Mast Cell Disease: Work up & Treatment

Erin Kolb, MSN, FNP-C

ASAP 2026 Education Summit | Round Rock, TX

Mast Cell Disease: Work up & Treatment

Objectives:

1. Recognize the clinical features and diagnostic criteria of clonal and non-clonal mast cell disorders

1. Select and interpret appropriate laboratory, genetic, and pathologic studies used in the evaluation of suspected mast cell disease

1. Implement individualized pharmacologic and non-pharmacologic treatment strategies based on disease subtype, symptom burden, and plausible underlying mechanisms

2. Identify potential comorbidities and some underlying drivers of mast cell activation to help individualize treatment

Mast Cell Disease: Work up & Treatment

Unofficial Objectives:

1. **Feel less dread** - When you see *“concern for mast cell disorder”* on a referral, or a patient says, *“I think I have MCAS”*

2. **Not break a sweat over the workup -** Know what basic testing to order and when additional diagnostic studies may be needed

3. **Totally rock your referrals -** Recognize when to involve other specialties and what histopathologic & molecular studies to request for suspected systemic mastocytosis

4. **Leave with confidence -** Have strong evidence-based foundation & knowledge of trusted resources to turn to when you want to know more

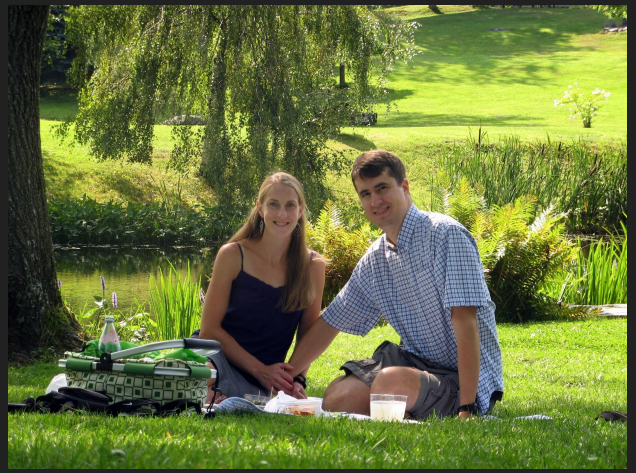
is

mast cell disease

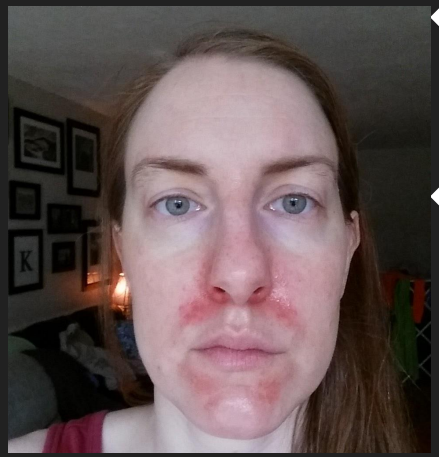
such a *passion* of mine?

My MCAS Story

Summer 2012



5 years of progressive MCAS



- **Daily symptoms**
  Felt triggered by “everything”
- **Frequent systemic flares**
  Repeated anaphylaxis
- **Weak & exhausted**
  Family helped care for my boys
- **Depressed & hopeless**

And then…

Combination of evidence-based treatment approaches

Symptoms gradually became less severe & less frequent

Neural retraining program seemed to provide a “reset” of my neuroimmune axis

MCAS & autonomic nervous system “calmed” dramatically
& developed systems to help “keep things in check”

Ongoing pharmacologic therapy & lifestyle strategies

Fall 2017

First day outside

Without mask or sun umbrella

Surprising friends & family

Raking leaves! Major milestone, as Fall had been time of increased anaphylaxis

Back to FNP practice!

3/2020- hired to specialize in mast cell disorders

Full circle:

from patient to colleague

Mast Cell Disease: Work up & Treatment

Evolution of Mast Cell Terminology

Older terminology

MCAD (Mast Cell Activation Disorder):

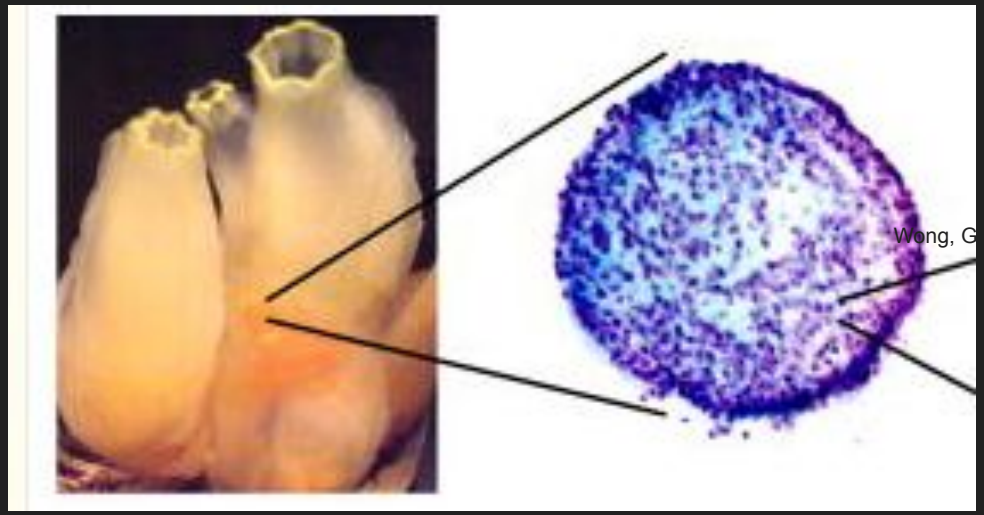
- Earlier publications and practice
- You will still encounter this term

Current terminology

MCD (Mast Cell Disease):

- **C**urrent preferred umbrella term by mast cell experts and organizations
- Includes:
  - Mastocytosis (cutaneous and systemic variants)
  - Mast Cell Activation Syndrome (MCAS)

Ancient Origin of Mast Cells

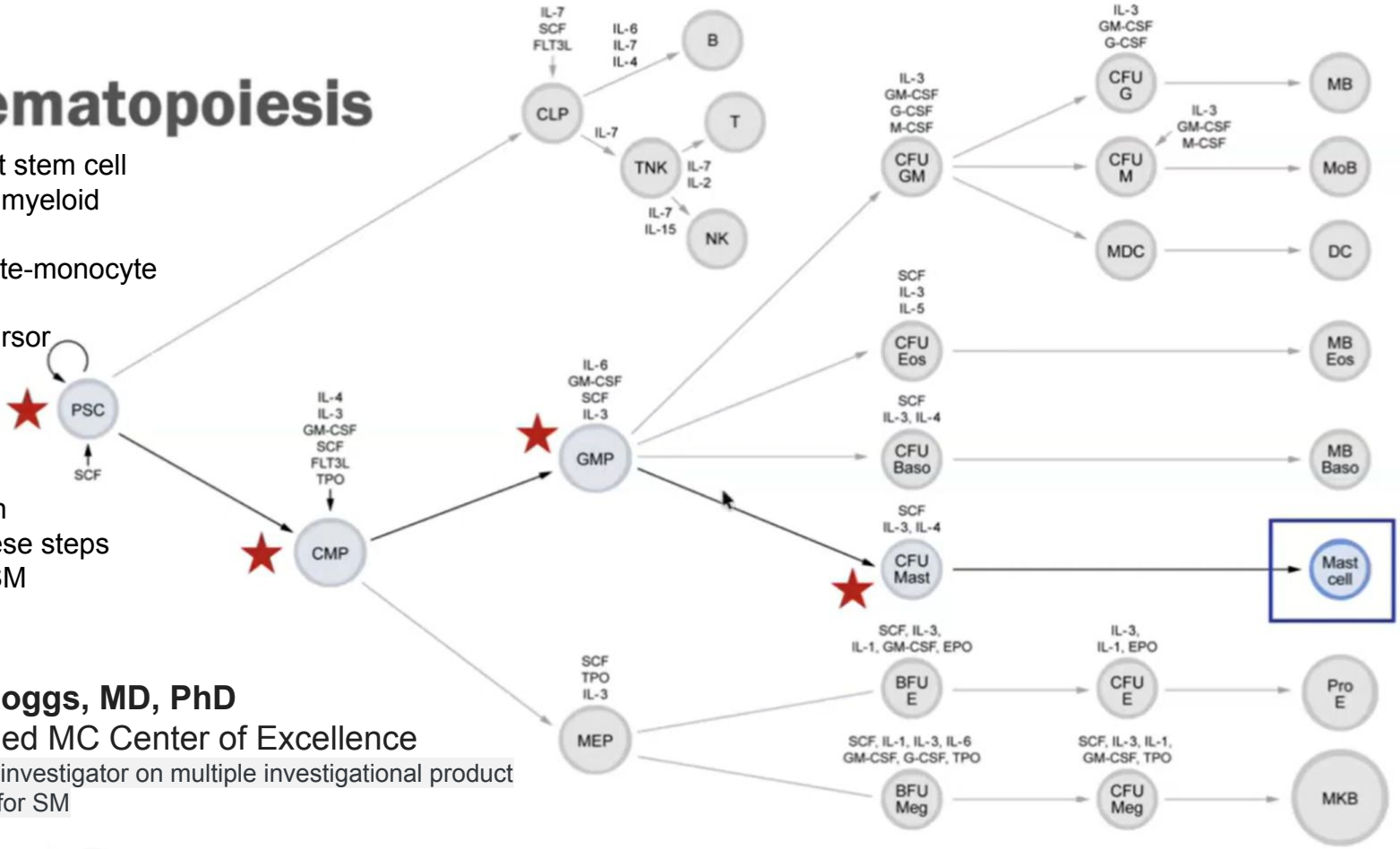


Sea squirts >500 million yrs ago - *Well before* adaptive immunity

Active roles in **Innate & Adaptive** immunity

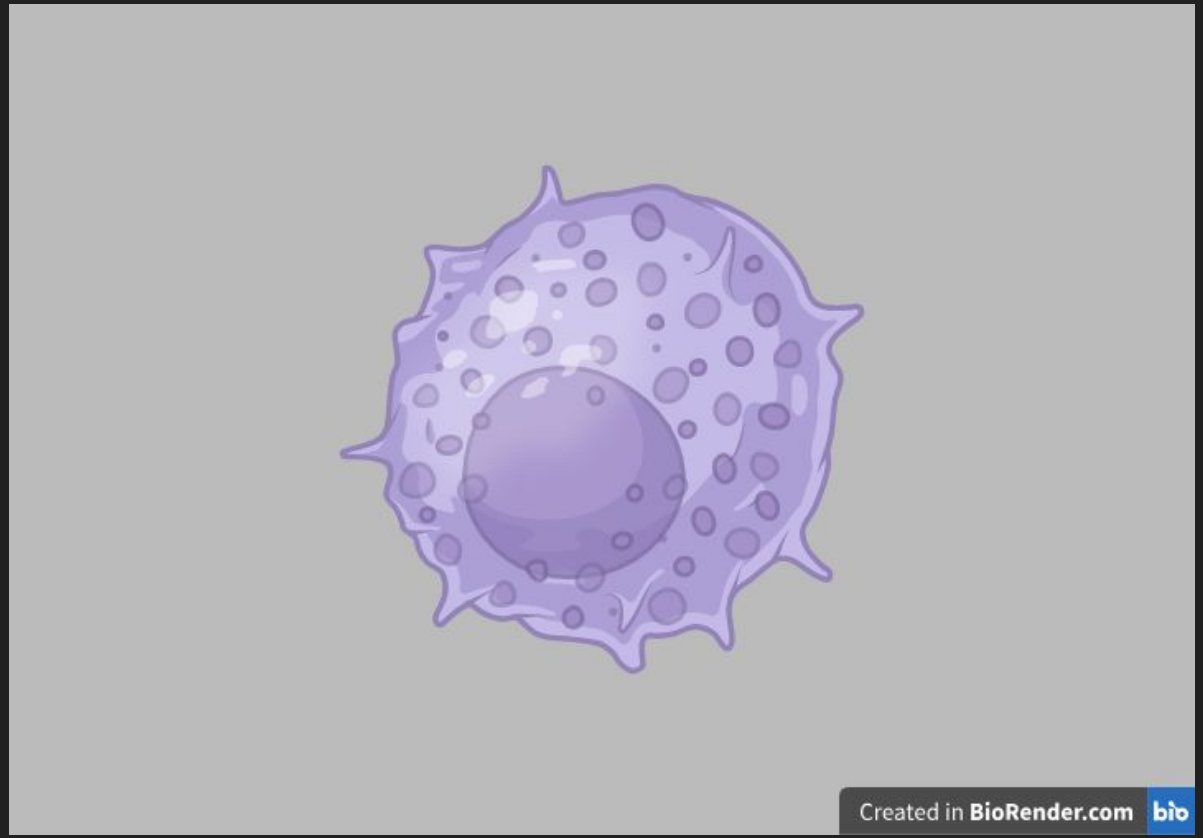
Wong, G et al. 2014. Ancient origin of mast cells. *Biochemical and biophysical research communications*, *451*(2), 314–318.

Bone Marrow

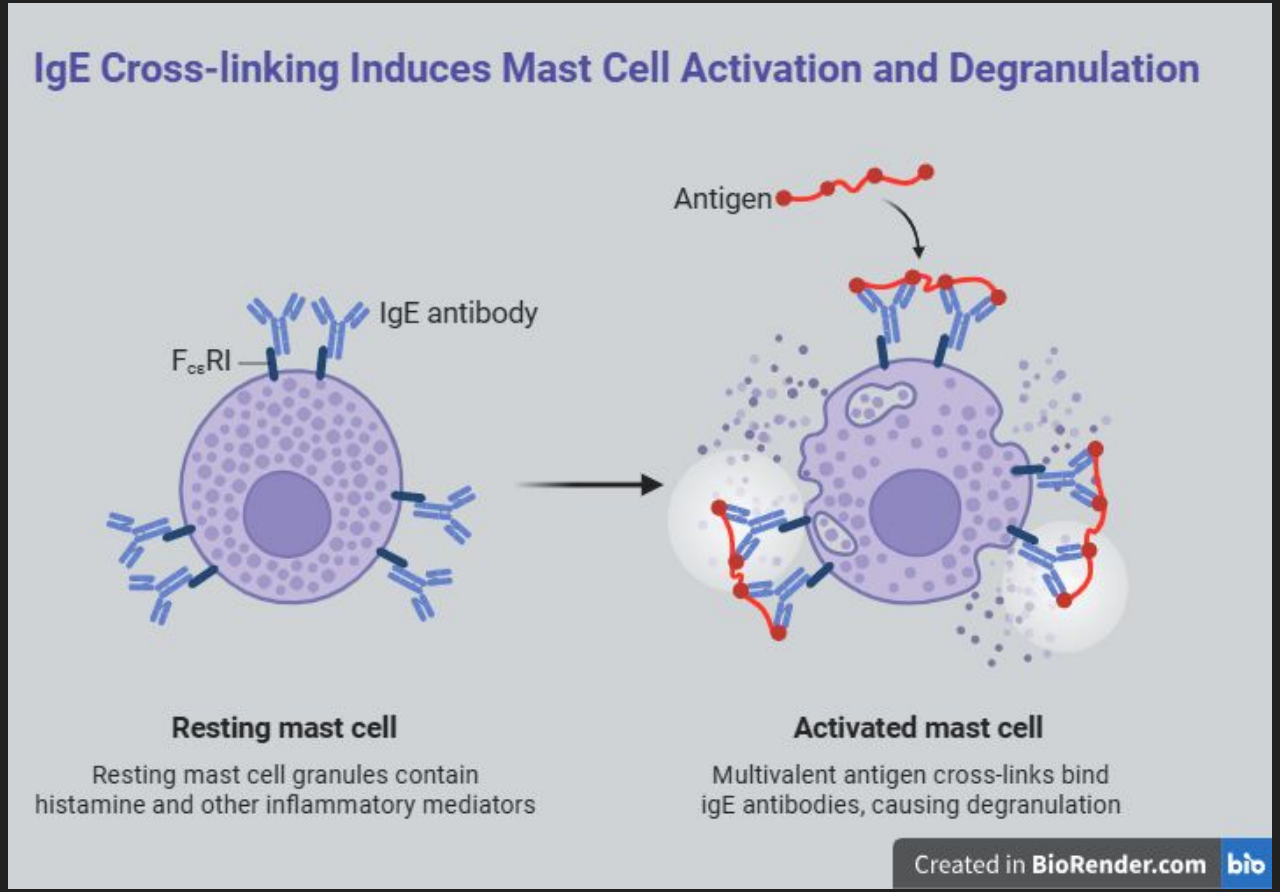


Nathan Boggs, MD, PhD
Walter Reed MC Center of Excellence
site principal investigator on multiple investigational product clinical trials for SM

What do we know about mast cells?

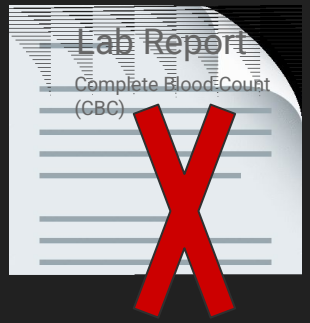


The “Classic” Mast Cell

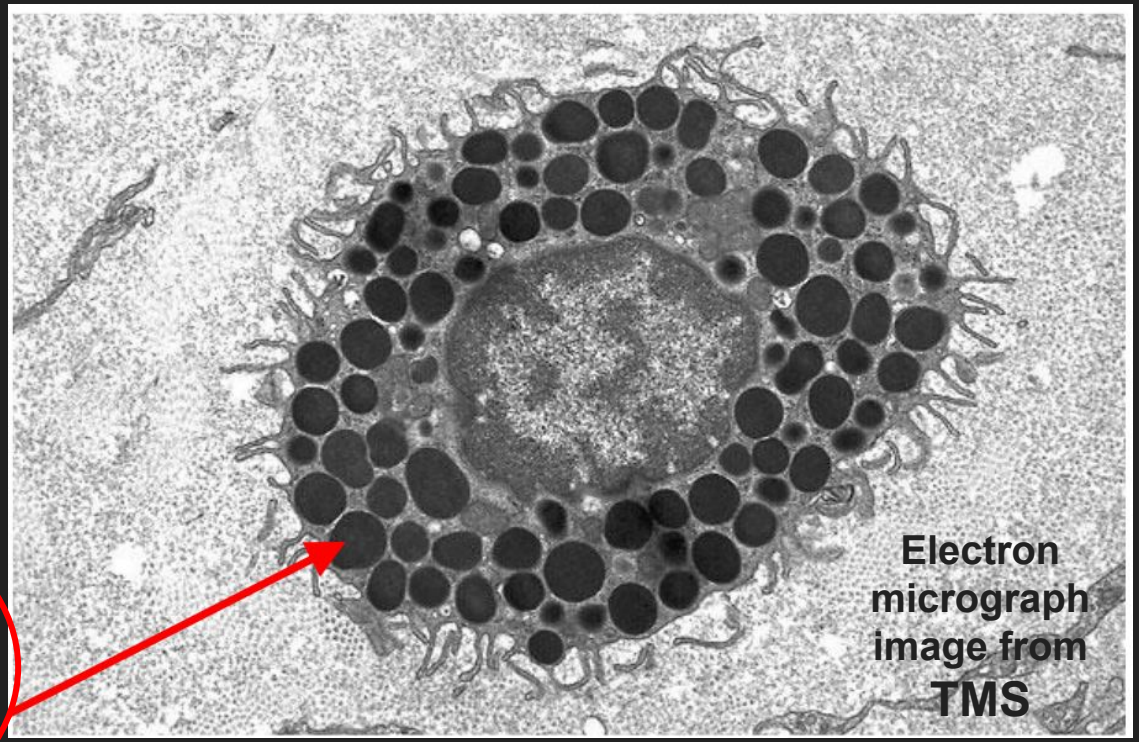


Mast Cells Mature in our Tissues

Not in our blood
like other WBCs



MC Mediators
-stored in membrane bound sacs, called **granules**
-such as **tryptase**, **histamine** & **heparin**



Mast Cells: Hero or Villain?

Protective

Wound healing & tissue repair:
all stages

Acute Inflammation:
immune cell recruitment

Host defense:
parasites, venoms

Pathologic

Allergic:
anaphylaxis, asthma, CSU, CRSwNP, EOE

Chronic Inflammation:
immune dysregulation, fibrosis

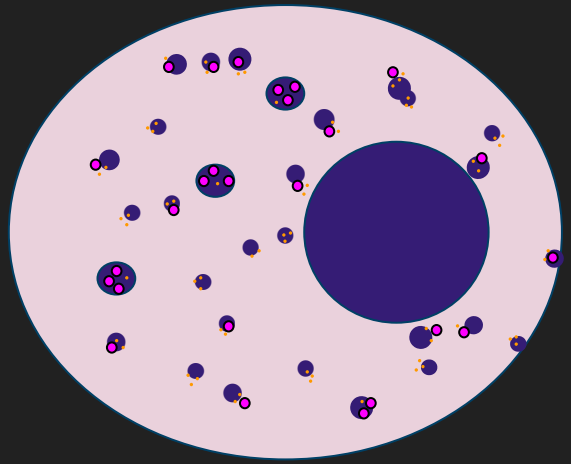
Myeloid neoplasms:
Mastocytosis, other myeloid neoplasms

Much remains to be learned!

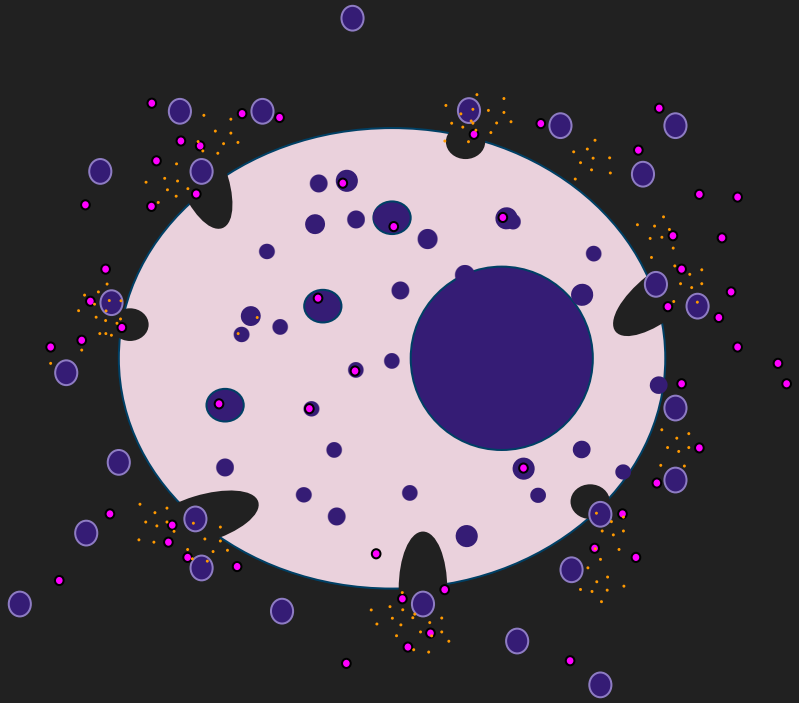
Evolving research & ongoing investigation

Mast Cell Activation

Resting, non-activated mast cell



Activated & degranulating mast cell



Mast Cell Mediators

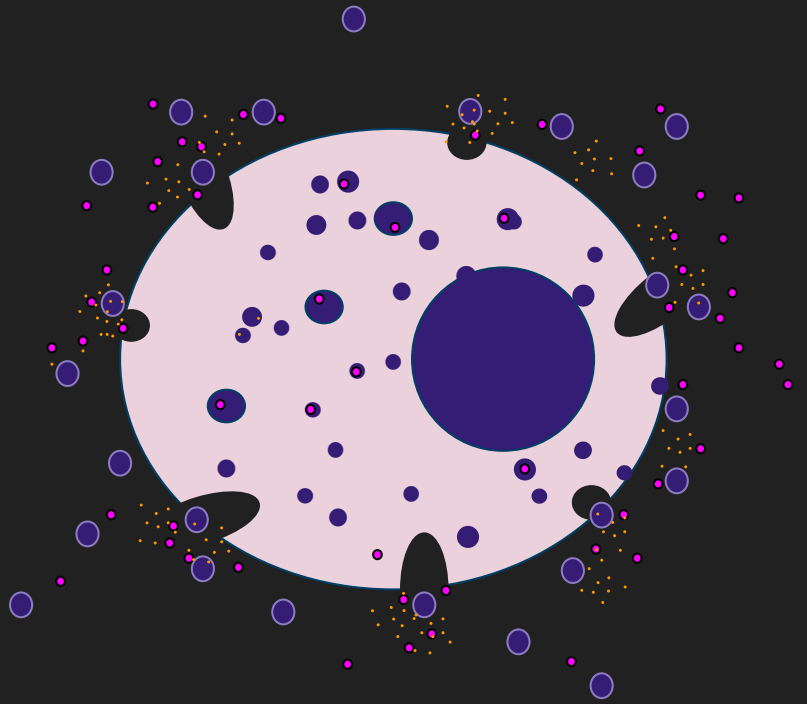
*Not a complete list

Immediate release:
histamine, tryptase, chymase, heparin

De novo synthesis lipid-derived:
prostaglandins, leukotrienes

Cytokines:
TNFα, IL-3, IL-4, IL-5, IL-6, IL-13

Chemokines:
numerous



Castells M, Butterfield J. *J Allergy Clin Immunol Pract* 2019;7(4):1097-1106.
Mukai K, Tsai M, Saito H, Galli SJ. *Immunological Reviews*. 2018;282(1):121-150.

Symptoms of Mast Cell Activation

Neurological
Headache, brain fog, anxiety, depression

Airway / Lungs
throat itching & swelling, wheezing, short of breath

Gastrointestinal
heartburn, nausea, cramps/gas/bloating, ABD pain, diarrhea

Skin
Flushing, itching, rashes, hives, angioedema

Naso-Ocular
itchy eyes, congestion, post nasal drip

Cardiovascular
palpitations, low blood pressure, chest pain, lightheadedness, fainting

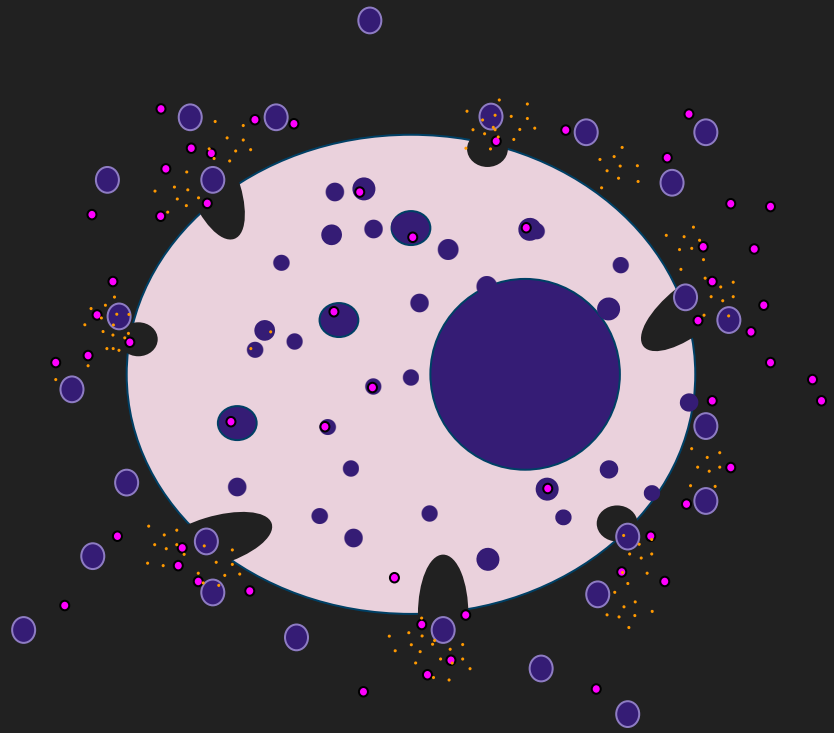
Bladder / Reproductive
bladder pain syndrome (ICS), uterine cramping & bleeding, vaginal irritation/burning

Musculoskeletal
Joint pain, bone pain, muscle aches, osteopenia/osteoporosis in SM

***Heterogeneous Symptoms & Numerous Differentials!**

Possible Triggers of MC Activation

Environmental allergens
Stress
Airborne fragrance/chemicals/odors
Foods
Alcohol
Medications
Sunlight
Heat
Cold
Pressure or Vibration
Exercise
Venom (bee, wasp)



Baran J, et al. *Cells* 2023;12(8):1187.

Mast cell activation (MCA)

Wide variety of receptors on MCs

This image directly from Komi et al., 2018

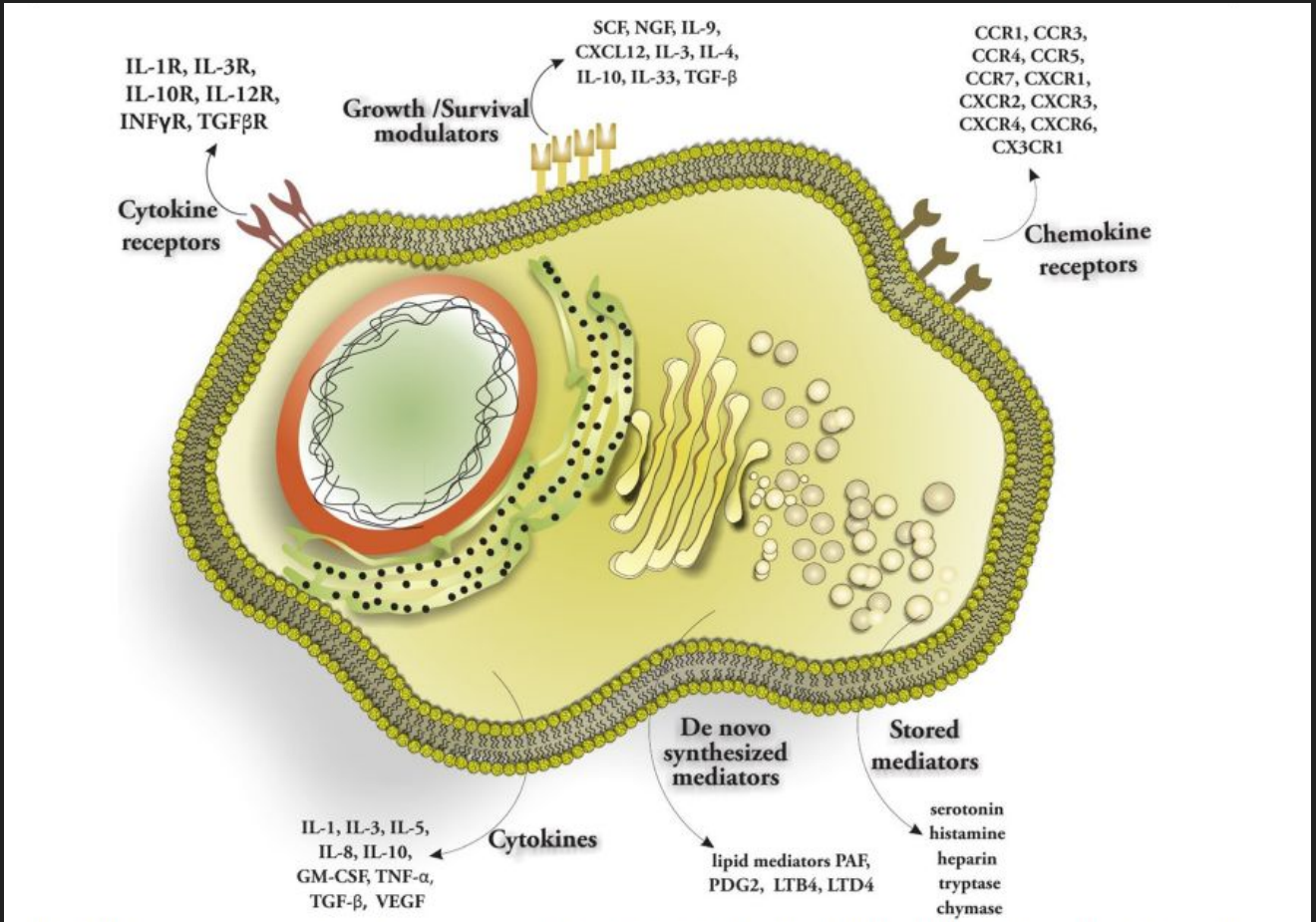


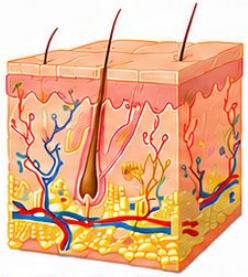
Fig. 2 MCs express a variety of chemokine and cytokine receptors on their surface. They release mediators including cytokines, de novo synthesized and stored mediators. MCs rapidly respond to environmental stimuli such as IgE-bound allergen and interact with other immune/non-immune cells

Komi DEA, Rambasek T, Wöhrl S. Mastocytosis: from a Molecular Point of View. Clinic Rev Allerg Immunol. 2018;54(3):397-411. doi:10.1007/s12016-017-8619-2

Features Associated with Aberrant Release of MC Mediators

Two Levels of Organ Involvement

Skin



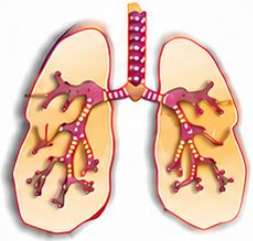
Pruritus: Histamine, PAF

Flushing: PGD_2

Urticaria: Histamine, PAF, LTC_4

Blistering: IL-6, Tryptase, PGD_2, PAF

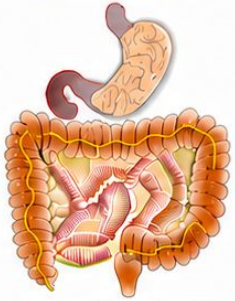
Lungs



Bronchoconstriction: Histamine, PGD_2, PAF, LTC_4, LTD_4, Endothelin

Mucous and edema: Histamine, PGD_2, PAF, LTC_4, Proteases

Gastrointestinal Tract



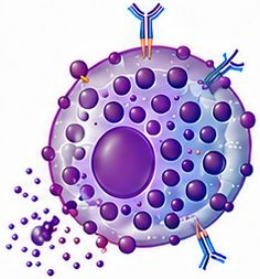
Increased gastric acid: Histamine

Intestinal cramping: Histamine, PAF, LTC_4

Bone

Osteoporosis: Heparin, Tryptase

Mast Cell Activation



Release of Mediators

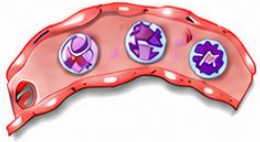
Tissue remodeling & fibrosis

TGF-β

Coagulation & vascular effects

Heparin

Hypotension and Swelling

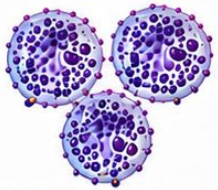


Histamine, PAF, PGD_2, LTC_4, LTD_4, LTE_4, Endothelin

Recruitment and activation of other immune cells

Numerous chemokines, cytokines, lipid mediators, preformed granules

Mast cell proliferation



SCF (KIT D816V mutation "locks" KIT receptor "On" without SCF)

IL-3, IL-4, IL-6, IL-10, more

Adapted from Valent P, et al. Clin Rev Allerg Immunol. 2018; 54:397–411. *Supplemented with Chia SL, et al. Immunological Reviews. 2023;315(1):31-53.*

When is a Disorder Involving Mast Cell Activation Labelled as Mast Cell Disease?

2 Main Categories

CLONAL

Cutaneous Mastocytosis (CM)
Systemic Mastocytosis (CM)

Proliferation and **accumulation** of long-lived, **clonal mast cells**

Well-defined diagnostic criteria

Primary disease

NON-CLONAL

Mast Cell Activation Syndrome (MCAS)

Inappropriate, episodic MCA symptoms in **≥2 organ systems** (e.g., skin + CV, GI + resp)

Debated dx criteria (“Consensus 1” vs. “2”)

Often **secondary**, sometimes **idiopathic**

Types of Mast Cell Disease/Disorders

1. Clonal/Monoclonal or Primary

- cutaneous mastocytosis (CM)
- systemic mastocytosis (SM)
  - -ISM, BMM, SSM, ASM
- monoclonal mast cell activation syndrome (MMAS)

2. Non-clonal

- secondary mast cell activation syndrome (2°MCAS)

3. Idiopathic

- idiopathic mast cell activation syndrome (iMCAS)

Special Factor:
Non-Clonal Genetic Trait

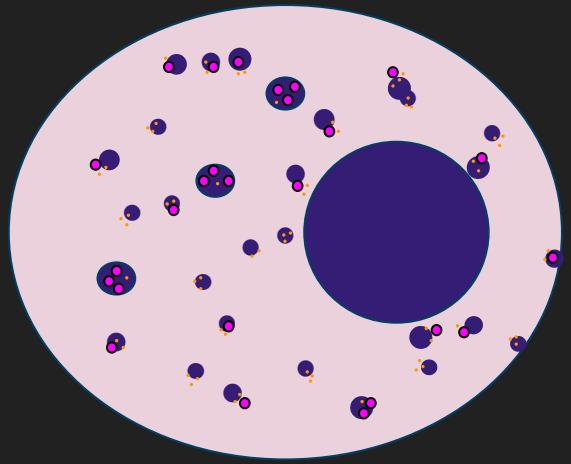
- hereditary alpha-tryptasemia (H∝T or HaT)

-NOT a disease/disorder on its own!

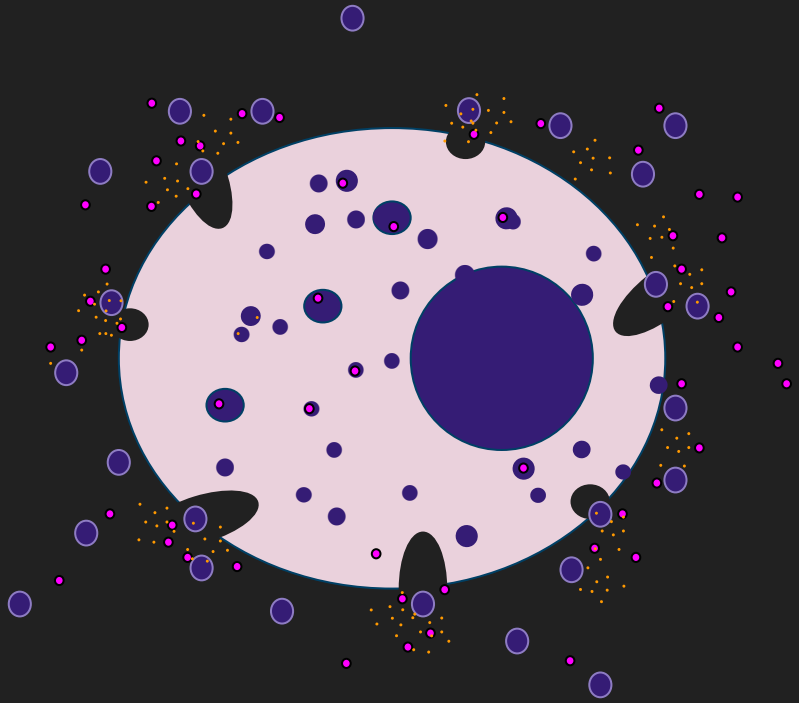
~6% people are born with HaT
& most don't have extra symptoms

Understanding Lab Testing For Mast Cell Disease

Resting, non-activated mast cell



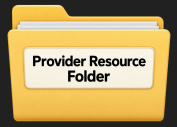
Activated & degranulating mast cell



Practical Tool!

Lab Testing For Mast Cell Disease

Current **testing codes** for most major laboratories end of the slide presentation



Lab Testing For Mast Cell Disease

Tryptase

Normal level ≤ 11-11.4

- **Basal serum tryptase (BST)**
  - -No severe symptoms/anaphylaxis in 2d
- **Acute measurement**
  - -1-4hrs after anaphylaxis/severe mast cell activation (MCA)
  - -1.2X + 2ng/ml = severe MCA

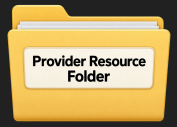
Example of a significant rise: patient with BST = 5

1.2 x 5 + 2 = 8

8 would indicate severe MCA for this patient

Gulen T. *Curr Allergy Asthma Rep* 2024;24(2):39-51.

Butterfield JH. *J Allergy Clin Immunol Pract* 2023;11(8):2542-6.

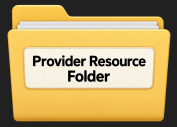


Lab Testing For Mast Cell Disease

Urine Markers

- **N-methylhistamine (NMH)**
- **Prostaglandin D2 (PGD2)**
- **Prostaglandin F2 (PGF2)** aka 2,3-Dinor 11 Beta prostaglandin F2 alpha
- **Leukotriene E4 (LTE4)**

Butterfield JH. *J Allergy Clin Immunol Pract* 2023;11(8):2542-6.



Lab Testing For Mast Cell Disease

Additional diagnostic testing discussed in upcoming slides

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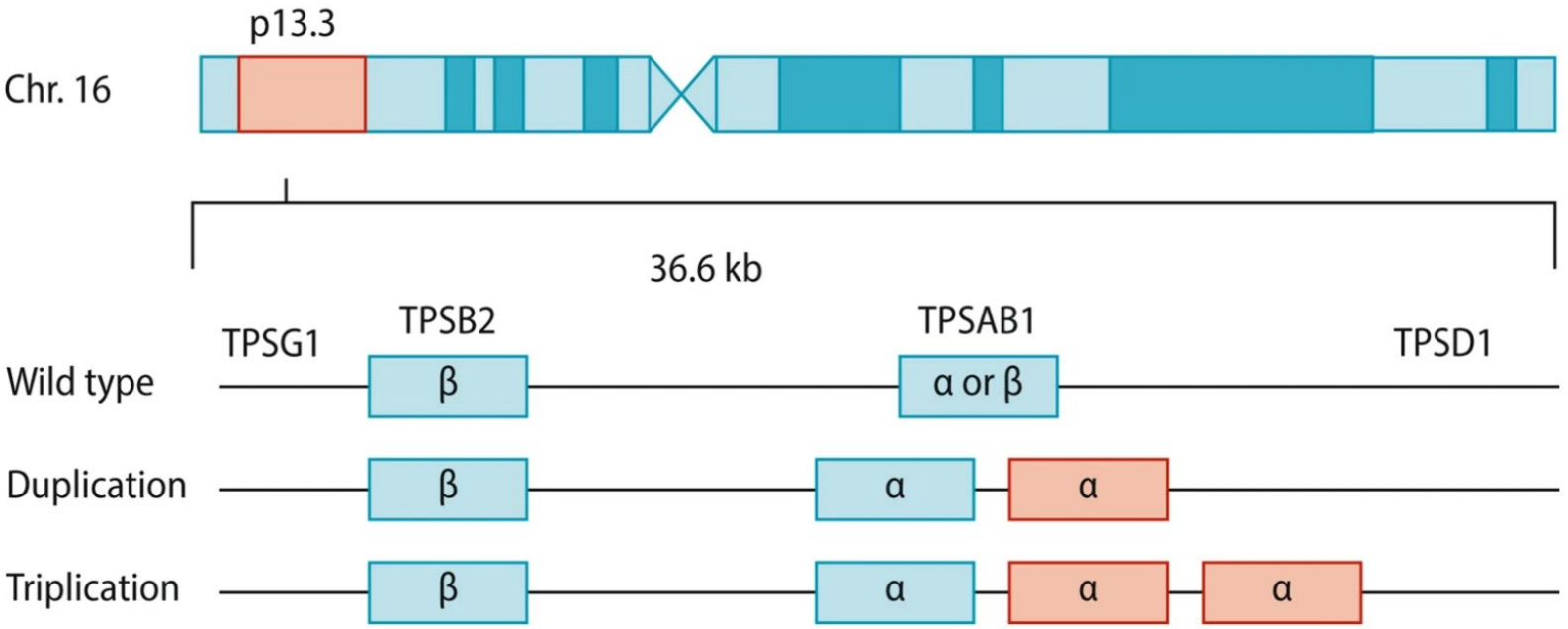
~6% people are born with HaT
& most don't have extra symptoms

Gulen T. *Curr Allergy Asthma Rep* 2024;24(2):39-51.

First described by Lyons et al. (2016) [40]
Copy number variation of the alpha-tryptase allele **TPSAB1**

5 % prevalence, autosomal dominant

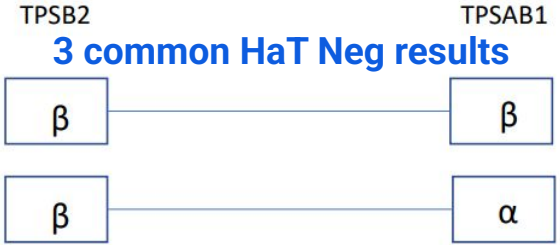


Association with idiopathic anaphylaxis, hymenoptera venom allergy, and systemic mastocytosis.

Brockow K, Franz TM, Saak M, et al. Only specific combinations of findings indicate mastocytosis, hereditary α-tryptasemia, histamine intolerance, or mast cell activation syndrome. Allergo J Int. 2026;35(4):101-108. doi:10.1007/s40629-026-00373-z

NORMAL RESULT: Alpha-tryptase copy number 2; beta-tryptase copy number 2

NORMAL RESULT: Alpha-tryptase copy number 1; beta-tryptase copy number 3



NORMAL RESULT: Alpha-tryptase copy number 0; beta-tryptase copy number 4

Provider Resource Folder

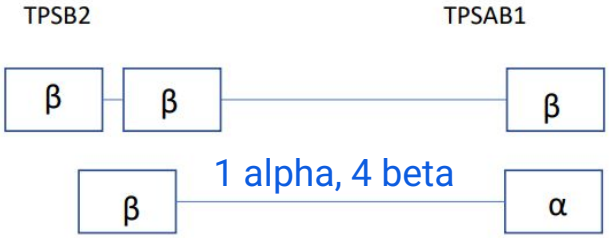
Hereditary alpha-tryptasemia (H∝T or HaT)

NORMAL Results:

No extra copies of TPSAB1

HaT negative

NORMAL RESULT: Alpha-tryptase copy number 1; beta-tryptase copy number 4. Although this genotype has a duplication, it is a duplication of the beta-tryptase which does not cause hereditary alpha tryptasemia.



Testing also available via ARUP

GENE BY GENE

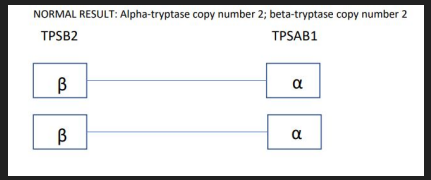
Hereditary alpha-tryptasemia (H∝T or HaT)

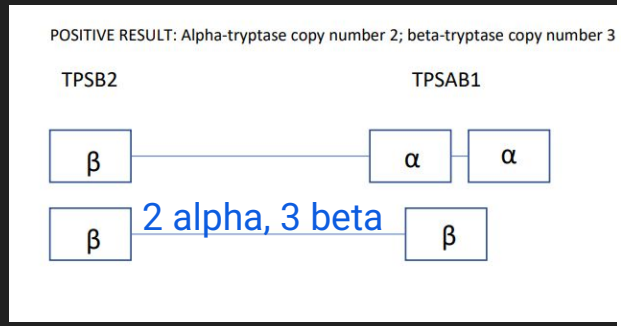
ABNORMAL Results:

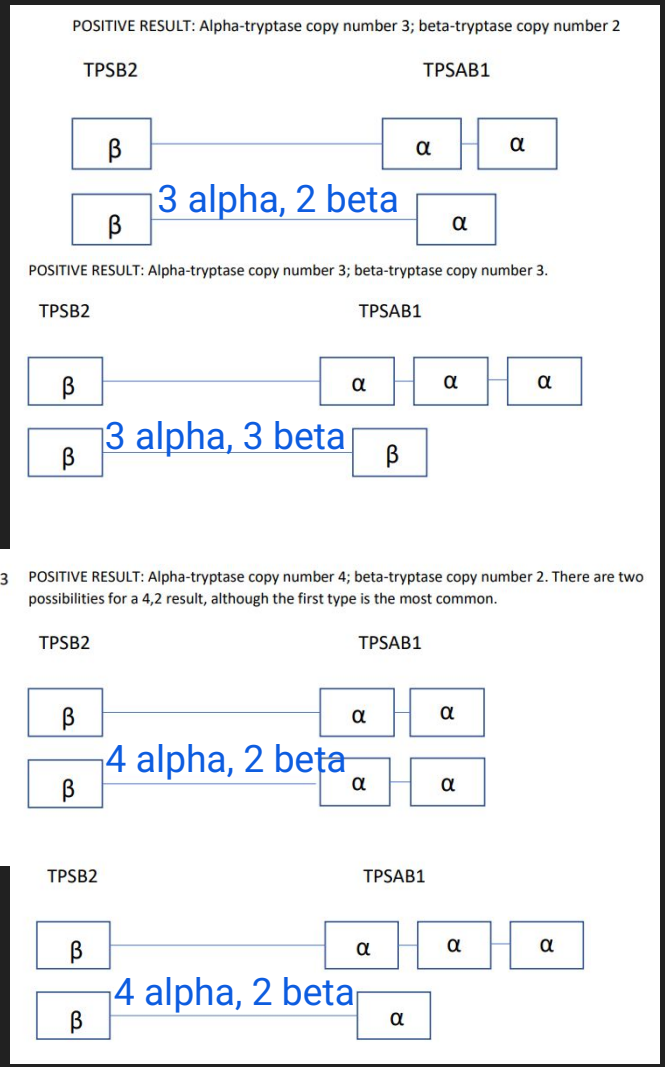
Extra copies of TPSAB1

HaT postive

Reminder negative/normal: 2 alpha, 2 beta







Testing also available via ARUP

Hereditary alpha-tryptasemia (H∝T or HaT)

Genetic Trait That Alters Baseline Tryptase Level

NOT a disease/disorder on its own!
Born with **Extra** TPSAB1 gene(s) encoding for ∝ tryptase

- - 5-6% gen population "HaT"
only ~⅓ with extra MCA symptoms "HaT + secondary MCAS"

- BST ≥ 8

-Tryptase rise/range larger 1.685X = severe MCA, anaphylaxis

-prior studies 12-18% SM have HaT (but may be closer to gen pop*)

Shin H, Lyons J. *Curr Allergy Asthma Reports* 2024;24:199-209. Valent P, et al. *J Allergy Clin Immunol Pract* 2022;10(8):1999-2012.
Mateja A, et al. *J Allergy Clin Immunol* 2022;149:1010-17.
*McMurray JC, Pacheco CS, Schornack BJ, et al. *Blood*. 2024;144(4):408-419.

Hereditary alpha-tryptasemia (H∝T or HaT)

Normal serum tryptase: ≤ 11.0-11.4

If tryptase is higher, then must determine cause!

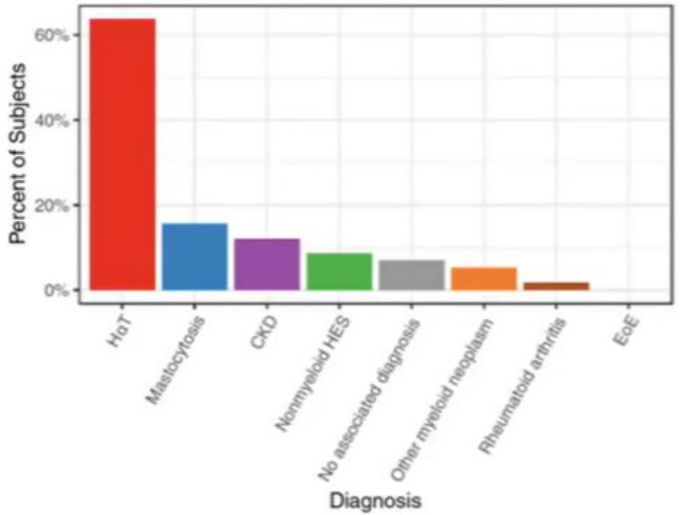
- HaT
- Advanced kidney disease
- Systemic mastocytosis (SM)
- Other myeloid neoplasms

Brockow K, Franz TM, Saak M, et al. *Allergo J Int*. 2026;35(4):101-108.

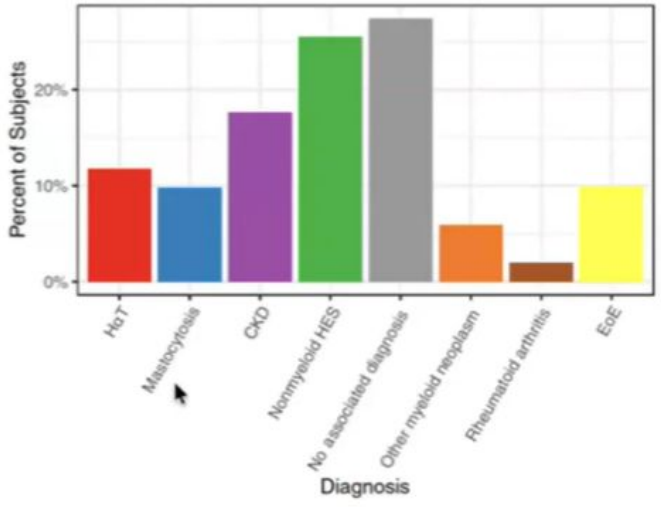
Waters AM, Park HJ, Weskamp AL, et al. *JACI: In Practice*. 2022;10(9):2424-2435.e5.

Etiologies of elevated and high-normal BST

BST ≥ 11.5 ng/mL



BST 7.5 ng/mL to 11.4 ng/mL



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- secondary mast cell activation syndrome (2°MCAS)

3. Idiopathic

- idiopathic mast cell activation syndrome (iMCAS)

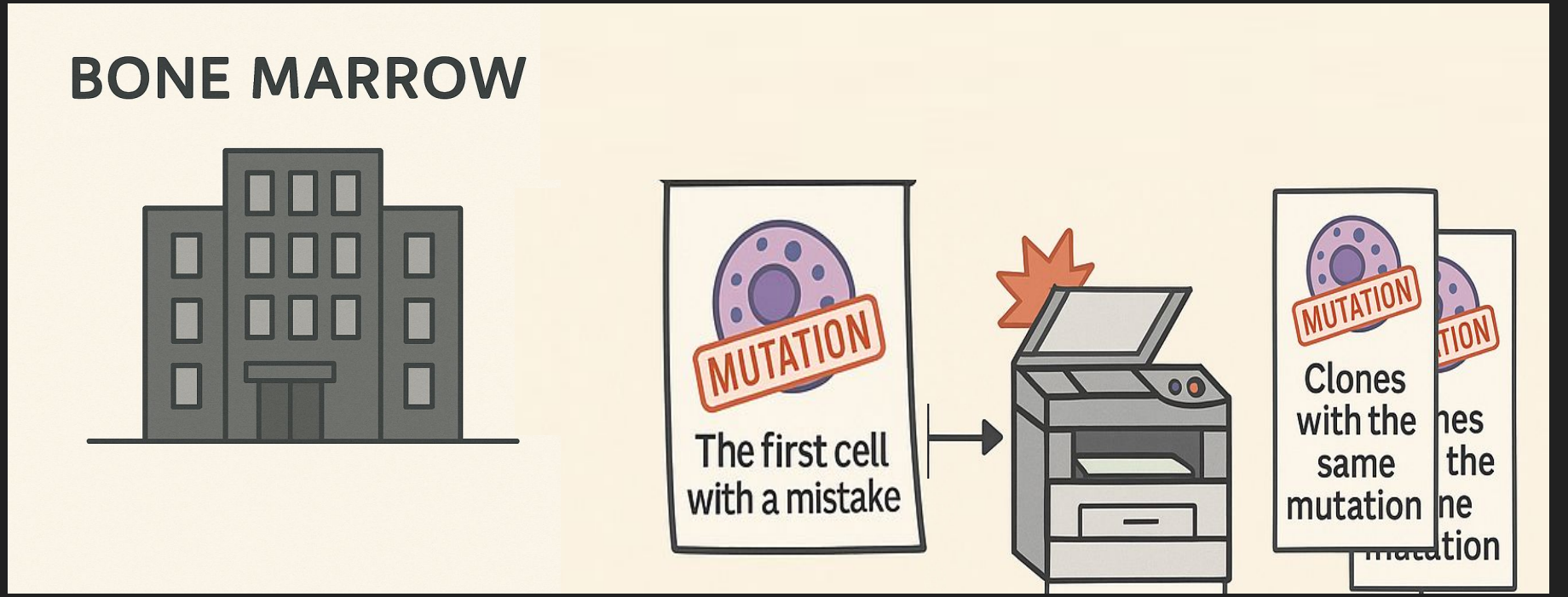
Special Factor: Non-Clonal Genetic Trait

- hereditary alpha-tryptasemia (H∝T or HaT)

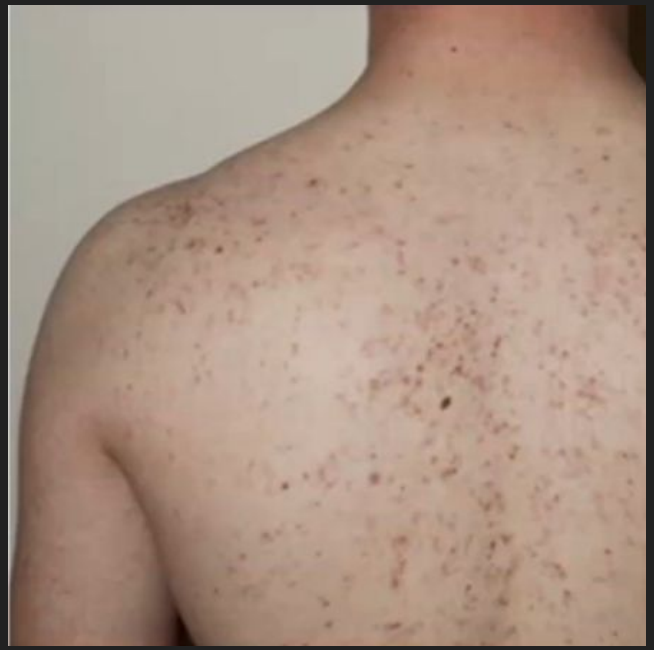
-NOT a disease/disorder on its own!

~6% people are born with HaT
& most don't have extra symptoms

In Mastocytosis, a CLONAL disorder,
the bone marrow acts like a factory or office
making bad copies



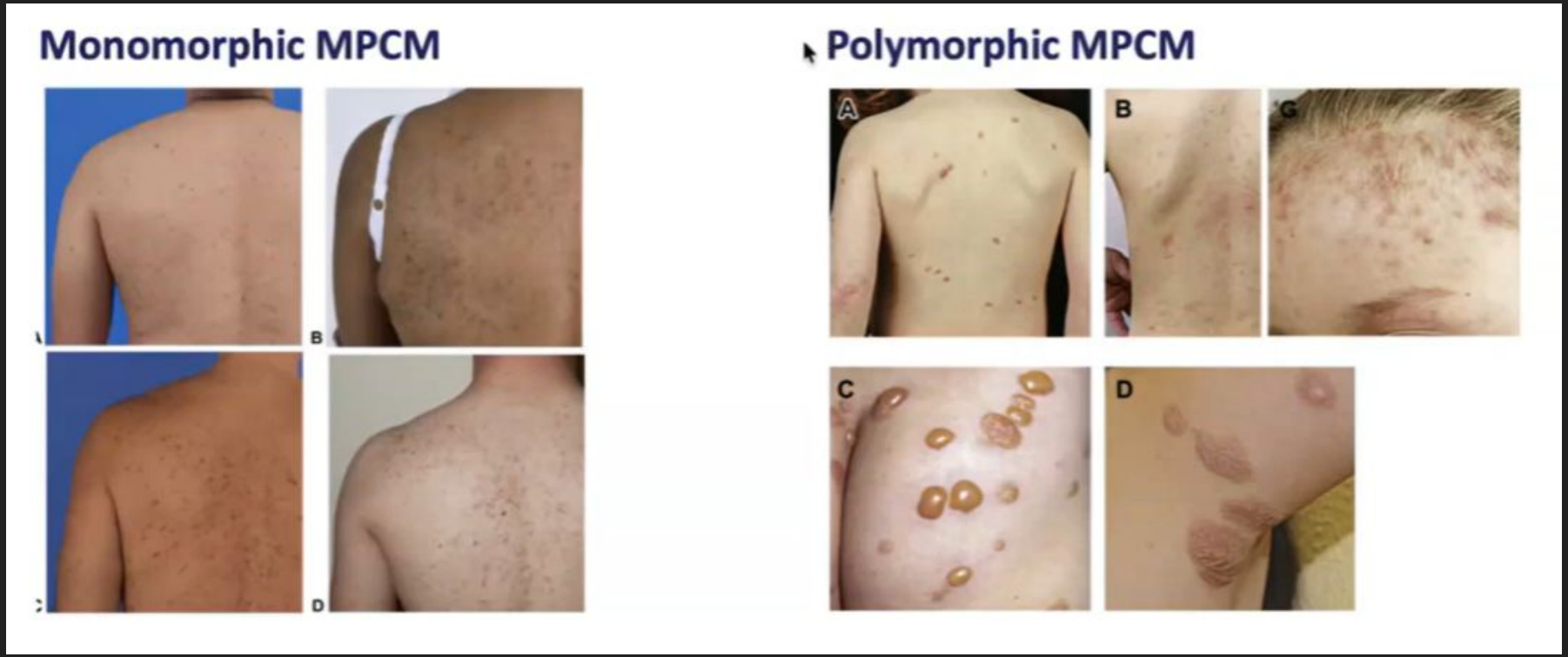
Cutaneous Mastocytosis



Monomorphic Maculopapular Cutaneous Mastocytosis (MPCM)
Typical adult form

Image: McMurray, WR & Boggs N. Walter Reed MC Center of Excellence

Cutaneous Mastocytosis



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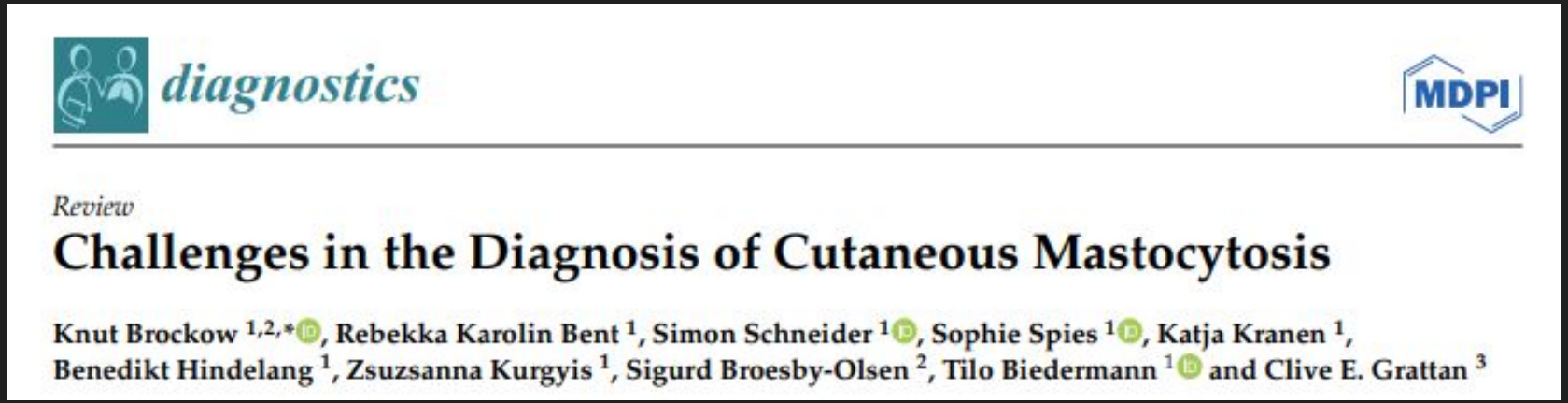
Cutaneous Mastocytosis

Excellent 2024 Open Access article



diagnostics

MDPI

Review

Challenges in the Diagnosis of Cutaneous Mastocytosis

Knut Brockow [1,2,*], Rebekka Karolin Bent [1], Simon Schneider [1], Sophie Spies [1], Katja Kranen [1], Benedikt Hindelang [1], Zsuzsanna Kurgyis [1], Sigurd Broesby-Olsen [2], Tilo Biedermann [1] and Clive E. Grattan [3]

Brockow K, Bent RK, Schneider S, et al. Challenges in the Diagnosis of Cutaneous Mastocytosis. *Diagnostics*. 2024;14(2):161.

Cutaneous Mastocytosis

Table 2. The WHO classification of mastocytosis.

2024

Form of Mastocytosis	Abbreviation	Characteristics
Cutaneous mastocytosis	CM	Only the skin is involved.
- Maculopapular CM	MPCM	Disseminated lesions.
- Monomorphic		Small uniform lesions, adult type.
- Polymorphic		Larger variable lesions, childhood type.
- Diffuse CM	DCM	Diffuse indurated skin lesions.
- Cutaneous mastocytoma	-	Solitary plaques or nodules.
- Isolated		One lesion.
- Multilocalised		Up to three lesions.

Table 1.

Proposed Classification and Criteria of CM.

2021

Variant and Subvariant(s)	Abbreviation	Features/Criteria
Maculopapular cutaneous mastocytosis	MPCM	Positive Darier's sign[a]
		Typical pigmented skin lesions
Urticaria pigmentosa	UP	Positive histology[b]
		KIT mutation in lesional skin
Monomorphic variant	MPCM-m	Monomorphic skin lesions[c]
Polymorphic variant	MPCM-p	Polymorphic skin lesions[c]

OLDER term

UP

No longer favored

Brockow K, Bent RK, Schneider S, et al. Challenges in the Diagnosis of Cutaneous Mastocytosis. *Diagnostics*. 2024;14(2):161.

Valent P, Akin C, Hartmann K, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. HemaSphere. 2021;5(11):e646.

KIT Mutations in SM: Majority of Adults with D816V

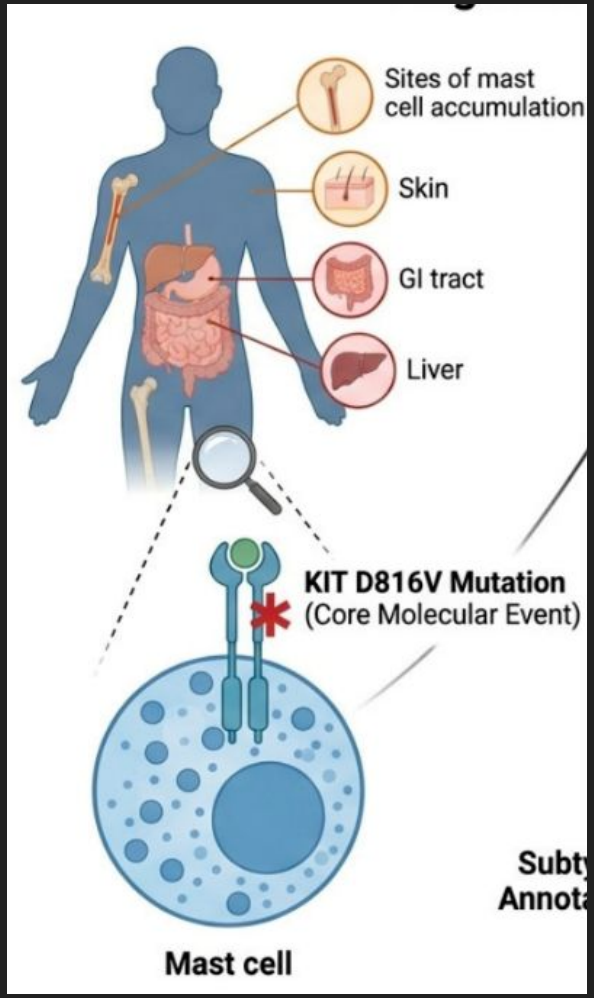
KIT is the focus of SM pathobiology both because activating *KIT* mutations are the most frequent molecular abnormality in SM

KIT encodes the *KIT* receptor tyrosine kinase, also known as CD117 or stem cell factor receptor

KIT D816V:

-somatic gain-of-function mutation in the *KIT* gene

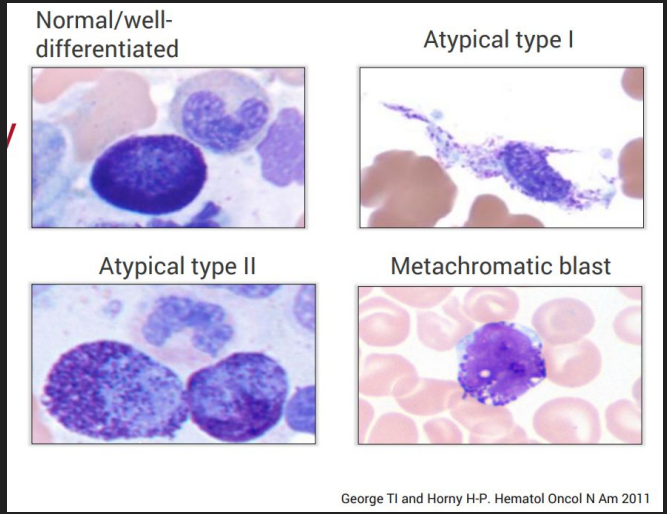
-drives **ligand-independent mast cell proliferation and survival**



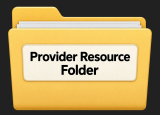
Alati C, Greve MB, Porto G, et al. *Cancers*. 2026;18(14):2205.

Clonal/Monoclonal Mast Cell Disease: Mastocytosis

- **Proliferate** & **accumulate**
- Atypical mast cell **morphology**
- Up to **30% ISM** pts can have **tryptase < 20**
- ~93-95% SM in adults = **KIT D816V** genetic mutation
- Prevalence: ~1/10,000 - 30,000 in US
  - **~95% Non-Advanced SM** (indolent or smoldering SM)
  - ~5% Advanced SM (organ damage, decreased survival)



K Brockow. Immunol Allergy Clin North Am 2014; CF Schuler et al. J Allergy Clin Immunol 2021; R Zanotti et al. Cancers (Basel) 2021.
Valent P, et al. *Annual Review of Pathology Mechanisms of Disease* 2023;18:361-86



Diagnostic Criteria for Systemic Mastocytosis:

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Activating Kit mutation *of any kind*

CD2 and/or CD25 and/or CD30 expression on mast cells

Basal serum tryptase ≥ 20 ng/mL

WHO 5th edition: 1 major + 1 minor criterion or 3 minor criteria

International Consensus Classification: 1 major criterion or 3 minor criteria

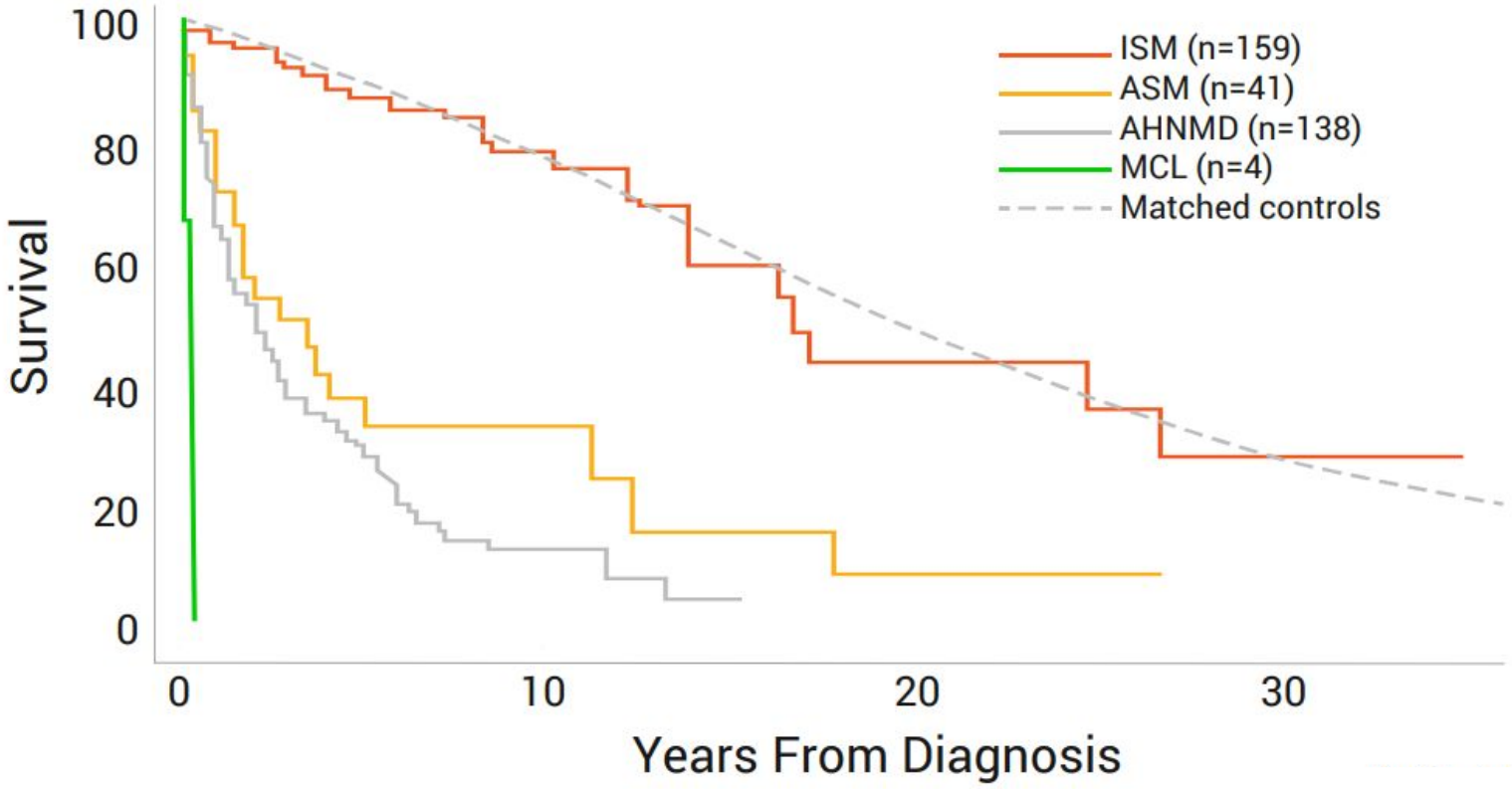
WHO 5th further considerations:

-Bone Marrow Mastocytosis (BMM) is now a separate subtype of SM: absence of MPCM skin lesions, no B-findings, BST<125ng/ml

-B-findings ("**B**urden of disease") & C-findings ("**C**ytopenias & **C**ytoreduction-requiring") underwent minor refinements. Most notable: *KIT D816V mutation with VAF>/= 10% qualifies as B-finding

Valent P et al. *Immunol Allergy Clin N Am.* 2023;43: 627-649

Overall Survival

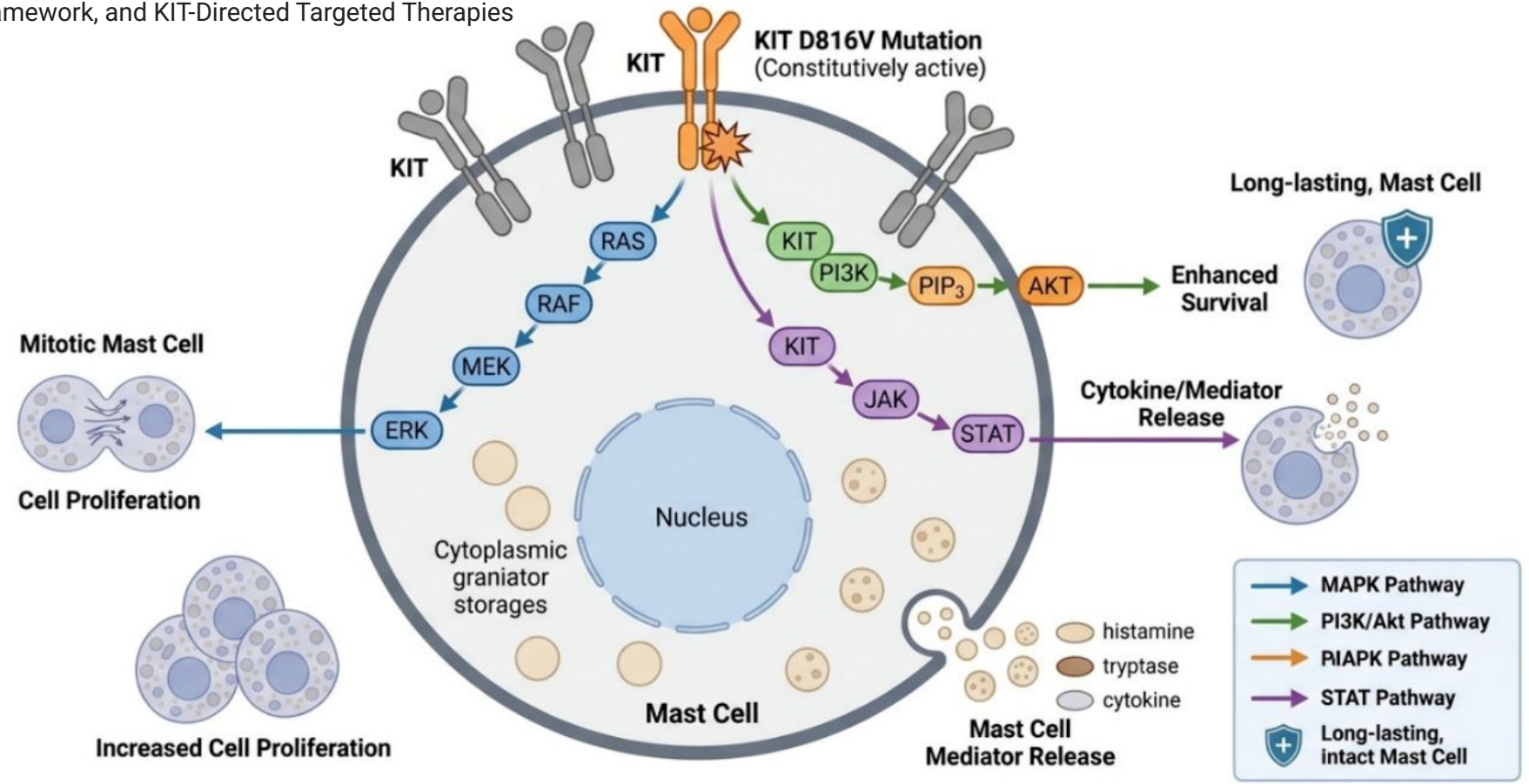


Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

Lim KH et al. Blood 2009

Core Molecular Event and KIT D816V-Driven Signaling in Systemic Mastocytosis

Image directly from 2026 hematology review by Alati, et al.: Systemic Mastocytosis: Molecular Pathophysiology, WHO Diagnostic Framework, and KIT-Directed Targeted Therapies



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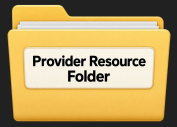


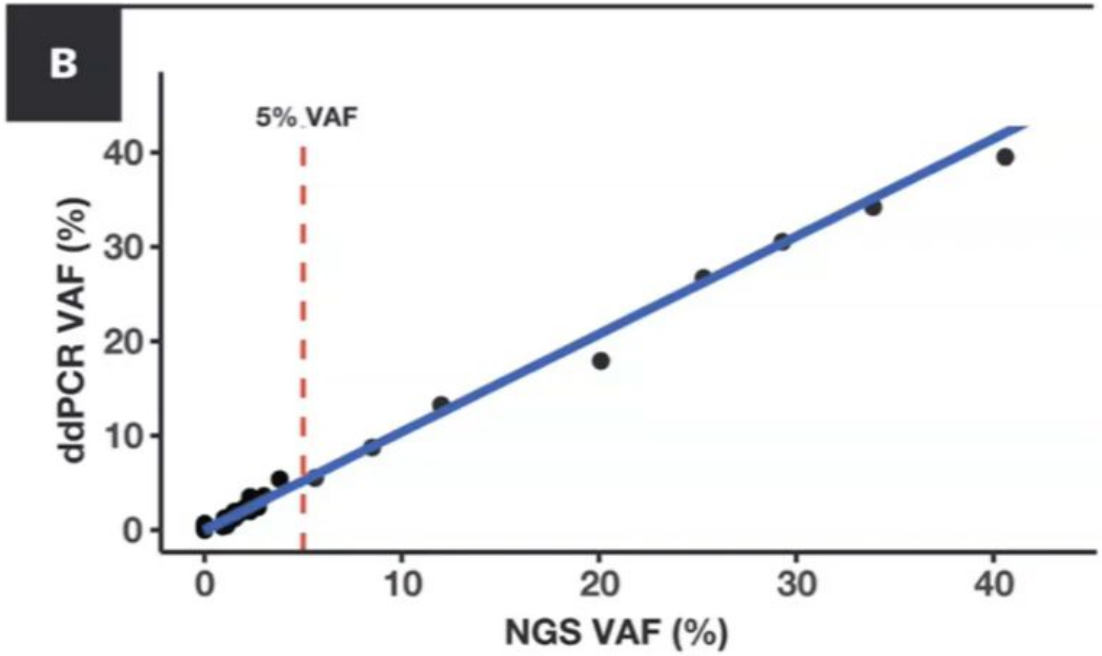
Lab Testing For Mast Cell Disease

ddPCR *KIT* D816V mutation analysis

≥ 93% adult SM cases have this clonal mutation in the KIT receptor

- serum test
- FRESH bone marrow aspirate, GI biopsies, other organ tissues
- Variant allele fraction (VAF) %

SM: *KIT* p.D816V testing methodology matters



PMID: 40036308 -showing at that time, SM pts missed with NGS vs ddPCR on BMB

SM: How low can Tryptase be?

		Blood					Marrow Aspirate					
Patient	Discordant	*Sanger*	*asoPCR*	*qPCR1*	*qPCR2*	*qPCR3*	*Sanger*	*NGS*	*asoPCR*	*qPCR1*	*qPCR3*	BST Range
1	Yes		Pos	Neg				Neg	Pos			15.8 – 23.8
2	Yes			0.02%				Neg	Neg			10 – 16.5
3	Yes		Neg	0.03%			Neg	Neg	Pos			6.3 – 8.2 ●
4	Yes			Neg		0.029%		Neg		Neg	0.04%	27.9 – 30.2
5	Yes			Neg		0.02%		Neg		Neg		6 – 7.3 ●
6	Yes			Neg		Neg		Neg		Neg	0.04%	15.1 – 28
7	Yes		Neg	Neg			Neg	Neg	Pos			10.4 – 13.3
8	Yes		Neg	Neg			Neg	Neg	Pos			6.4 – 8 ●
9	Yes	Neg		0.02%				Neg		0.05%		6.1 – 18 ●
10	Yes		Pos	0.27%			Neg					14.8 – 19
11	Yes				0.08%		Neg					17.1 – 21.1
12	Yes			Neg	0.04%							13.3 – 16.6
13	No											15.1 – 39
14	No			0.34%								12 – 21.8
15	No		Neg	Neg		Neg	Neg	Neg	Neg	Neg	Neg	40.6 – 49.3

New to me this year… realizing that should repeat ddPCR at different lab depending on level suspicion of ISM. * should improve w/upcoming ultrasens testing PMID: 3684636

McMurray JC, Pacheco CS, Schornack BJ, et al. *Blood*. 2024;144(4):408-419.

Etiologies associated with elevated BST

Somatic etiologies

- SM
- Myeloid hypereosinophilic syndromes (HES)
- Myelodysplastic syndrome (MDS)
- Acute myeloid leukemia (AML)

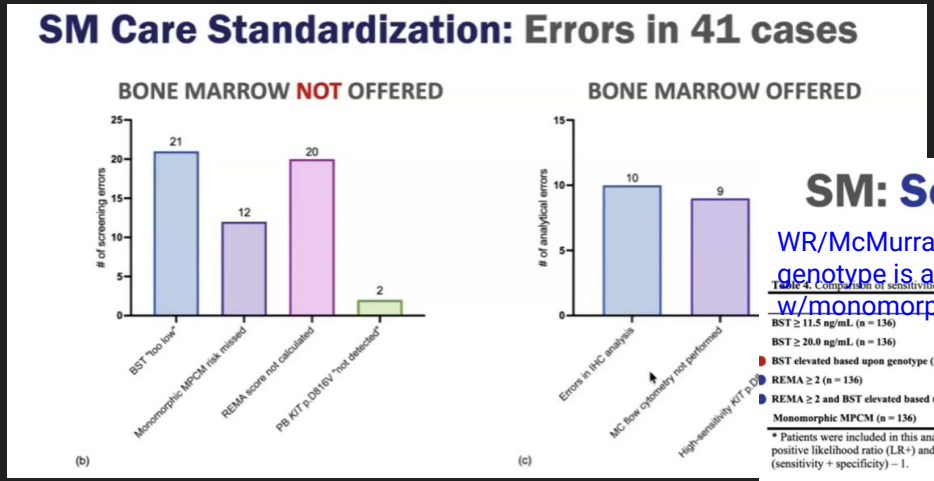
Germline & acquired etiologies

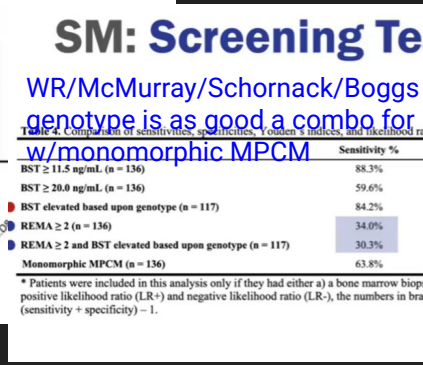
- Chronic Kidney Disease (CKD)
- Eosinophilic Esophagitis (EoE)
- Rheumatoid arthritis (RA)
- Hereditary-α tryptasemia (HαT)

PMID: 27749843, 12676775, 19522836, 11568008, 12148892, 20349428, 30267171, 24433328, 3295549

REMA score

Can be helpful in deciding whether to push for BMB, esp clinical sxs. Gender~...





VARIABLE		SCORE
GENDER	Male	+1
	Female	-1
CLINICAL SYMPTOMS	Absence of urticaria and angioedema	+1
	Urticaria and/or angioedema	-2
	Presyncope and/or syncope	+3
TRYPTASE*	<15 ng/mL	-1
	>25 ng/mL	+2

*Baseline serum tryptase

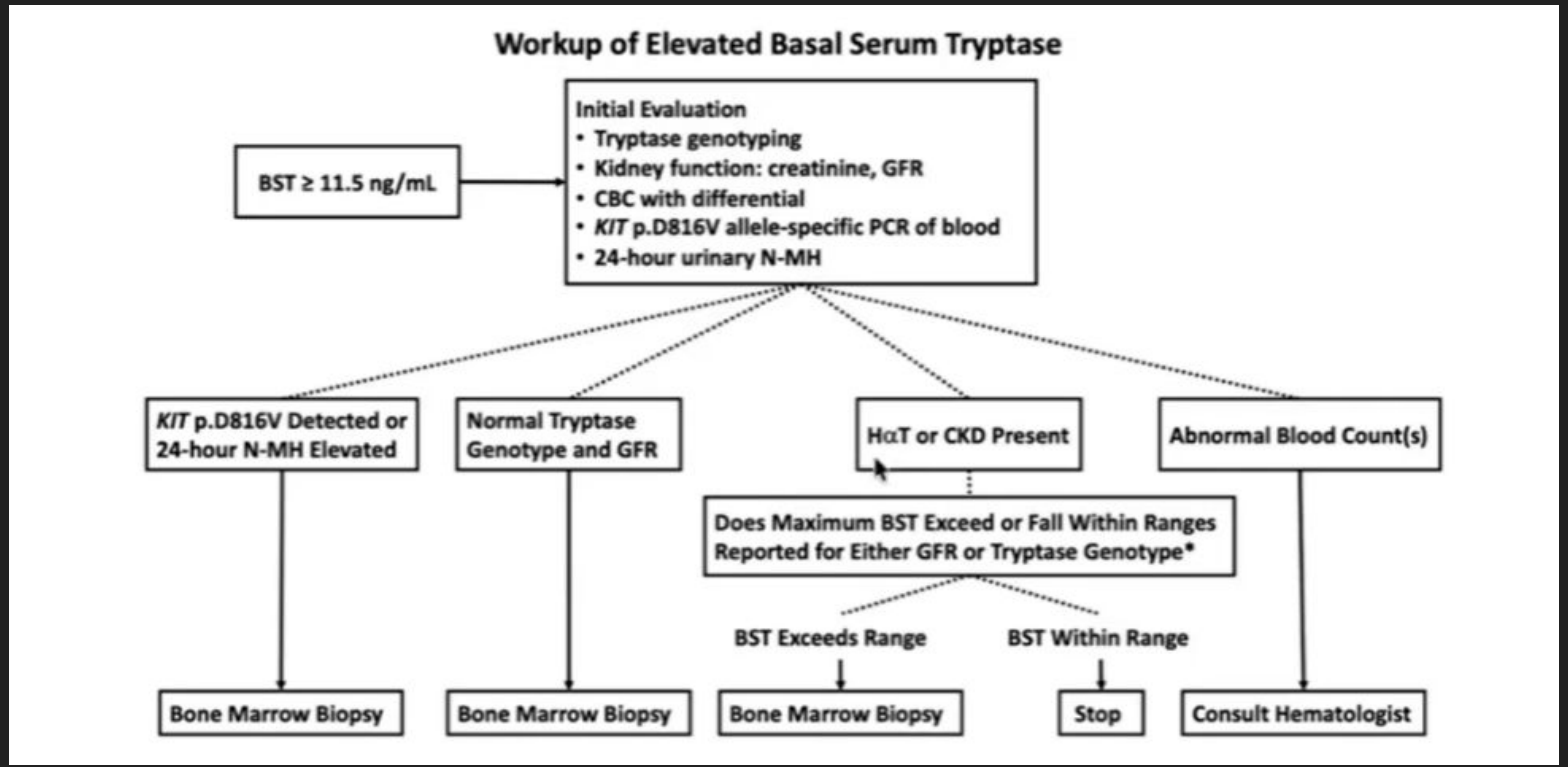
REMA

SCORE < 2: low probability of clonal MCAD
SCORE ≥ 2: high probability of clonal MCAD

McMurray, Schornack, et al Boggs presented at AIM paper re: SM Care Standardization study at Walter Reed 1.

McMurray JC, Pacheco CS, Schornack BJ, et al. Standardized indolent systemic mastocytosis evaluations across a health care system: implications for screening accuracy. *Blood*. 2024;144(4):408-419. doi:10.1182/blood.2023023347

Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, et al. *Int Arch Allergy Immunol*. 2012;157(3):275-280.

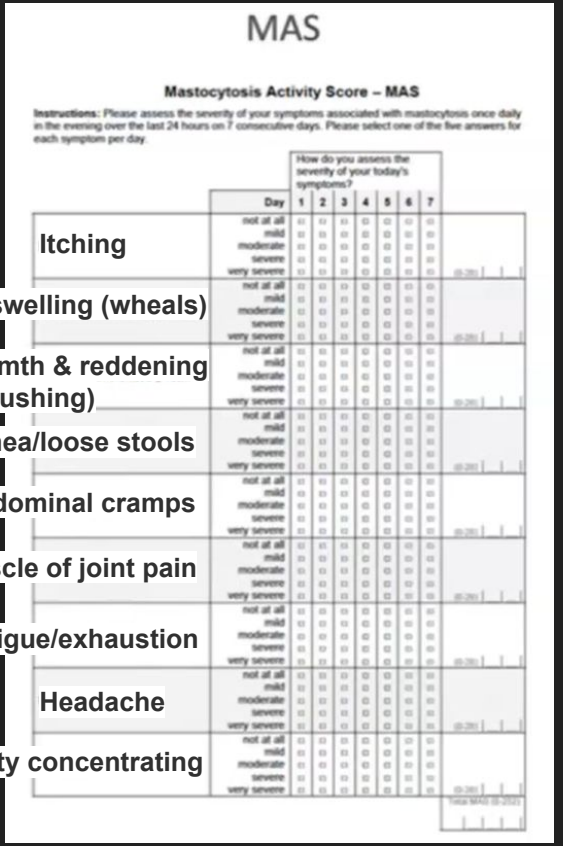


Waters AM, Park HJ, Weskamp AL, et al. *JACI: In Practice*. 2022;10(9):2424-2435.e5.

SM Symptoms

MC-QoL

	None	Some-what	Moderately	Very	Very Much
How severely were you affected by the following symptoms in **the last 2 weeks**?					
1. Itching	❑	❑	❑	❑	❑
2. Skin Redness/Swelling	❑	❑	❑	❑	❑
3. Sudden feeling of warmth and reddening of the face (Flush episodes)	❑	❑	❑	❑	❑
4. Diarrhea/loose stools	❑	❑	❑	❑	❑
5. Fatigue/Exhaustion	❑	❑	❑	❑	❑
6. Headache	❑	❑	❑	❑	❑
7. Muscle or joint pain	❑	❑	❑	❑	❑
8. Difficulty concentrating	❑	❑	❑	❑	❑



Severe and sometimes fatal anaphylaxis

Bone: discrete bone lesions, reduced bone mineral density, fractures, bone pain

Red Flags & When to Suspect SM

- **Recurrent unexplained anaphylaxis, syncope, or presyncope**
- **Severe anaphylaxis to Hymenoptera (bee/wasp) stings**
- **Elevated basal serum tryptase (11.4-20 & >20 ng/mL)**
- **Typical maculopapular skin lesions (monomorphic MPCM) in an adult**
- **Unexplained osteoporosis, especially in an otherwise healthy man**, or osteosclerotic/osteolytic bone lesions mimicking myeloma or metastases. Osteoporosis occurs in up to 30% of SM.
- **Chronic mediator symptoms without another explanation**
- **Unexplained hematologic or organ abnormalities**: cytopenias, dysplasia on smear; hepatomegaly, splenomegaly, or lymphadenopathy

Akin C, Arock M, Carter MC, George TI, Valent P. Mastocytosis. *Nat Rev Dis Primers*. 2025;11(1):30.
Pardanani A. *American J Hematol*. 2026;101(9):2371-2392.

SM DXA & Fractures

DXA Findings

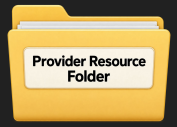
- ~28% of patients with SM have low BMD by DXA
- Bone loss often most pronounced in the lumbar spine
- Consider SM in unexplained osteoporosis, particularly in younger adults

Fracture Findings

- >50% of patients with SM experience fractures
- Vertebral fractures are the most common
- Male sex and older age independently increase fracture risk

1.

Degboé Y, Eischen M, Nigon D, et al. *Bone*. 2017;105:219-225.
Gehlen M, Schmidt N, Pfeifer M, et al. *Calcif Tissue Int*. 2021;109(6):685-695.



Lab Testing For Mast Cell Disease

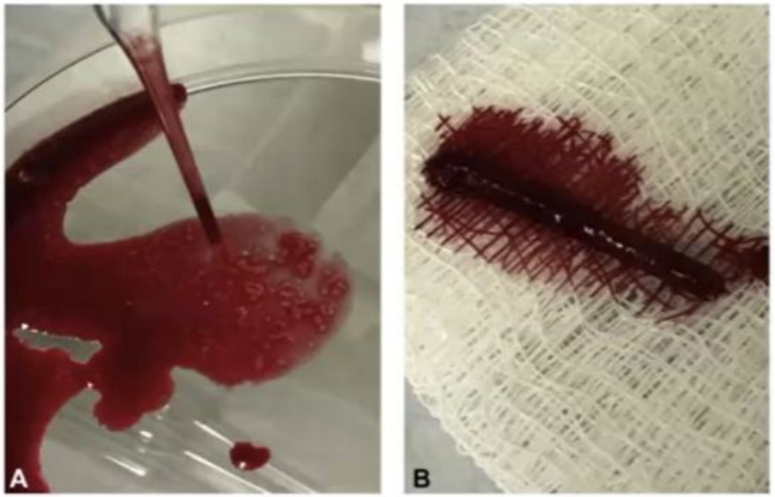
Pathology

Bone Marrow Biopsy (BMB)

Endoscopy &/or Colonoscopy with biopsies

Skin Exam (possible biopsy)

Bone Marrow Aspirate & Core Needle Biopsy

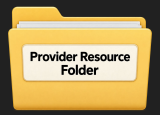


Aspirate

- Aspirate smears
- Molecular testing
  - High sensitivity *KIT* p.D816V PCR
  - Myeloid gene NGS panel
- Leukemia/lymphoma flow cytometry panel with mast cell markers

Core Needle Biopsy & Clot Sections

- H&E
- CD117 and tryptase IHC
- CD2, CD25, CD30 IHC



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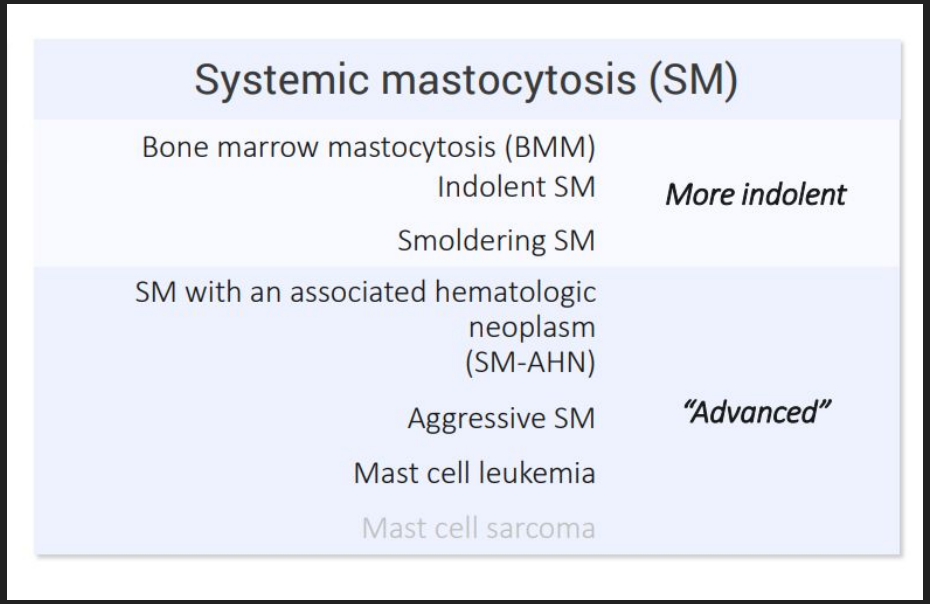
Valent P et al. *Immunol Allergy Clin N Am.* 2023;43: 627-649



Non AdvSM	Diagnostic features
BMM	0 B-findings, no skin lesions, serum tryptase <125 ng/mL
ISM	<2 B-findings, typical skin lesions
SSM	≥2 B-findings, often high MC burden

Alati C, Greve MB, Porto G, et al. *Cancers*. 2026;18(14):2205.

Table 4.

Proposed Refined B-findings and C-findings.

B-findings	C-findings (SM-induced Organ Damage)
High MC burden: Infiltration grade (MC) in BM ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL[a] and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes	-
Signs of myeloproliferation and/or myelodysplasia[b]: Hypercellular BM with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or discrete signs of myelodysplasia (<10% neutrophils, erythrocytes, and megakaryocytes)	Cytopenia/s: ANC < 1 × 10^9/L Hb < 10 g/dL PLT < 100 × 10^9/L (one or more found)
Organomegaly: Palpable hepatomegaly without ascites or other signs of organ damage or/and palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy palpable or visceral LN-enlargement found in ULS or CT (>2 cm)	Hepatopathy: Ascites and elevated liver enzymes[c] ± hepatomegaly or cirrhotic liver ± portal hypertension Spleen: Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia GI tract: Malabsorption with hypoalbuminemia ± weight loss Bone: Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain

Valent P, Akin C, Hartmann K, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. HemaSphere. 2021;5(11):e646.

Classification Dilemma: Monoclonal MCAS

TABLE II. Classification of MCA disorders

MCAS variant	Main diagnostic features
Primary, clonal, monoclonal	• Primary: *KIT* D816V mutation is detected; MCs may display CD25 and/or CD30. • Clonal: confirmed mastocytosis (cutaneous mastocytosis or SM). • Monoclonal: only 2 minor SM criteria.
Secondary	No neoplastic MCs or *KIT* D816V mutation. MCA is associated with IgE-mediated allergy, other hypersensitivity reactions, or immunologic disease.*
Combined	Criteria for primary and secondary MCAS are fulfilled; HαT may be detected.
HαT positive	HαT is detected, and all diagnostic MCAS criteria are fulfilled.
Idiopathic	Criteria to diagnose MCAS are met, but no other variant criteria are met.

McMurray JC, Pacheco CS, Schornack BJ, et al. *Blood*. 2024;144(4):408-419.

Advanced Systemic Mastocytosis

Mast cell leukemia

≥ 20% mast cells on aspirate/PB*

SM + AHN/AMN

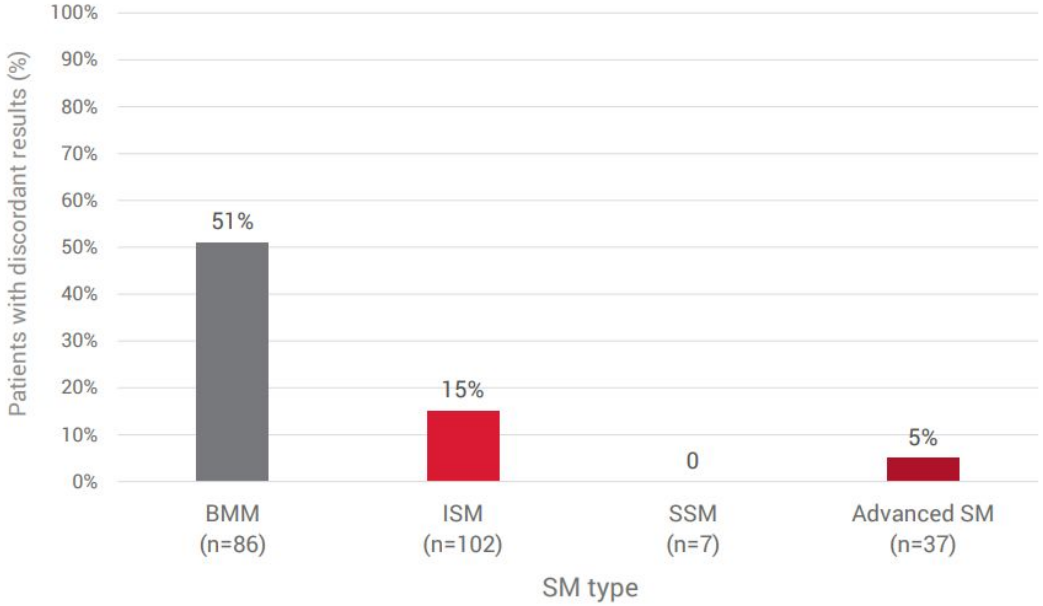
- Meets WHO criteria for an associated hematological neoplasm
- Meets SM criteria

ASM (1+ C-findings)

- Cytopenias
- Hepatomegaly with impaired liver function
- Skeletal involvement → osteolytic lesions and/or pathological fractures
- Splenomegaly with hypersplenism
- Malabsorption due to GI mast cell infiltrates

*MCs must be immature per ICC only

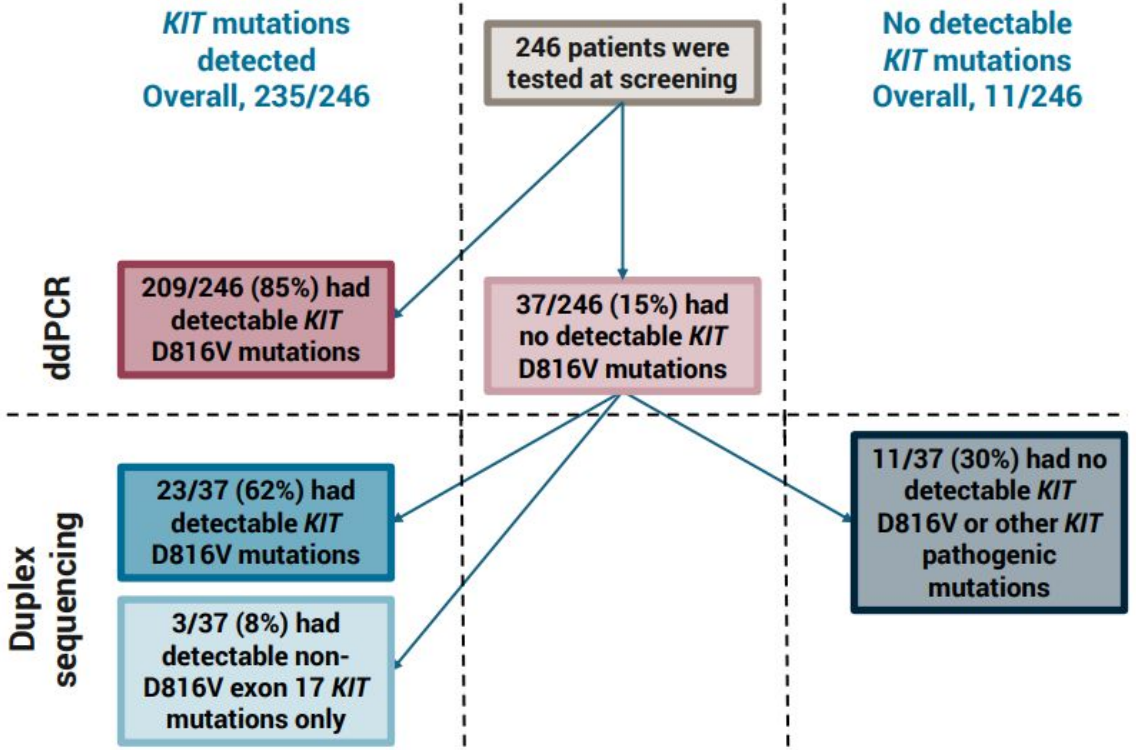
Higher discordance rates in peripheral blood vs bone marrow *KIT* D186V testing in Non-Advanced SM



Navarro-Navarro P et al. Allergy 2023.

Ultra-high sensitivity testing improves upon sensitivity of ddPCR for detection of *KIT* D816V

- Patients who had no detectable *KIT* mutations in PB by ddPCR were further tested with duplex sequencing
- Of 37 patients with no detectable *KIT* mutations by ddPCR, 26 had *KIT* mutations detectable by duplex sequencing
- Combining results from clinical ddPCR testing and research duplex sequencing showed that 97% of patients from PIONEER had detectable *KIT* activating mutations

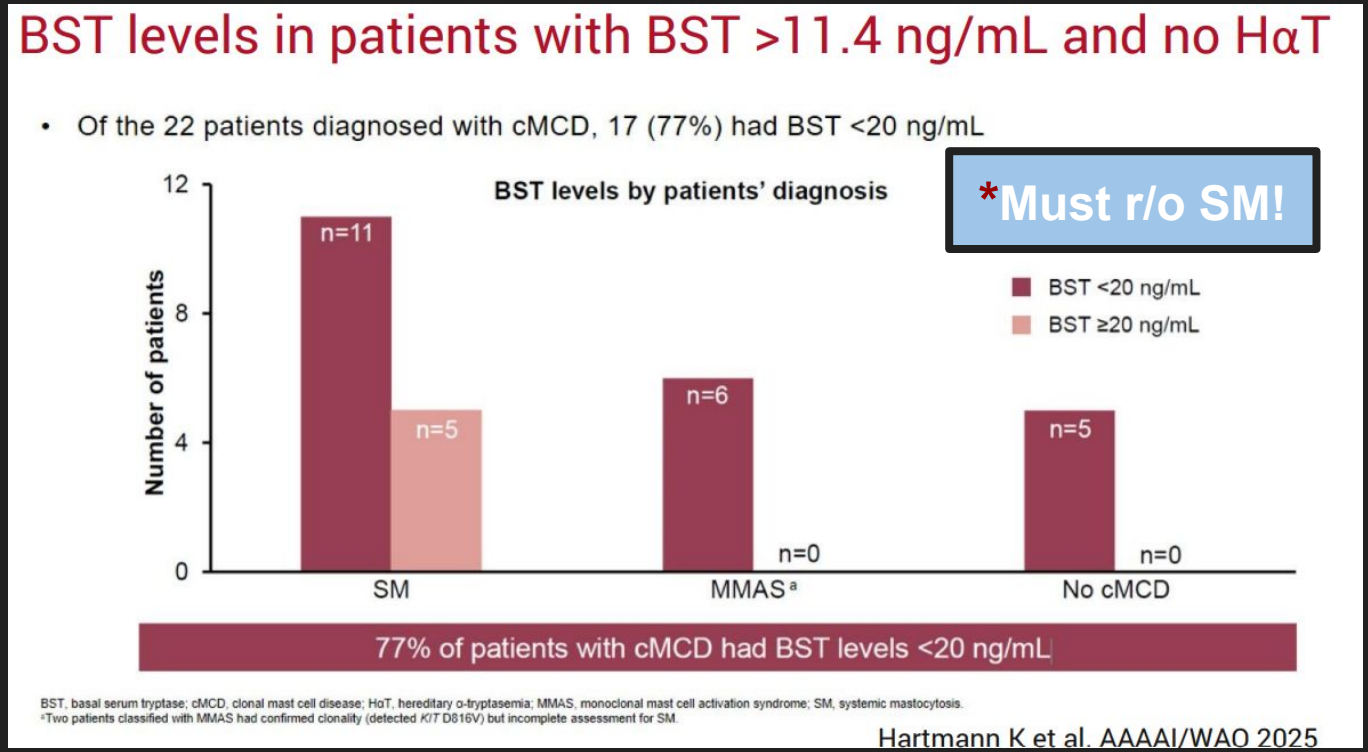


Pongdee T et al. AAAAI 2025

Hereditary alpha-tryptasemia (H∝T or HaT)

27 pts with BST >11.4 & no HaT: 22 of these had clonal mast cell disease (cMCD)

- 77% <20 ng/mL



Post Hoc analysis PROSPECTOR study

Types of Mast Cell Disease/Disorders

1. Clonal/Monoclonal or Primary

- cutaneous mastocytosis (CM)
- systemic mastocytosis (SM)
  - -ISM, BMM, SSM, ASM
- monoclonal mast cell activation syndrome (MMAS)

2. Non-clonal

- secondary mast cell activation syndrome (2°MCAS)

3. Idiopathic

- idiopathic mast cell activation syndrome (iMCAS)

Special Factor:
Non-Clonal Genetic Trait

- hereditary alpha-tryptasemia (H∝T or HaT)

-NOT a disease/disorder on its own!

~6% people are born with HaT
& most don't have extra symptoms

Current “Consensus 1” Criteria for

MCAS Diagnosis

(Non-Clonal MCD)

Recurrent symptoms ≥ 2 organs systems

Skin
GI
Respiratory
Systemic
Naso-ocular
Cardiovascular
Brain

+

Significant help from anti-mediator therapy

H1 antihistamines
H2 antihistamines
MC stabilizers
Biologics
Leukotriene blockers
Prostaglandin blockers

+

Acute rise in MC mediator labs ≥ 2 occasions

Serum tryptase
(1.2X+2 or HaT 1.68X, X = BST)

Urine markers
(≥ 30% rise above baseline)

Supported by AAAAI, ACAAI, AIM, ECNM

Valent P, et al. *J Allergy Clin Immunol Pract* 2022;10(8):1999-2012.
Castells M, et al.*J Allergy Clin Immunol* 2024;154(2):255-63.

MCAS Diagnosis

Global Classification of Mast Cell Activation Disorders:
An ICD-10-CM–Adjusted Proposal of the ECNM-AIM Consortium

Journal of Allergy and Clinical Immunology: In Practice

TABLE I. Diagnostic consensus criteria for MCAS*

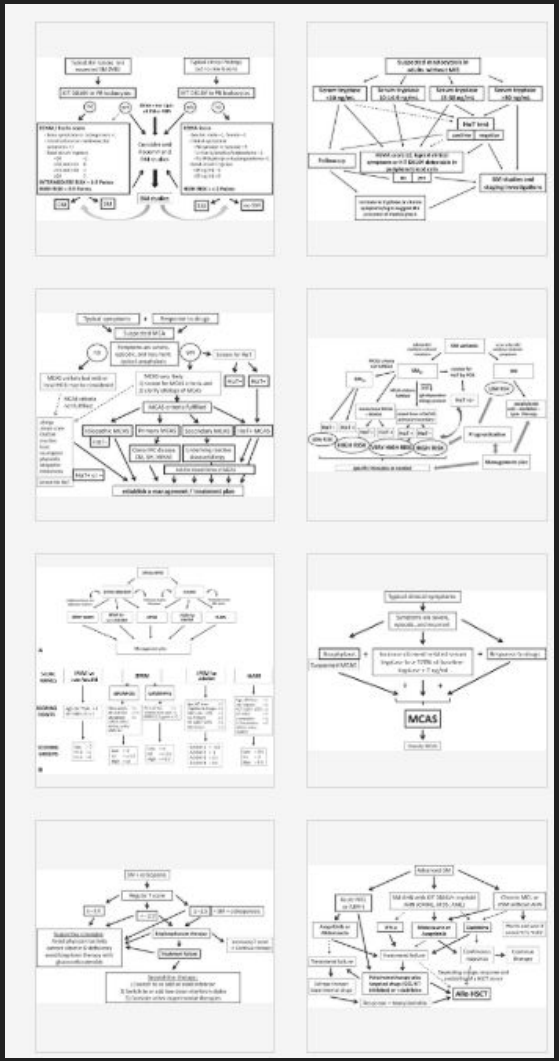
A. Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in the form of anaphylaxis) (definition of systemic: involving at least 2 organ systems)

B. Involvement of MCs is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to 120% + 2 ng/mL†

C. Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or the effects of MC-derived mediators‡

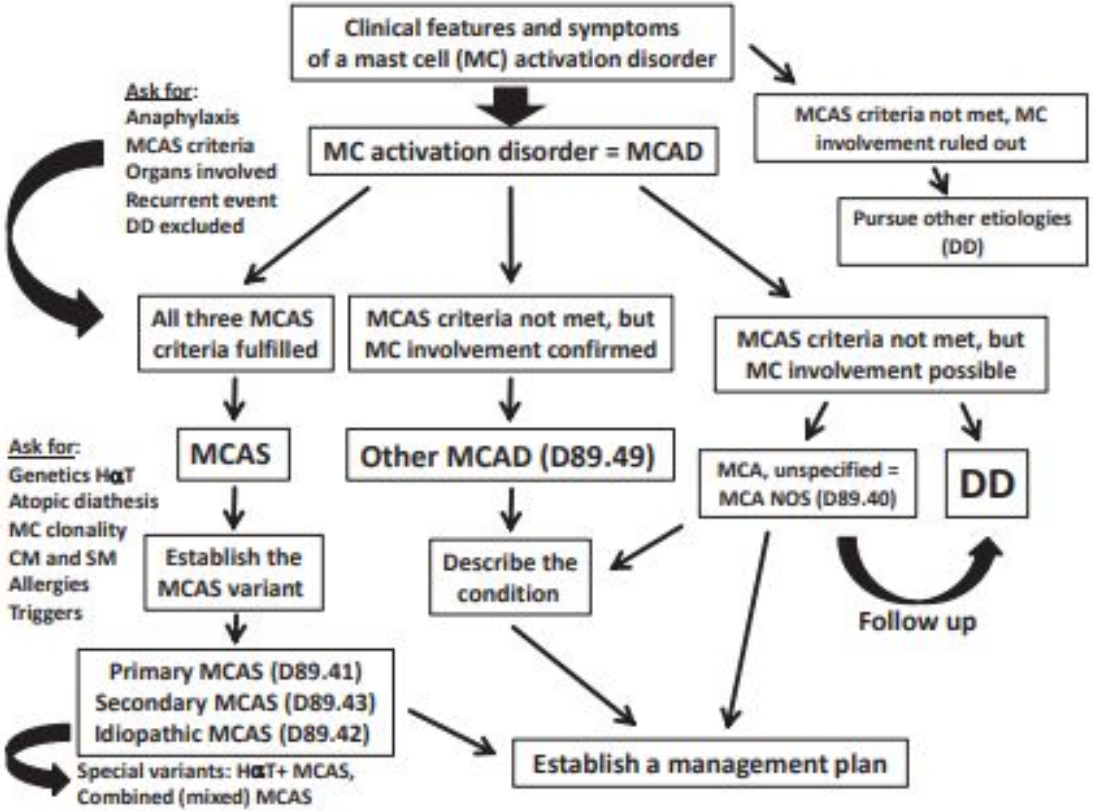
*All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.
†Other MC-derived biomarkers of MC activation (recommended: 24-h or spot urinary histamine metabolites or PGD_2 metabolites) may also be used, but are less specific compared with the increase in serum tryptase level. In addition, to date, no diagnostic thresholds for the increase in these urinary biomarkers have been defined and validated. Nevertheless, these alternative markers are recommended when the tryptase test is not available or its result is inconclusive. A proposed diagnostic threshold for histamine or PGD2 metabolites is >200% of the individual's baseline (increase by >+100%) provided that the test result is above the normal range for the assay.
‡Example: histamine receptor blockers.

Valent P, Hartmann K, Bonadonna P, et al. 2022;10(8):1941-1950. doi:10.1016/j.jaip.2022.05.007



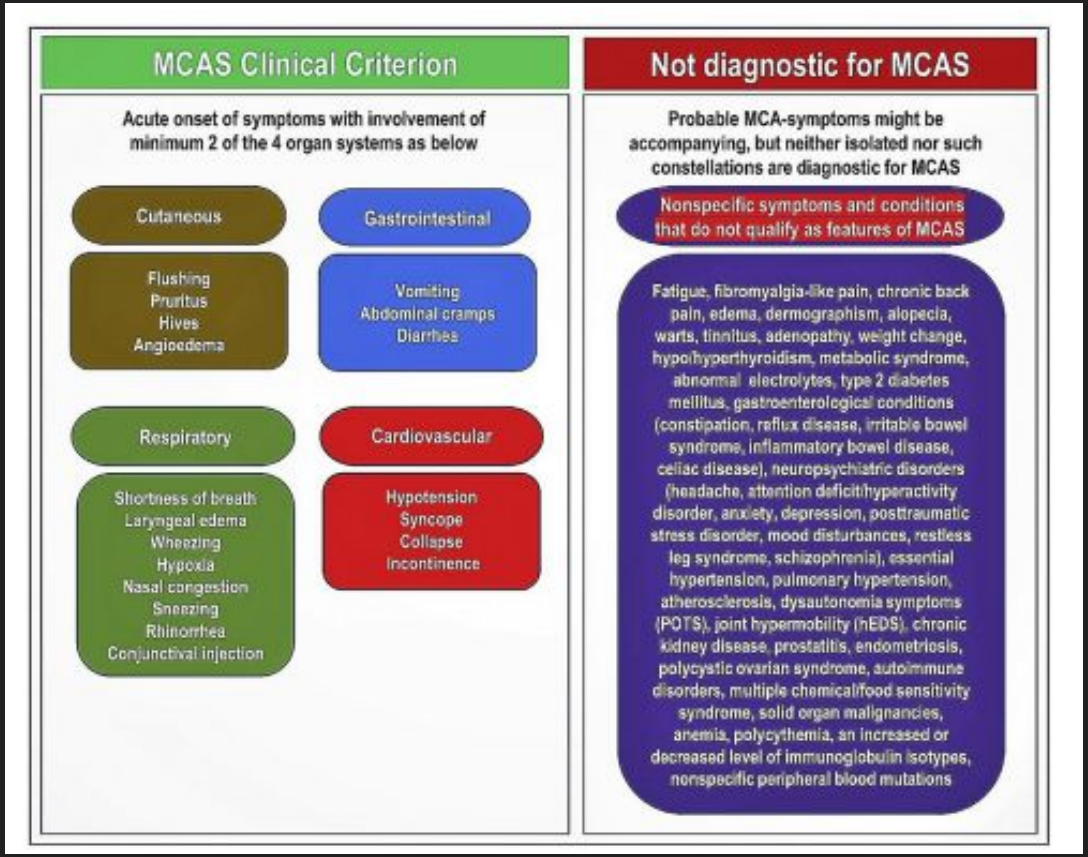
VERY Helpful Diagnostic Flowcharts For Mast Cell Disease

Valent P, Hartmann K, Schwaab J, et al. **Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice.** *The Journal of Allergy and Clinical Immunology: In Practice.* 2022;10(8):1999-2012.e6. doi:10.1016/j.jaip.2022.03.007



Valent P, Hartmann K, Bonadonna P, et al. *JACI: In Practice*. 2022;10(8):1941-1950.

Differential Diagnoses for Mast Cell Disease



Gülen T, Akin C, Bonadonna P, et al. *The Journal of Allergy and Clinical Immunology: In Practice*. 2021;9(11):3918-3928.

Treatment of Mast Cell Disease

Evidence-based pharmacological recommendations

High certainty for *some* therapies

Most therapies are not labelled specifically for SM or MCAS, except those targeting KIT receptor

Consensus guidelines, and recommendations per AIM, AAAAI, ACAAI, ECNM

Treatment of Mast Cell Disease:
H1 Antihistamines

*2nd Generation	1st Generation
loratadine (Claritin)	diphenhydramine (Benadryl)
fexofenadine (Allegra)	hydroxyzine (Atarax or Vistaril)
cetirizine (Zyrtec)	chlorpheniramine
levocetirizine (Xyzal)	cyproheptadine (Periactin)

Desire is for *2nd generation *longer acting, nonsedating* antihistamines

Castells M, Giannetti MP, Hamilton MJ, et al. *Journal of Allergy and Clinical Immunology*. 2024;154(2):255-263.

Treatment of Mast Cell Disease:
H2 Antihistamines

Famotidine (Pepcid)

Cimetidine (Tagamet)

Ranitidine (Zantac)... making a return?!

Castells M, Giannetti MP, Hamilton MJ, et al. *Journal of Allergy and Clinical Immunology*. 2024;154(2):255-263.

Treatment of Mast Cell Disease:

Other therapies

Nasal sprays & eye drops:
steroid, antihistamine,
MC stabilizer

Montelukast (Singulair)

Inhalers

Epinephrine autoinjectors

Immunotherapy (SCIT)

Treatment of Mast Cell Disease:
Mast Cell Stabilizers

Aspirin

- Non-steroidal anti-inflammatory drug (NSAID)
- Irreversibly inhibits cyclooxygenase (COX) isoenzymes
- Normalizes levels of PGD2 metabolites
- Beneficial in patients with mastocytosis

Sabato V, Beyens M, Toscano A, Van Gasse A, Ebo DG. Mast Cell–Targeting Therapies in Mast Cell Activation Syndromes. *Curr Allergy Asthma Rep*. 2024;24(2):63-71.
Komi DEA, Rambasek T, Wöhrl S. Mastocytosis: from a Molecular Point of View. Clinic Rev Allerg Immunol. 2018;54(3):397-411. doi:10.1007/s12016-017-8619-2

Treatment of Mast Cell Disease:
Mast Cell Stabilizers

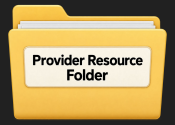
Cromolyn (Gastrocrom)

Ketotifen

Bioflavonoid supplements: Quercetin, Luteolin

~ Others

Sabato V, Beyens M, Toscano A, Van Gasse A, Ebo DG. Mast Cell–Targeting Therapies in Mast Cell Activation Syndromes. *Curr Allergy Asthma Rep*. 2024;24(2):63-71.
Yamada S, Shirai M, Inaba Y, Takara T. Effects of repeated oral intake of a quercetin-containing supplement on allergic reaction: a randomized, placebo-controlled, double-blind parallel-group study. *Eur Rev Med Pharmacol Sci*. 2022;26(12):4331-4345.



Treatment of Mast Cell Disease

Slowly Increasing Cromolyn is Important

Guide for Slow & Steady Increase of Oral Cromolyn

-Each ampule or vial contains cromolyn 100 mg/5mL and should be taken mixed with about 1/2 cup (4oz) of water, 15-60 mins before meals and at bedtime.
-You do not have to eat after cromolyn, so you will still take it if you're skipping a meal, or if you don't normally have a snack at bedtime.
-Consistency with the number of doses a day is what matters most, not perfection/exact timing.
-It travels easily in a pocket or bag. Protect it from light. Don't leave it in a vehicle due to temperature.
-During titration phase, half ampules can be kept upright in a cup placed inside a kitchen cabinet (dark & room temp) & used within 24-48hrs
-Cromolyn can temporarily cause increased GI symptoms of heartburn, nausea, abdominal cramps, bloating and/or some diarrhea at first, which is why we suggest you titrate up slowly. The dose can be increased when there aren't extra symptoms from *your baseline/typical level of GI symptoms.* Some people can go up on cromolyn more quickly, and others may need to go more slowly. Most people can increase their cromolyn dose every 2-4 days, but some people may need to wait 5-7 days for their GI tract to return to baseline. (If you are having a really difficult time due to GI symptoms, we typically suggest that you try 1/4 ampule steps, or simply pick a day of the week to increase your dose by 1/2 ampule and plug steadily along.)

1. Start with half an ampule before breakfast x 2-4 days.
2. Then take half an ampule before breakfast and half an ampule before dinner x 2-4 days.
3. Then take one whole ampule before breakfast and half an ampule before dinner x 2-4 days.
4. Then take one ampule before breakfast and one ampule before dinner x 2-4 days (if at this point, you didn't notice much GI trouble, you may be able to go through remainder of steps more quickly)
5. Then take one ampule before breakfast, half an ampule before lunch, and one ampule before dinner x 2-4 days.
6. Then take one ampule before breakfast, one ampule before lunch, and one ampule before dinner x 2-4 days.
7. Then take one ampule before breakfast, one ampule before lunch, and one ampule before dinner, and half an ampule before bedtime x 2-4 days.
8. Then take one ampule before breakfast, one ampule before lunch, and one ampule before dinner, and one ampule before bedtime x 2-4 days.
9. Then take 1 ½ ampules before breakfast, one ampule before lunch, and 1 ½ ampules before dinner, and one ampule before bedtime x 2-4 days.
10. Then take 2 ampules before breakfast, one ampule before lunch, and 2 ampules before dinner, and one ampule before bedtime x 2-4 days.
11. Then take 2 ampules before breakfast, 1 ½ ampules before lunch, and 2 ampules before dinner, and 1 ½ ampules before bedtime x 2-4 days.
12. Then take 2 ampules before breakfast, 2 ampules before lunch, and 2 ampules before dinner, and 2 ampules before bedtime x 2-4 days.

Treatment of Mast Cell Disease:
Monoclonal Antibodies/Biologic Therapies

Omalizumab (Xolair)
Targets IgE

Dupilumab (Dupixent)
Suppresses IL-4 & IL-13

Tezepelumab-ekko (Tezpire)
Binds to TSLP

Baran J, et al. *Cells* 2023;12(8):1187.
Sabato V, et al. *Curr Allergy Asthma Rep* 2024;(24)63–71.

Treatment of Mast Cell Disease:
Monoclonal Antibodies/Biologic Therapies

Omalizumab (Xolair)

- Humanized (murine-derived) monoclonal antibody
- Binds free serum IgE in vivo
- Reduces IgE binding to FcεRI on mast cells and basophils
- Serves as an add-on measure to control immediate symptoms of mast cell activation

Komi DEA, Rambasek T, Wöhrl S. Mastocytosis: from a Molecular Point of View. Clinic Rev Allerg Immunol. 2018;54(3):397-411. doi:10.1007/s12016-017-8619-2

Treatment of Mast Cell Disease:

Tyrosine Kinase Inhibitors (TKIs)

avapritinib (Ayvakit)

imatinib (Gleevac)

midostaurin (Rydapt)

still in trials: mastinib, bezuclastinib, elenestinib

Akin C. *Immunol Allergy Clin North Am* 2023;43(4):743-50.

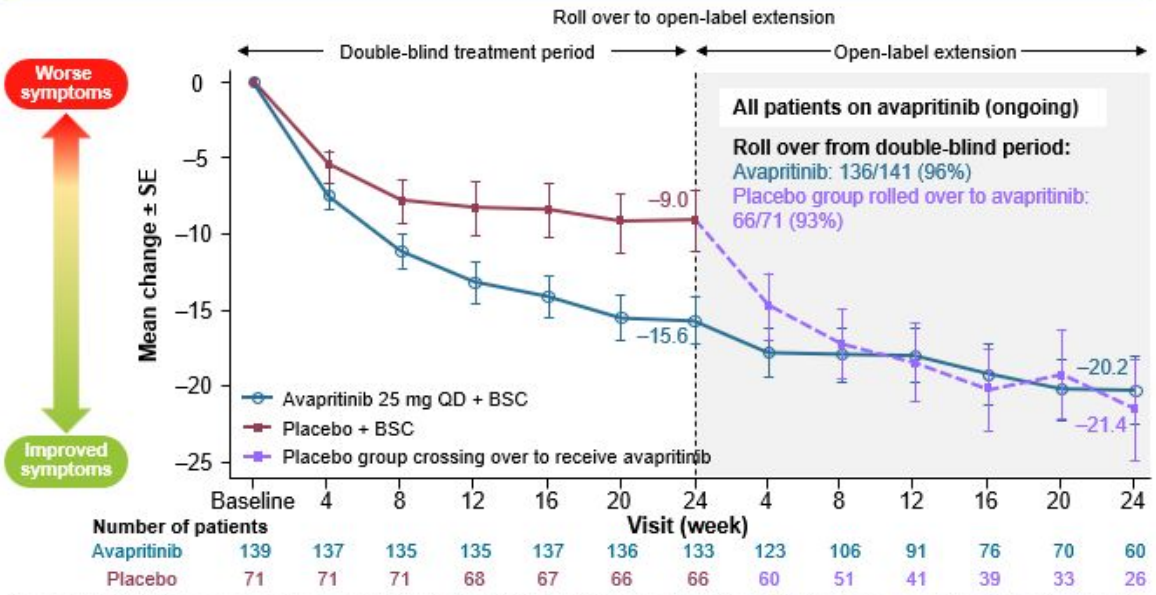
TKI for SM: avapritinib

Indication	Recommended dose	Administration	Notable dose caveat
Indolent SM (ISM)	25 mg PO once daily	Empty stomach	Not recommended if platelets <50 × 10^9/L; approved based on the PIONEER trial [1-2]
Advanced SM (ASM, SM-AHN, MCL)	200 mg PO once daily	Empty stomach	Do NOT initiate if platelets <50 × 10^9/L; reduce starting dose to 50 mg daily if platelets 50–<75 × 10^9/L [1]

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. *NEJM Evidence*. 2023;2(6).

Avapritinib demonstrated significant improvement in symptoms *versus* placebo at Week 24[1]

TSS over time



Number of patients													
Avapritinib	139	137	135	135	137	136	133	123	106	91	76	70	60
Placebo	71	71	71	68	67	66	66	60	51	41	39	33	26

Primary endpoint

A one-sided P-value of <0.025 was needed to declare avapritinib as superior in reducing TSS *versus* placebo[a]

At Week 24	Avapritinib 25 mg QD + BSC (n=128/141)	Placebo + BSC (n=65/71)	One-sided P-value
Mean change in TSS (95% CI)	−15.6 (−18.6, −12.6)	−9.2 (−13.1, −5.2)	0.003

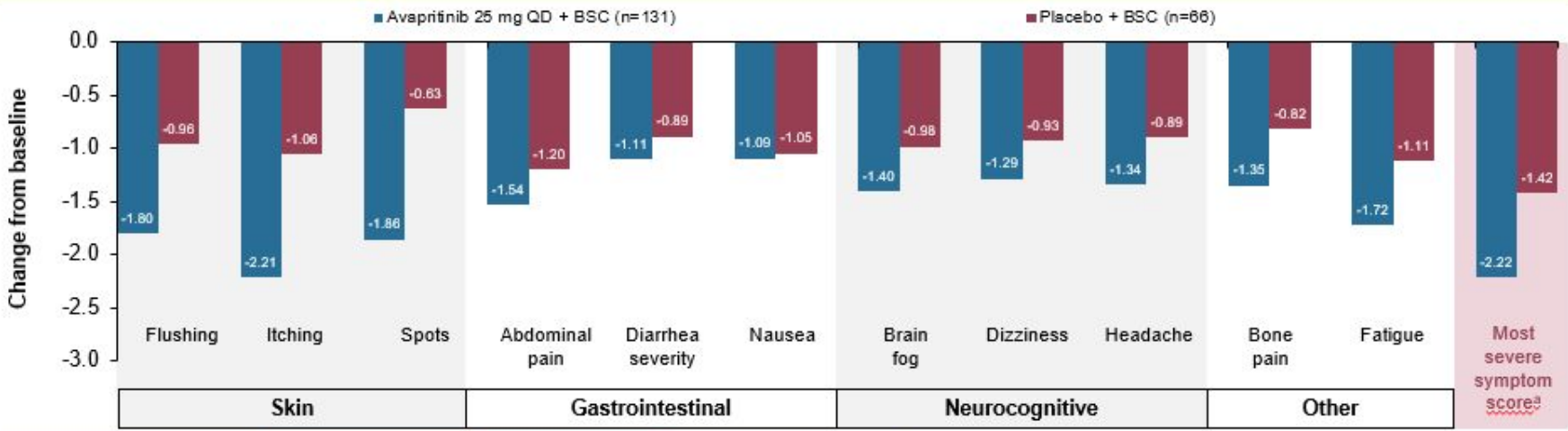
Change in ISM-SAF TSS score was the primary endpoint in Part 2 of the PIONEER trial[2]. Data cut-off date of June 23, 2022. Analysis was on the basis of the intent-to-treat population; however, patients using high-dose glucocorticoids (three patients treated with avapritinib and one in the placebo group) were included in this analysis of mean change in TSS over time, but per the prespecified statistical analysis plan, these patients were not included in the primary end point calculation because of the potential for high-dose glucocorticoids to influence symptoms. [a]A gatekeeping procedure was used to ensure that the family-wise type I error was strongly controlled at a one-sided α of 0.025 for primary and key secondary end points[1]. BSC, best supportive care; CI; confidence interval; QD, once daily; SE, standard error; TSS, total symptom score.

1. Gotlib J et al. *NEJM Evidence*. 2023;2(6); 2. PIONEER. NCT03731260. 2023. https://www.clinicaltrials.gov/ct2/show/NCT03731260. Accessed February 16, 2023

add notes

At 24 weeks, improvement was observed in all individual ISM symptoms, including the most severe symptom at baseline, with avapritinib treatment[a]

Mean TSS absolute change from baseline to 24 weeks, individual ISM-SAF, by treatment group[1]



At Week 24	Avapritinib 25 mg QD + BSC (n=131)	Placebo + BSC (n=66)	One-sided P-value
Mean change in most severe symptom score (SD)	–2.2 (2.3)[2]	–1.4 (1.9)[2]	0.015[1]

Avapritinib reduced most severe symptoms at baseline *versus* placebo, regardless of symptom group[1]

Change in ISM symptoms was an additional secondary endpoint in Part 2 of the PIONEER trial[3]. Data cut-off date of June 23, 2022[2].
[a]These endpoints were prespecified but not ranked or adjusted for multiplicity, cannot be considered statistically significant, and no conclusions can be made. Results should be interpreted with caution.
BSC, best supportive care; ISM, indolent systemic mastocytosis; ISM-SAF, ISM-symptom assessment form; QD, once daily; SD, standard deviation; TSS, total symptom score.
1. Castells M et al. Presented at AAAAI 2023. Oral 627; 2. Gotlib J et al. *NEJM Evidence*. 2023;2(6); 3. PIONEER. NCT03731260. 2023. https://www.clinicaltrials.gov/ct2/show/NCT03731260. Accessed February 16, 2023

TKI for SM: avapritinib

Patient selection: symptomatic ISM (or smoldering SM managed on the same pathway). It is listed "for ISM only" among the preferred options and is contraindicated/not recommended when platelet count is <50 × 10^9/L.

Concurrent anti-mediator therapy remains foundational

Monitoring on therapy: H&P and labs every 6–12 months (or sooner for new issues), serial DEXA scans based on severity/extent of bone disease, and assessment of symptom burden and quality of life using the MSAF and MQLQ instruments.
*package insert for dose modifications and adverse-reaction monitoring.

Response assessment is based on improvement in disease-related symptoms and/or B-findings.

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. *NEJM Evidence*. 2023;2(6).

Treatment of Mast Cell Disease:

Bruton Tyrosine Kinase (BTK) Inhibitors

remibrutinib (Rhapsido)

- **Recently approved for CSU**

And more medications in trials!

Supportive Habits/Lifestyle:

Hydration & Electrolytes- ***common/freq need***

⅛th teaspoon sea salt (~250mg sodium) with 8oz water & some food

1000mg sodium with 32oz water

- LMNT, Liquid IV packets

Various sodium amounts

- Vitassium capsules
- Salt tablets

Treatment of Mast Cell Disease:

Neuroimmune axis & bidirectional “cycling” *UPDATE & cite*

EMDR DNRS Gupta … others

& techniques/therapies such as CBT & MBSR

Sleep

Neuroimmune & systemic benefits

NOT another medication/pill & need to address the stress & trauma that typically accompanies severe chronic illness

Supportive Habits/Lifestyle:

Stretching & Movement Relaxation

pilates, yoga, tai chi

walking, weights

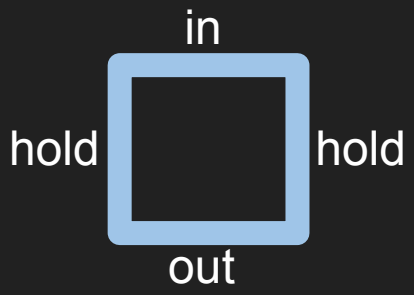
breathing techniques

Bed rest = Bad news
for dysautonomia

Supportive Habits/Lifestyle:

Relaxation Techniques

Breathing techniques (breathwork)



- Box breathing: same length of time/count for each “side of a box”
- 4-4-8: 4 count in through nose - 4 count hold- 8 count slowly breathe out through pursed lips
- Many more!

Mast Cell Disease Resource Folder

Practical Tools!

https://drive.google.com/drive/folders/13DuZWAsMYkHKmhwJD0in4H1y8M0q2vFJ?usp=sharing

Mast Cell Disease: Work up & Treatment

Objectives:

1. Recognize the clinical features and diagnostic criteria of clonal and non-clonal mast cell disorders

1. Select and interpret appropriate laboratory, genetic, and pathologic studies used in the evaluation of suspected mast cell disease

1. Identify potential comorbidities and underlying drivers of mast cell activation to guide individualized management

1. Implement individualized pharmacologic and nonpharmacologic treatment strategies based on disease subtype, symptom burden, and underlying mechanisms

Encouragement & Hope

Stay Curious. Stay Humble. Keep Looking.

- We don’t know everything
- Unexplained doesn’t mean unreal
- Do what you can when a patient has a visit, little by little
- Keep learning- this is a really exciting time in the world of mast cell disease!

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Thank you!

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