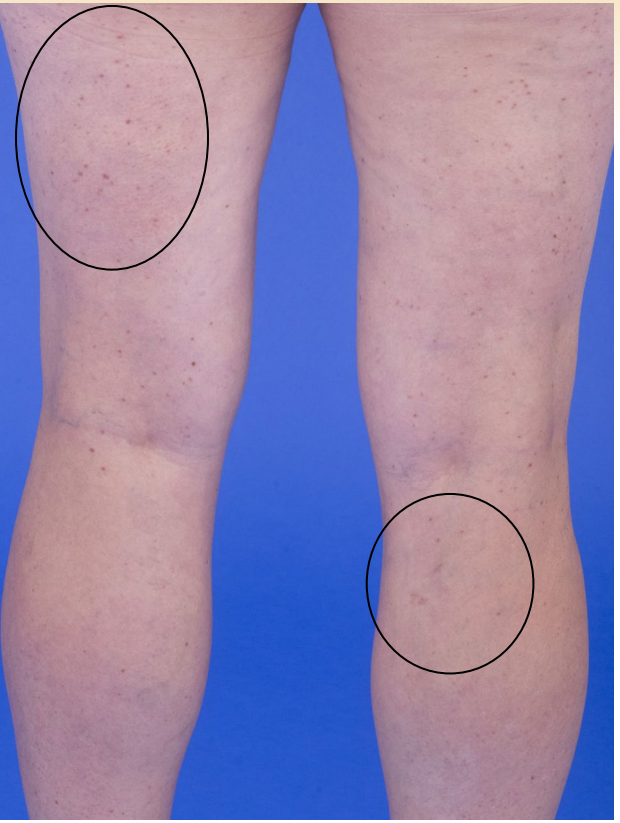
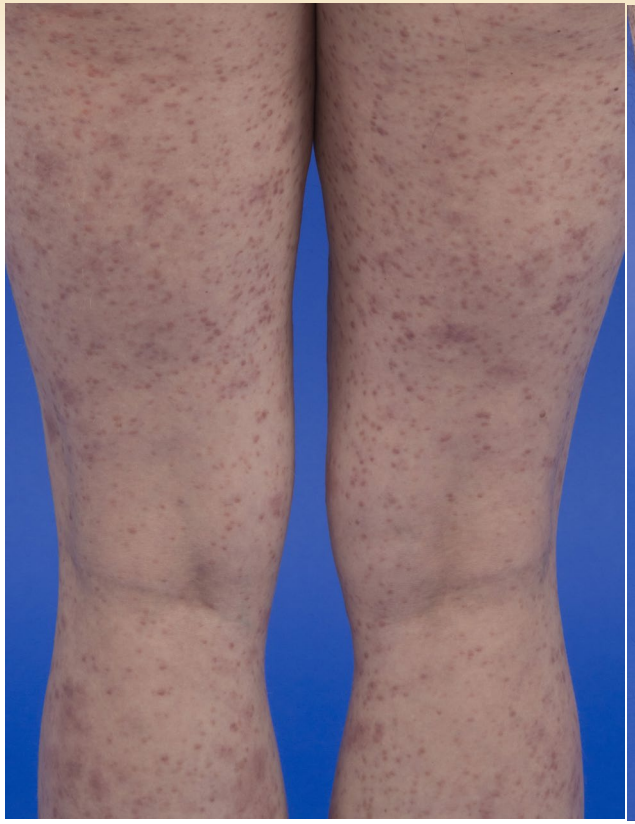
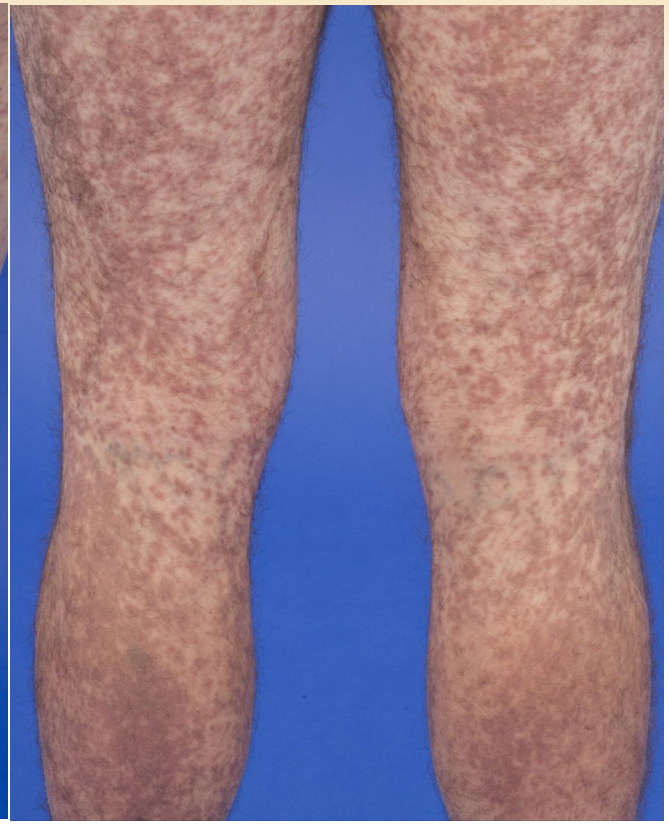
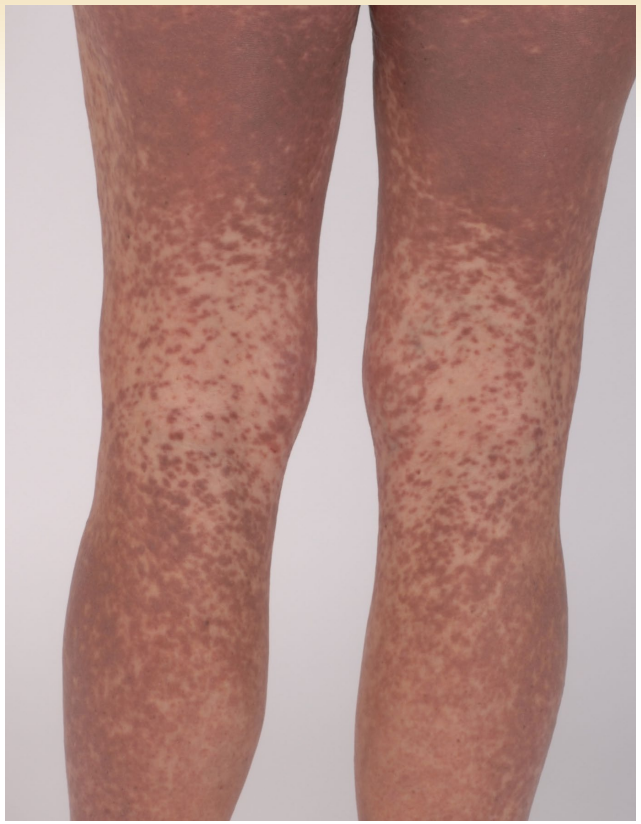
A Pardanani, Am J Hematol. 2019

Mastocytosis

- Cutaneous mastocytosis (CM) describes forms of mastocytosis that are limited to the skin.

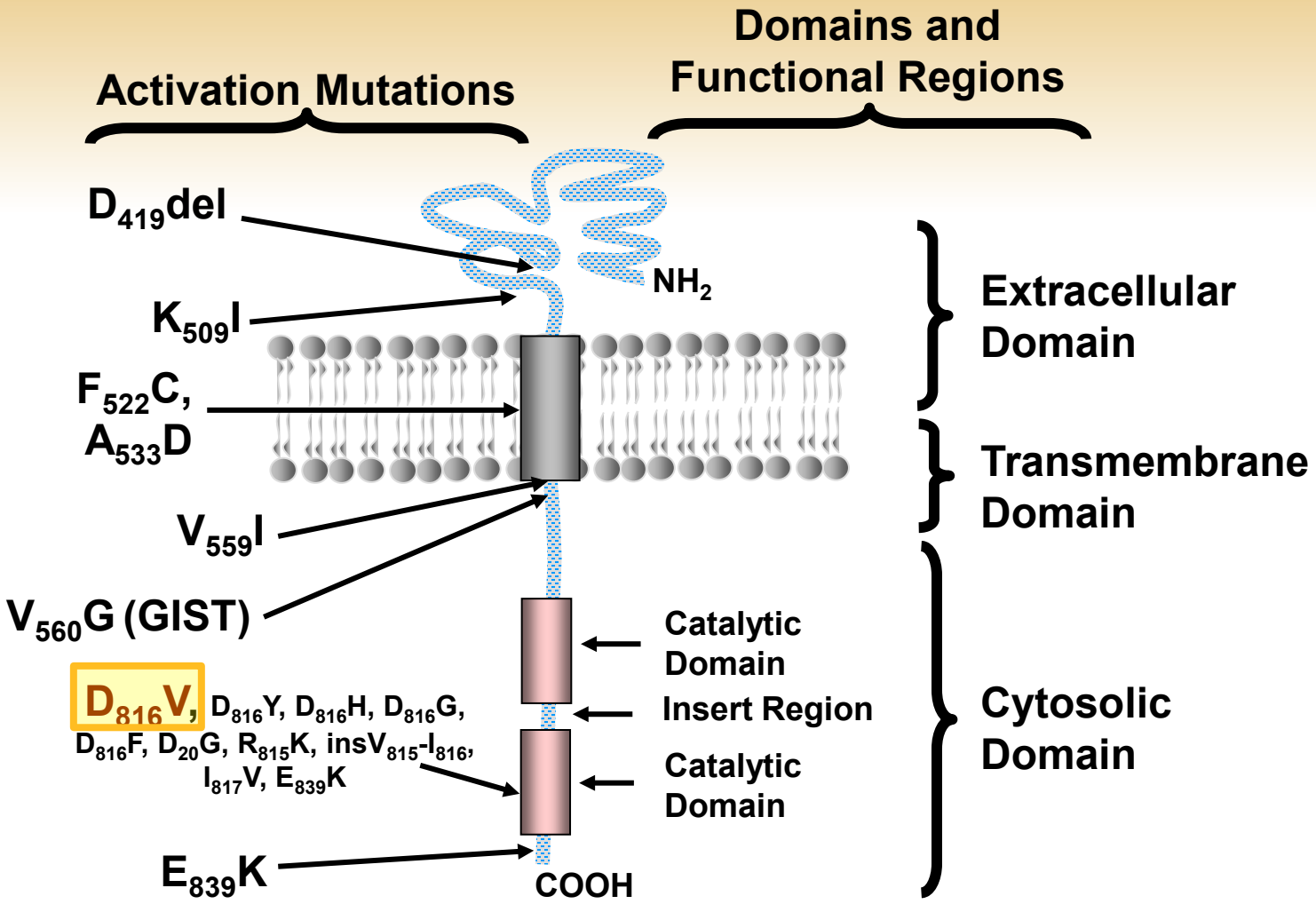
- Systemic mastocytosis (SM) describes forms of mastocytosis in which pathologic mast cells infiltrate multiple extracutaneous organs, with or without skin involvement.

Maculopapular Cutaneous Mastocytosis-Adult

Carter & Metcalfe, *Brit J Haematol*, in review

Activating Mutations in *KIT* that Promote Mast Cell Proliferation



M Arock, et. al. *Leukemia* 2015

MMAS

- Monoclonal mast cell activation syndrome (MMAS) was first described in 2007[1]
- Monoclonal mast cell activation syndrome (MMAS) might be as rare as 1 in 10,000 to 20,000 subjects[2]
- These patients do not have UP/MPCM or the characteristic mast cell aggregates in their bone marrow (a major criterion for SM)
- Baseline serum tryptase values that are normal or only mildly increased
- MMAS typically presents in adults with recurrent and episodic symptoms of mast cell activation

[1]Sonneck K, et al, *Int Arch Allergy Immunol* 2007
[2]Cem Akin et al *JACI* 2017

Pathogenesis of Idiopathic Anaphylaxis

- Previously reported that some patients with unexplained (idiopathic) anaphylaxis had an underlying monoclonal mast cell disorder.[1]

- Ongoing study (91 patients):
  - **Determine prevalence:** 12 (18.6%) had a clonal mast cell disorder
  - **Criteria for marrow biopsy:** Developed a scoring system (100% specificity and 96% sensitivity) using gender, reaction severity, tryptase levels, and qPCR.[2]
  - Expanded the differential for IA to include HαT(13%), Alpha-gal syndrome (5%), and clonal mast cell disease.
  - Determine prevalence of clonal MC disease in patients with venom, food, & drug anaphylaxis

[1]Akin C et al *Blood* 2007
[2]Carter MC et al *JACI* 2018

Clonal Mast Cell Prediction: NICAS

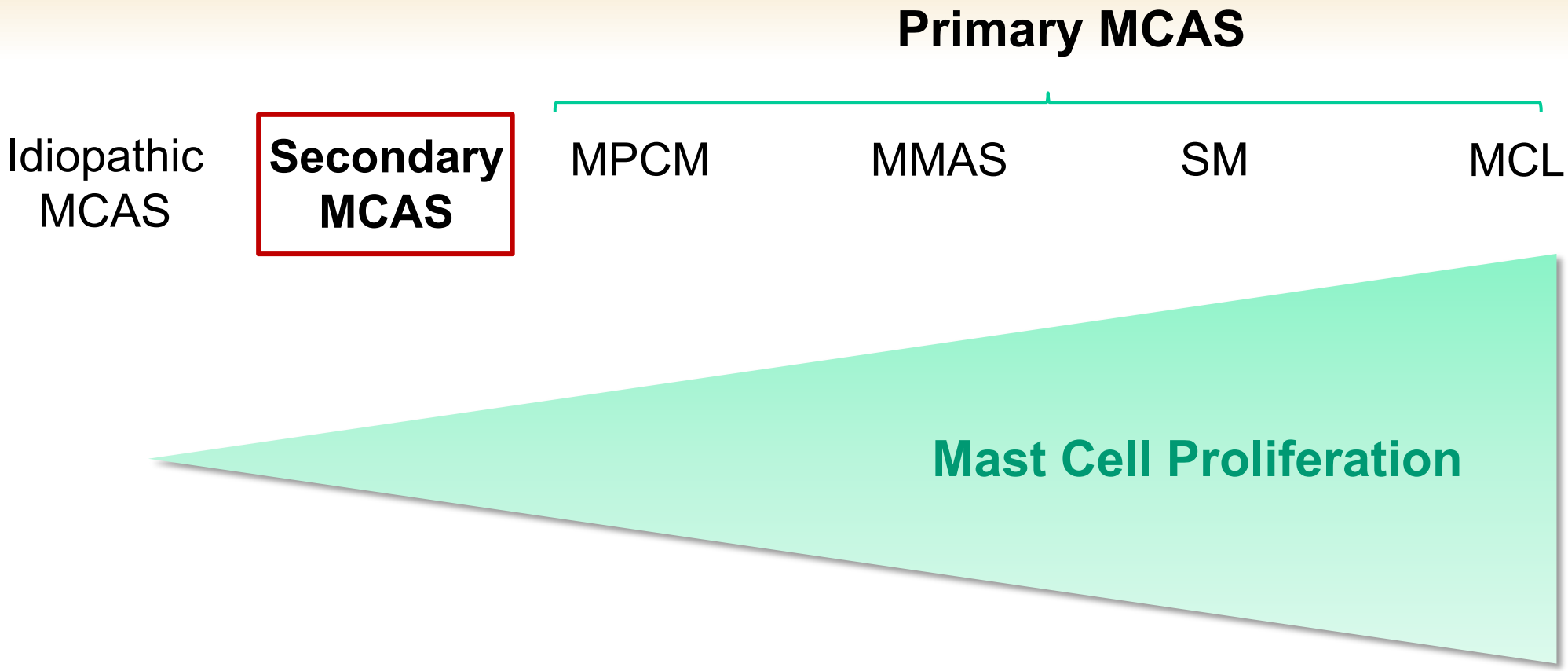
NICAS-NIH Idiopathic Clonal Anaphylaxis Score

VARIABLE		SCORE
GENDER	Male	+1
	Female	-1
CLINICAL SYMPTOMS	Absence of angioedema	+1
	Flushing	-1
	Urticaria	+1
	Syncope	+3
TRYPTASE	<11.4 ng/ml	-1
	>11.4 ng/ml	+1
ALLELE-SPECIFIC PCR-ASP *KIT* D816V	Negative	-1
	Positive	+3

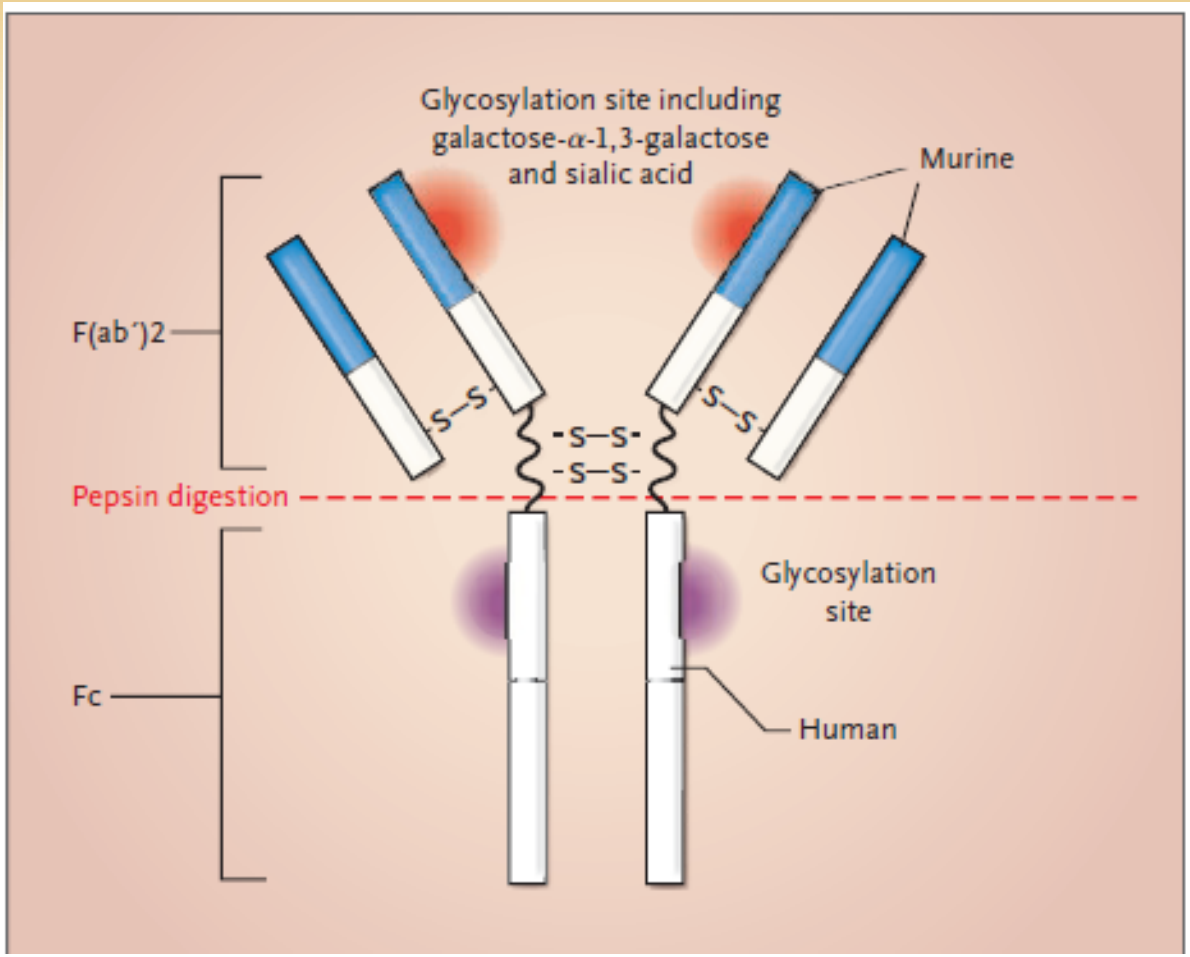
Predictive Symptoms	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
REMA score (≥2) with a sBT cut-off 15-25ng/ml-NIH data	62.5% (24.4-91.5%)	71.43% (56.7%-83.4%)	26.32% (9.1%-51.2%)	92.11% (78.6%-98.3%)
Gulen-Modified REMA score (≥2) with a sBT cut-off 11-20ng/ml-NIH data	62.5% (24.4-91.5%)	71.43% (56.7%-83.4%)	26.32% (9.1%-51.2%)	92.11% (78.6%-98.3%)
ASP	37.5%	100%	100%	90.74%
NIH-modified REMA with a sBT cut-off 11.4 ng/ml	96% (90.1%-98.9%)	100% (96.4%-100%)	100% (96.2%-100%)	96% 90.4%-98.4%)

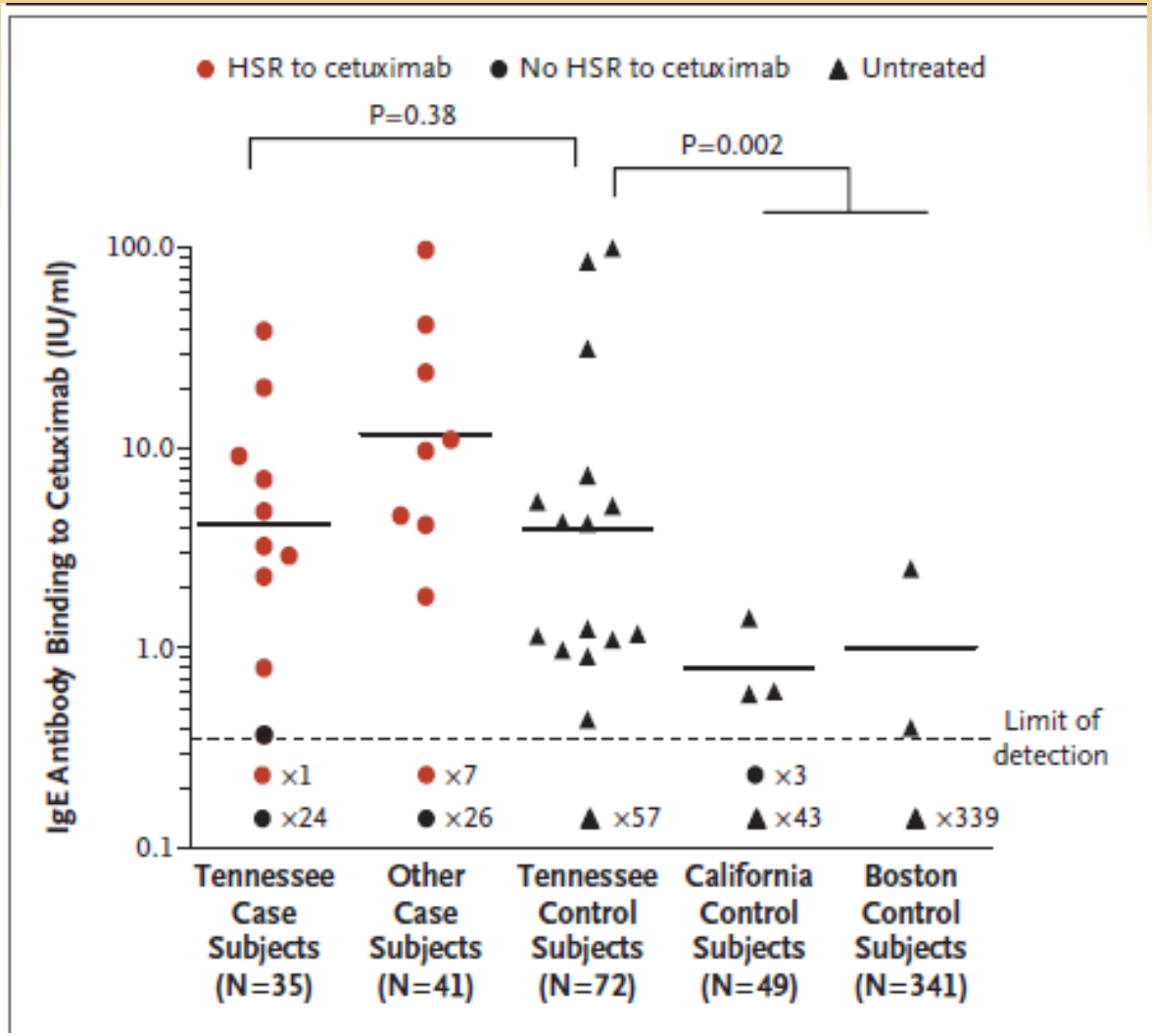
Carter et al *JACI* 2018

Spectrum of Mast Cell Disorders



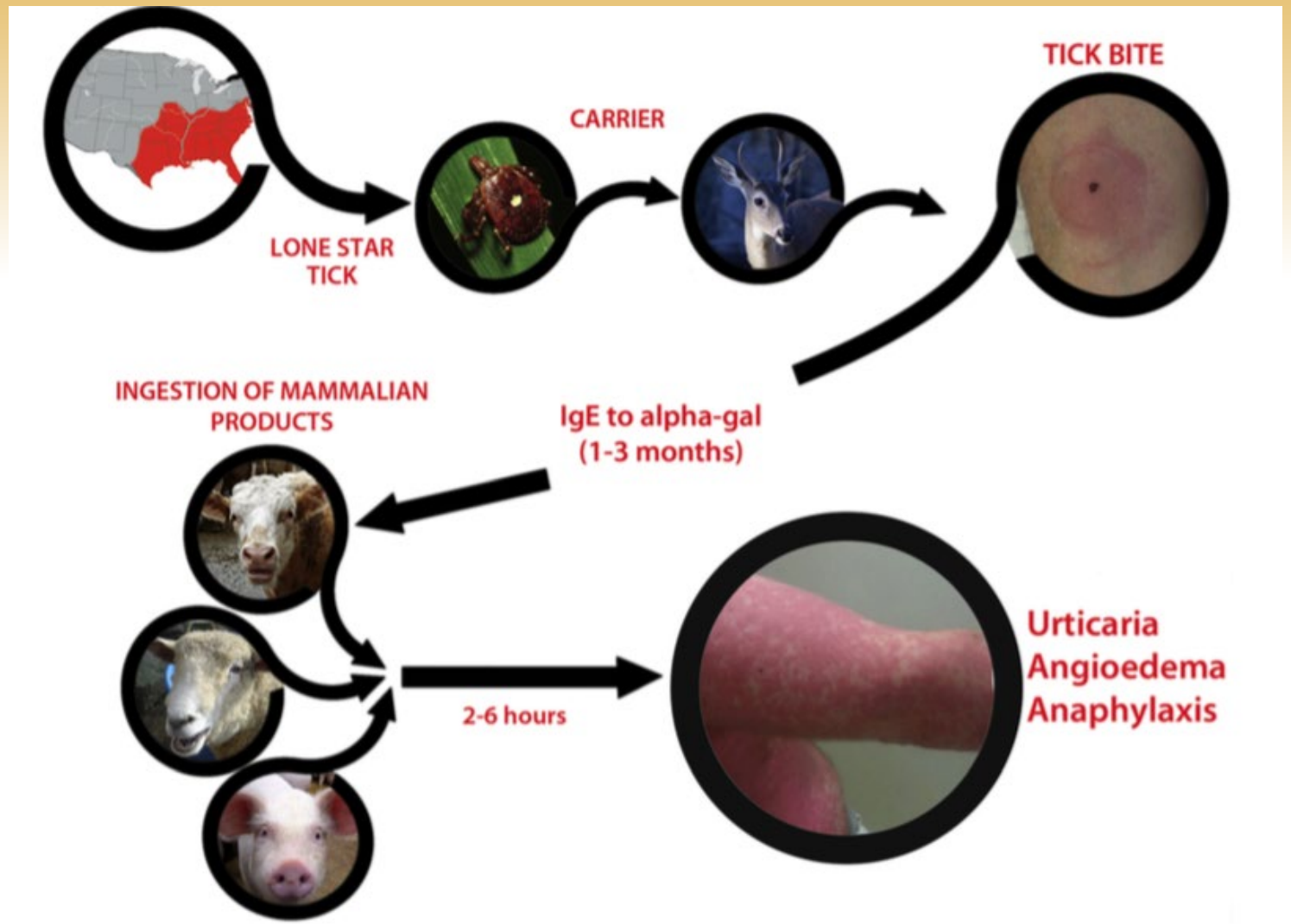
Cetuximab-Induced Anaphylaxis & IgE-specific Gal-α-1-3 Gal





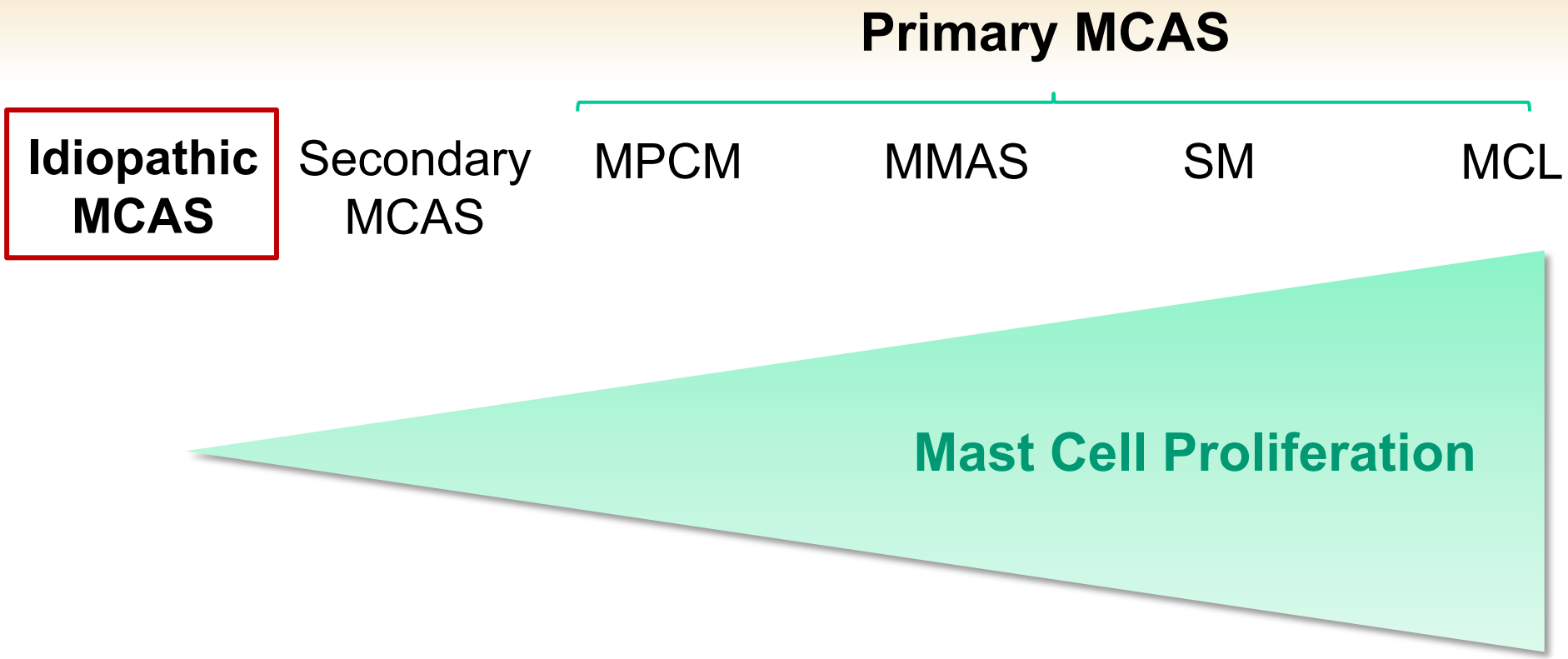
Chung C et al *NEJM* 2008

Summary of Alpha-Gal Sensitization



(Steinke, JW et. al, 2014)

Non-clonal mast cell disease

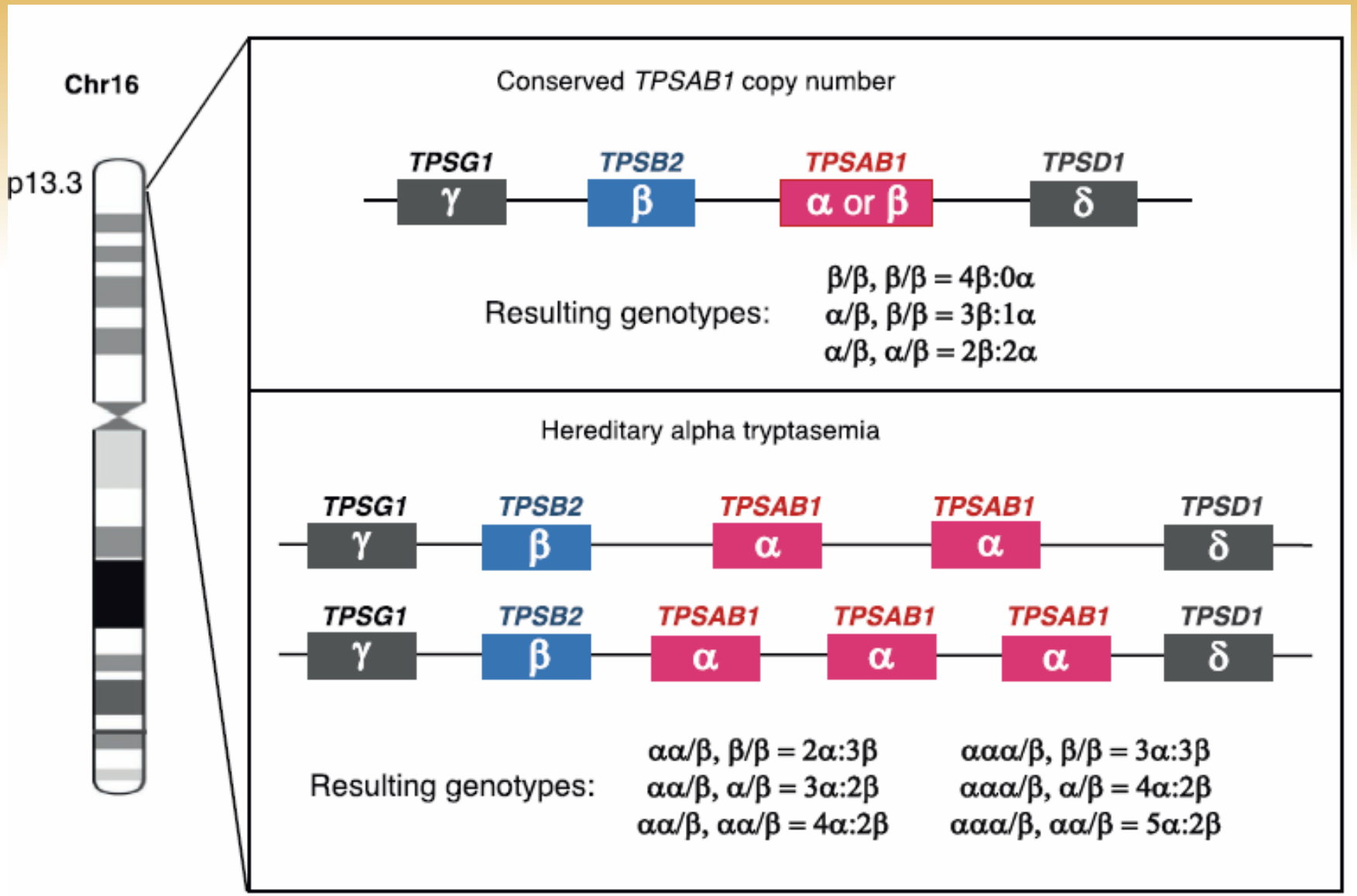


Hereditary Alpha Tryptasemia

- All individuals identified to date with increased alpha-encoding *TPSAB1* copy number have basal serum tryptase (bST) above 8 ng/mL
- Elevated BST, currently defined clinically as >11.4 ng/mL has been reported in 4% to 6% of the general population
- A gene-dosage effect exists between number of additional *TPSAB1* copies, bST and severity of clinical symptoms in affected individuals
- 20% patients have systemic reactions with IgE-mediated hypersensitivity to venom

JJ Lyons, MD, *Immunol Allergy Clin N Am*, 2018

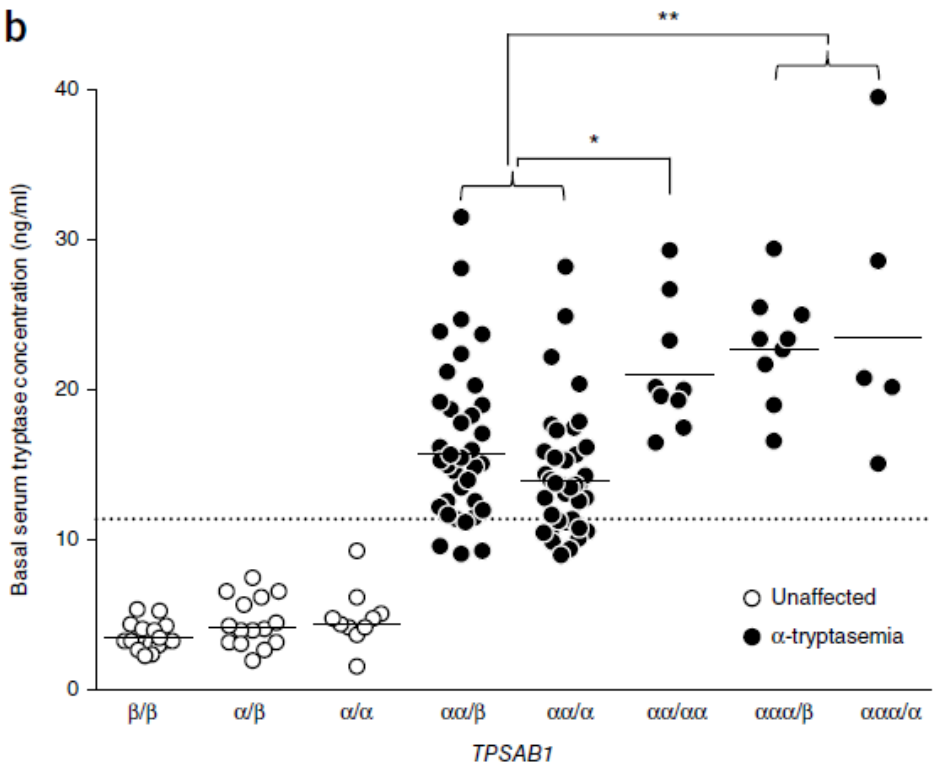
Hereditary Alpha Tryptasemia

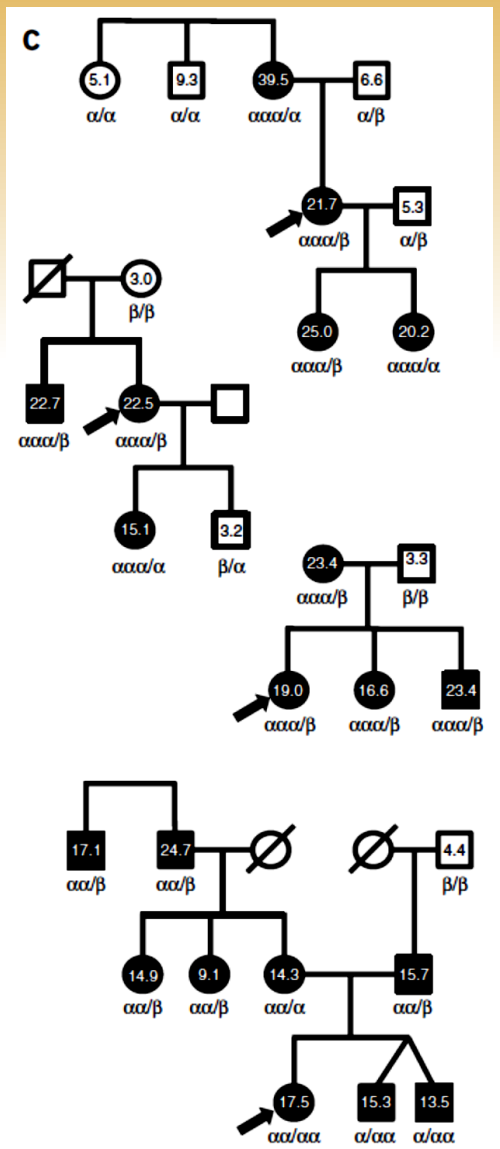


JJ Lyons, MD, *Immunol Allergy Clin N Am*, 2018

Alpha-tryptasemia

	TOTAL (n = 96)
Age, mean (range)	39 years (2-89)
Gender, n (%)	
Male	36 (37.5)
Female	60 (62.5)
Ethnicity, n (%)	
Caucasian	96 (100)





Lyons et al *Nature Genetics* 2016

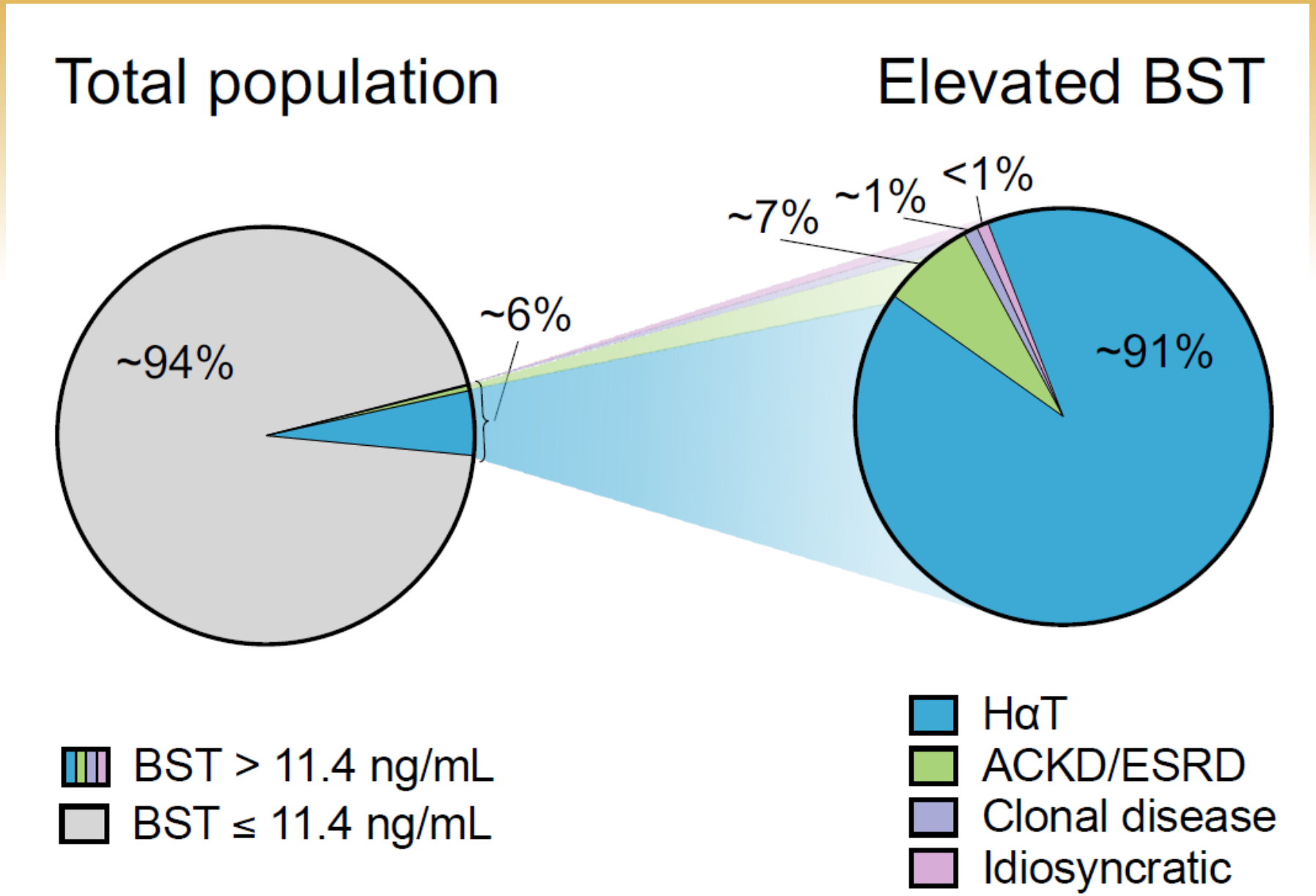
Hereditary Alpha Tryptasemia

Table 1
Clinical features reported in association with hereditary alpha tryptasemia

Manifestation	Reported Prevalence,[a] %	Association Supported in an Unselected Cohort[b]
Basal serum tryptase >8 ng/mL	100	Yes
Chronic gastroesophageal reflux symptoms	56–77	No
Arthralgia	44–45	No
Body pain/headache	33–47	No
Flushing/pruritus	32–55	Yes
Irritable bowel syndrome (Rome III)	28–49	Yes
Sleep disruption	22–39	No
Systemic immediate hypersensitivity reaction	21–28	No
Retained primary dentition	20–33	Yes
Systemic venom reaction	14–22	Yes
Congenital skeletal abnormality	11–26	No
Joint hypermobility	0–28	No
Positive Tilt-table test	0–11	No

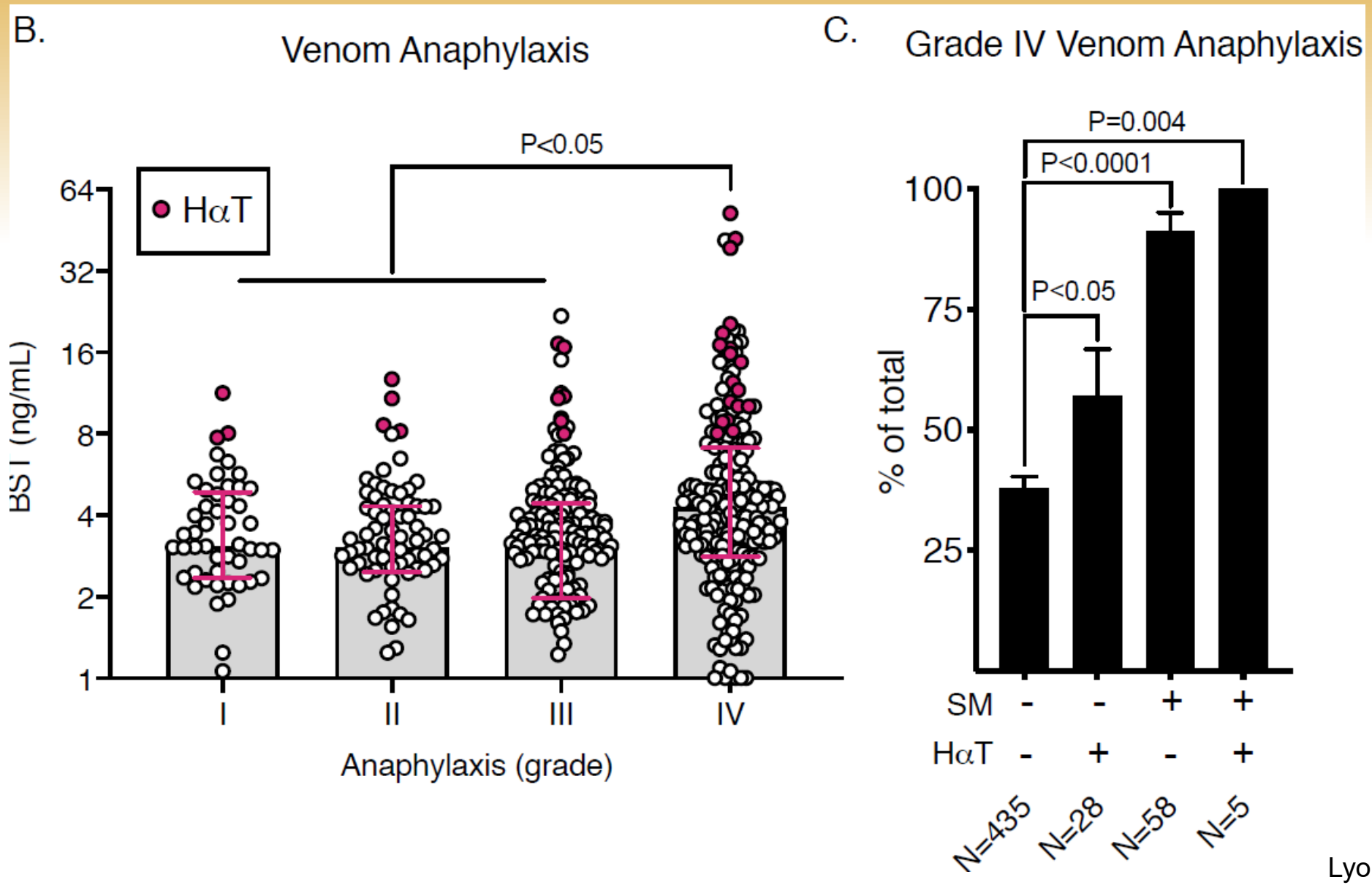
JJ Lyons, MD, *Immunol Allergy Clin N Am*, 2018

Prevalence of HαT



Lyons J *Ann Allergy Asthma Immunol* 2021

HαT in patients with anaphylaxis



Lyons et al *JACI* 2021

Clinical Criteria for Diagnosis of Anaphylaxis

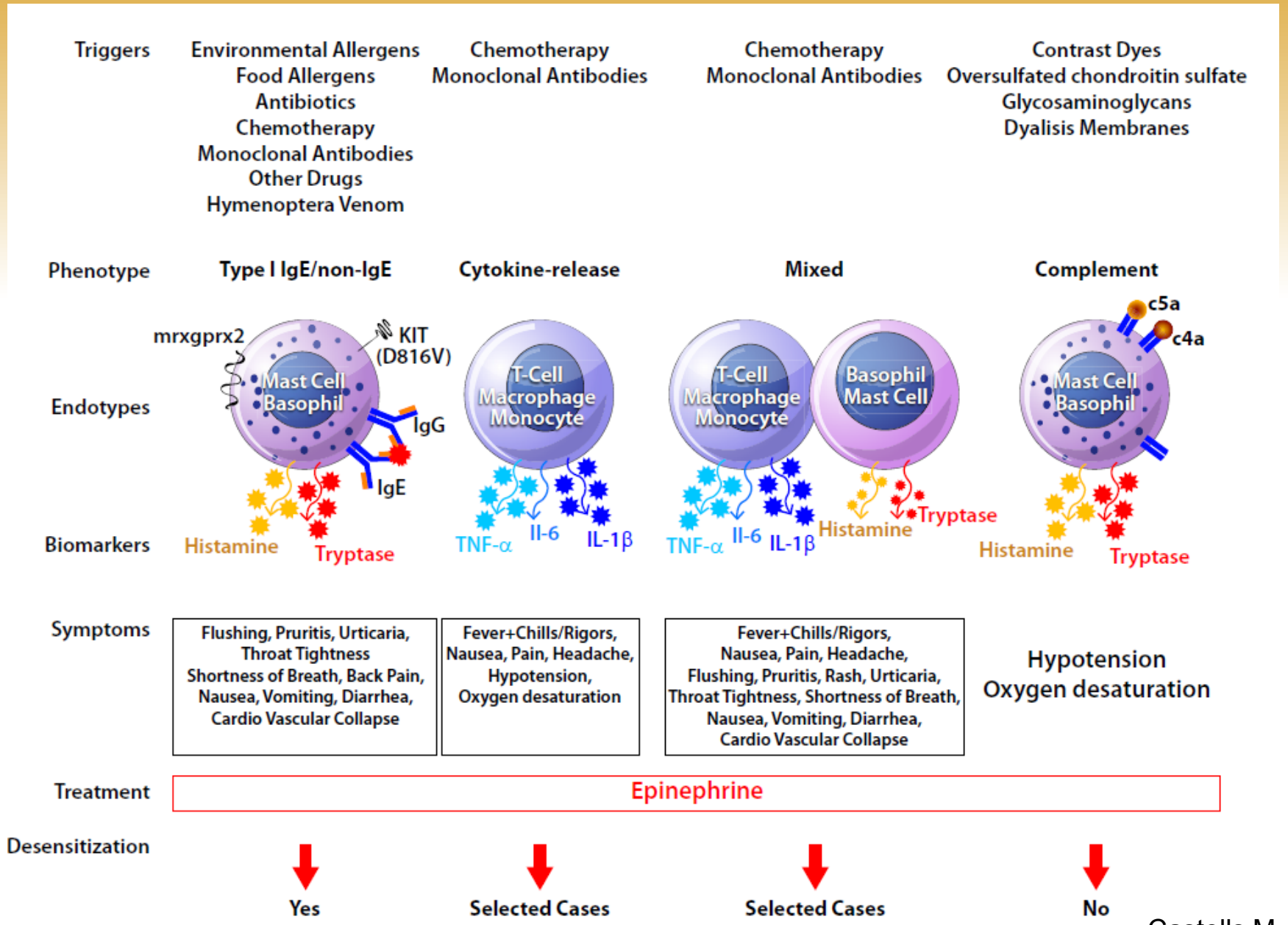
1. **Acute onset of illness with involvement of the skin, mucosal tissue, or both**
   AND AT LEAST ONE OF THE FOLLOWING
   - **a. Respiratory compromise**
   - **b. Reduced BP or associated symptoms of end-organ dysfunction**

2. **Two or more of the following that occur rapidly after exposure to a *likely* allergen for the patient**
   - **a. Involvement of the skin-mucosal tissue**
   - **b. Respiratory compromise**
   - **c. Reduced BP or associated symptoms**
   - **d. Gastrointestinal symptoms**

3. **Reduced BP after exposure to *known* allergen for the patient**
   - **a. Infants and children:**
     - **low systemic BP (age specific) or greater than 30% decrease in systolic BP (age specific)**
   - **b. Adults:**
     - **systolic BP less than 90 mm Hg or greater than 30% decrease in that person's baseline**

Sampson et al, *JACI* 2006

Pathways of Anaphylaxis



Castells M J *Allergy Clin Immunol* 2017

Differential Diagnosis of Anaphylaxis

Respiratory
- Severe asthma exacerbation
- Vocal cord dysfunction
- Pulmonary embolism

Cardiac
- Myocardial infarction
- Aortic stenosis with syncope

Gastrointestinal
- Food-induced anaphylaxis (unknown allergy)
- Delayed anaphylaxis-alpha-gal syndrome
- Food intoxication-e.g. scombroid poisoning

Neurologic
- Seizures

Endocrine
- Pheochromocytoma
- Carcinoid syndrome

Allergy/Immunologic
- Latex allergy
- Drug allergy
- Hereditary/Acquired angioedema

Psychiatric/Psychological
- Anxiety/Panic attack
- Globus hystericus
- Somatoform disorder

Other
- Clonal mast cell disease (mastocytosis, MMAS)
- Exercise-induced anaphylaxis
- Cholinergic urticaria and anaphylaxis
- Hereditary alpha tryptasemia syndrome

Anaphylaxis Endotypes

- IgE-mediated (mast cells and basophils)
- Non-IgE-mediated
  - FcγR (MCs, basophils, neutrophils, monocytes, macrophages)
  - C3a/C5a (MCs, basophils, macrophages)
  - MRGPRX2 (MCs, basophils, neutrophils)
  - Contact and coagulation systems (endothelial cells (EC)
  - TNF-α, IL-1β, IL-6-cytokine release rxn (MCs, monocytes, T cells, EC)
- Non-immunological
  - Contact and coagulation systems

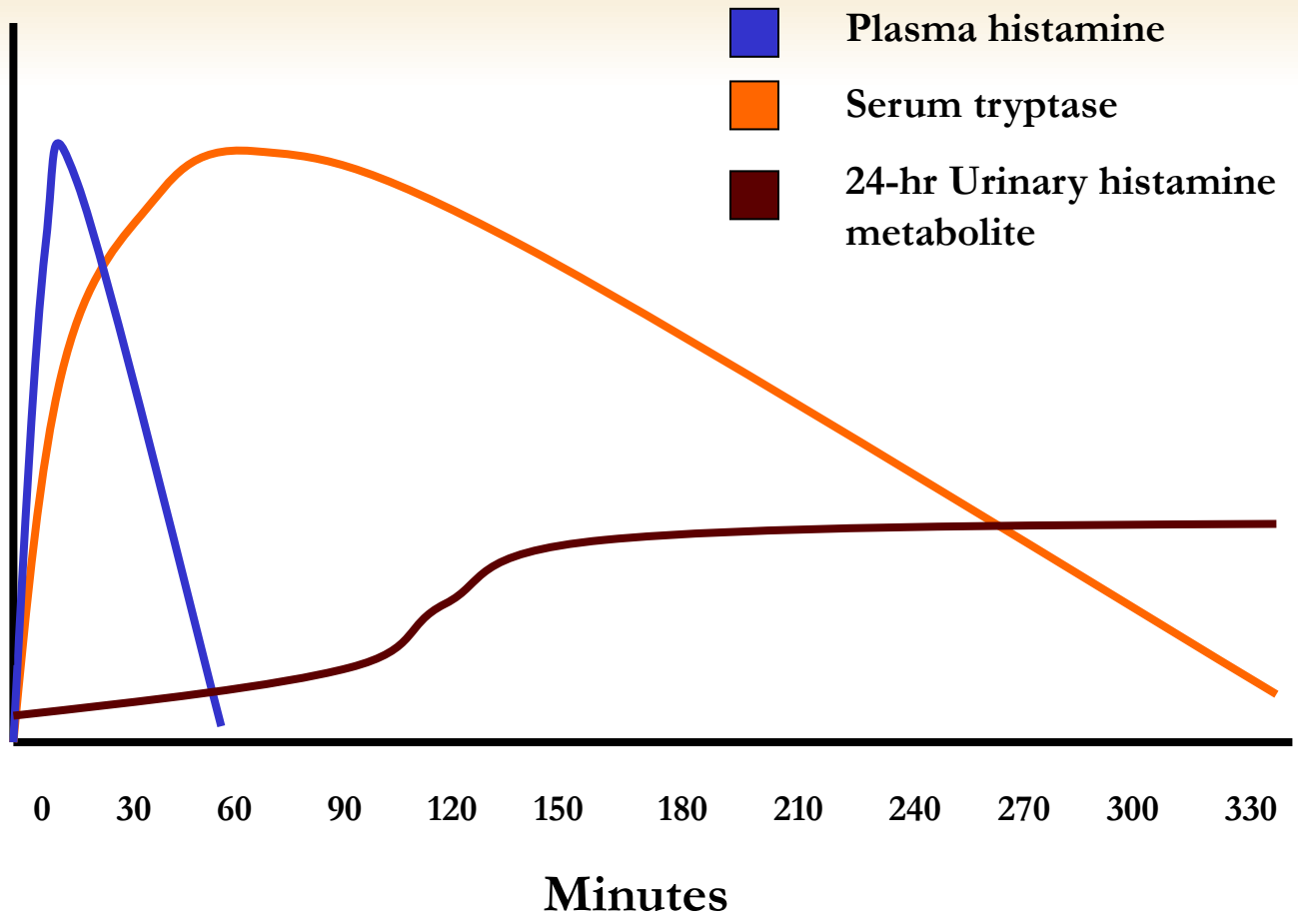
Galvan-Blasco et al *Curr Treat Options Allergy* 2022

Idiopathic Anaphylaxis

- Two categories
  - Generalized
  - Angioedema
- Occurrence
  - Frequent: 2 episodes/past 2 months or 6 episodes/past year
  - Infrequent: <6 episodes/past year
- Severity
  - Mild, moderate, severe

Greenberger P *Immunol Allergy Clin N Am* 2007

Markers of Anaphylaxis



Biomarkers beyond tryptase

- Histamine-plasma, 0-30 mins
- N-methyl histamine-urine, 0-24 hrs
- LTE4-urine, 0-24 hrs (Mayo)
- 9α,11β-PGF2-urine, 0-24 hrs (Mayo)
- IL-10, IL-6-serum, plasma
- Correlated with anaphylaxis (not commercially available)
  - PAF-plasma
  - PGD2-serum
  - Heparin-plasma
  - miRNAs

Lab tests and outcomes for probable MCAS

Laboratory parameter	Laboratory outcome	Probable indicator
Serum tryptase	Change from baseline ≥20% + 2.0 ng/mL[44]	Mast cell activation
Urine histamine metabolites	Elevated from baseline[42]	Mast cell activation
Urine 11βPGF2α	Elevated from baseline[42]	Mast cell activation
Urine prostaglandin D2	Elevated from baseline[44]	Possible mastocytosis, acetylsalicylic acid sensitivity
KIT D816V mutation	Positive[42]	Mastocytosis
Skin test/serum IgE levels	Positive	Allergen sensitivity
Alpha-gal	Positive	Alpha-gal sensitivity
Serum serotonin	>400 ng/mL[121]	Carcinoid syndrome[117]
24-hour urinary 5-HIAA	>15 mg per 24 hours[121]	Carcinoid syndrome[117]
Serum chromogranin A	>36.4 ng/mL[122]	Neuroendocrine tumor
Vasoactive intestinal peptide	>200 pg/mL[116]	Vasoactive intestinal peptide tumor[117]
Serum calcitonin	>8 pg/mL in women and >16 pg/mL in men[a,121]	Medullary carcinoma of the thyroid[117]
24-hour urinary fractioned catecholamines	Norepinephrine >1005 nmol/d[123] Epinephrine >191 nmol/d Dopamine >4571 nmol/d	Pheochromocytoma[117]
24-hour urine metanephrines	≥1.3 mg/24 h[123]	Pheochromocytoma[117]
Plasma fractionated metanephrines	Metanephrine ≥0.5 nmol/L[124] Normetanephrine ≥0.9 nmol/L	Pheochromocytoma[117]

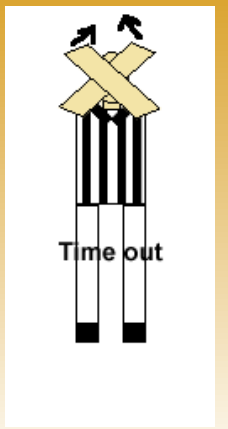
Carter et al *Ann Allergy Asthma Immunol* 2020

Case Report

- 23 yo female dx with MCAS, Ehrler's Danlos, dysautonomia, +Sjorgren's Abs, +Gad65, +TPO, HAE with nl C1q inhibitor

- ICU x3 months with recurrent severe episodes of angioedema of the tongue and abdominal distension
- On continuous Benadryl drip with boluses up to 600 mg/day, cont. epi drip and additional IM boluses
- Other meds-imatinib, IVIG, rituximab, cellcept, methotrexate, ruconest, tofacitinib, tranexamic acid, plasmapharesis
- No response to any therapy thus far
- Meds considering-bortezomib, ibrutinib, eculizumab

Question?



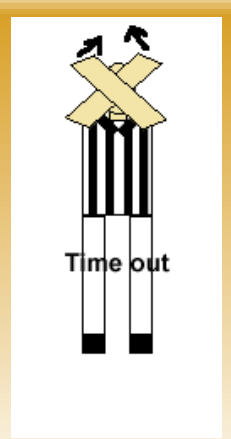
- What laboratory investigation(s) are missing?

1. BP and pulse ox during an event
2. Baseline serum tryptase
3. Visualization of the cords with an event
4. Factor XII antibodies
5. Serum tryptase or 24-hour N-methyl histamine with an event

MCAS?

Case Report

- 20 yo female with worsening angioedema that started in 2016
- Triggers-foods (SPTs neg), environmental→ER visits treated with antihistamines and epinephrine
- Gastroparesis & bone pain →DX with a functional disorder →symptoms suggestive of anaphylaxis with tongue swelling →intubated & G-tube placement. DVTs due to central lines
- DX-HAE-nl C1 inhibitor, C1esterase nl →C1 esterase inhibitor-non-efficacious
- DX-lymphocyte variant HES TX with Nucala, CEL TX with Gleevec
- Dr. Afrin- DX with MCAS, mildly↑ N-methyl histamine & plasma heparin, anti-factor Xa, tryptase nl, anti-IgE Abs neg
- GI BX- ↑MCs duo 38, gastric 26, terminal ileum 38, cecum 39/hpf, respectively & ↑ eos. Highest peripheral eos 8.4%. DX ISM →BM BX neg
- Meds-IV Benadryl, OCS, famotidine, prn epi



Case Report, cont.

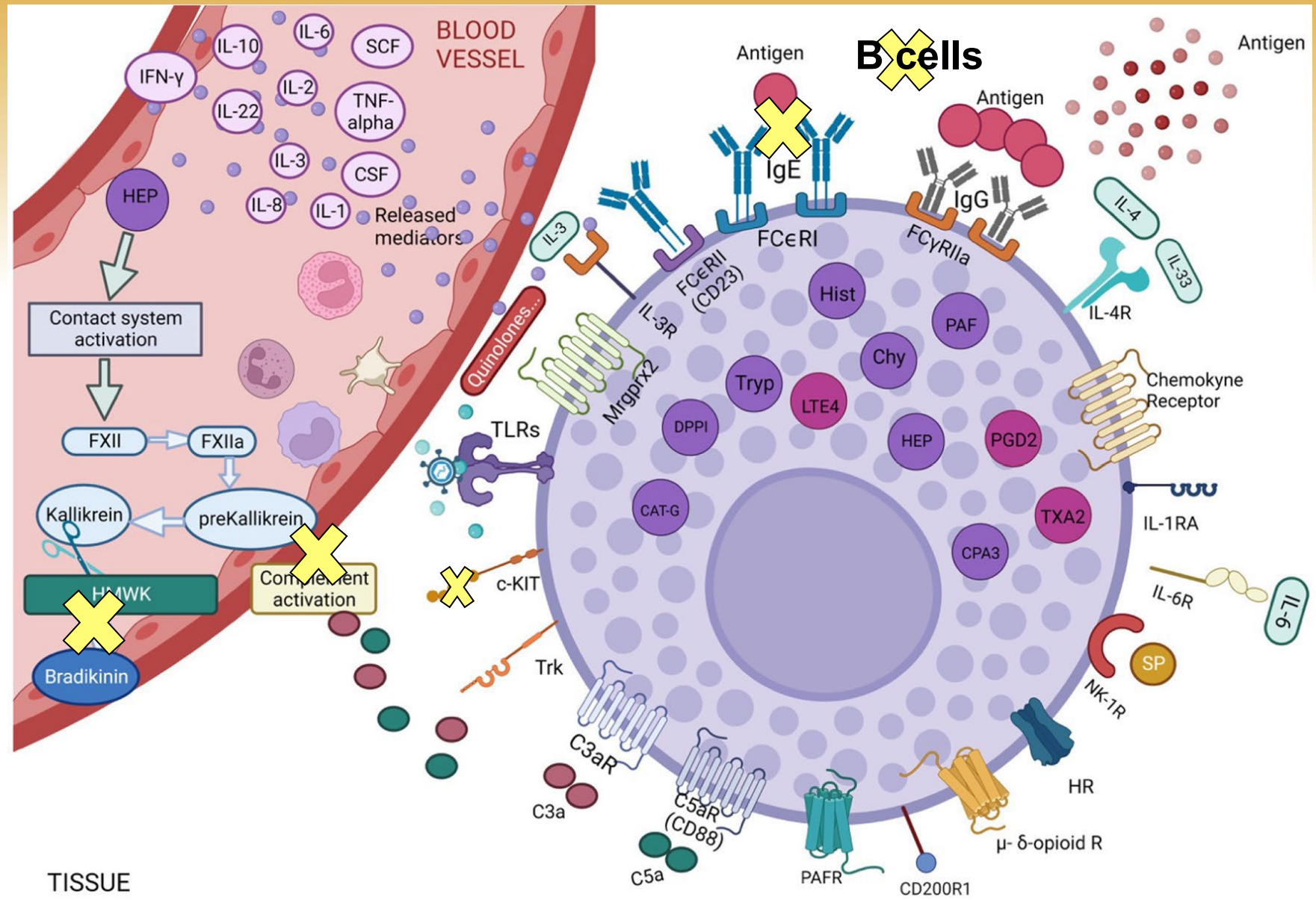
While hospitalized:
Anaphylaxis every 1-2 days
Complains of throat tightness, VCD not ruled out
Oxygen sat 98-100% on RA
No wheezing, hives, flushing
No hypotension
No event serum tryptase

MCAS?

DX: lymphangioma

Something Else

JAK2
T cells



Galvan-Blasco et al *Curr Treat Options Allergy* 2022

Mast Cell Biology Section

QUESTIONS?