

Tryptase: From Anaphylaxis to Mastocytosis

New Concepts in Mast Cell Mediators
WAO2011
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Disclosure Slide
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<p>Employment</p> <ul style="list-style-type: none"> - VCU/HS <p>Research Interests</p> <ul style="list-style-type: none"> - NIH - Genentech, Novartis, GSK, Pharming, Ception, Cephalon <p>Science Advisory Board</p> <ul style="list-style-type: none"> - Mast Cell Pharm - Genentech <p>J Clin Immunol</p> <ul style="list-style-type: none"> - Associate Editor 	<p>Consulting</p> <ul style="list-style-type: none"> - Sanofi-Aventis, Exochemis <p>Financial Interests</p> <ul style="list-style-type: none"> - VCU-Phadia: Royalties for tryptase test - VCU-Millipore, -Santa Cruz, -BioLegend, -Hycult BioTec: Royalties for mAbs - Up-To-Date Card royalties - Cecil's Textbook of Medicine chapter royalties - NIH Study Section
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Clinical Vignettes: Can a biomarker of mast cell involvement be clinically helpful?

56 y/o stung by an insect, underlying HBP (HCTZ, lisinopril), c/o dizziness, dyspnea and chest pain. ER: MI

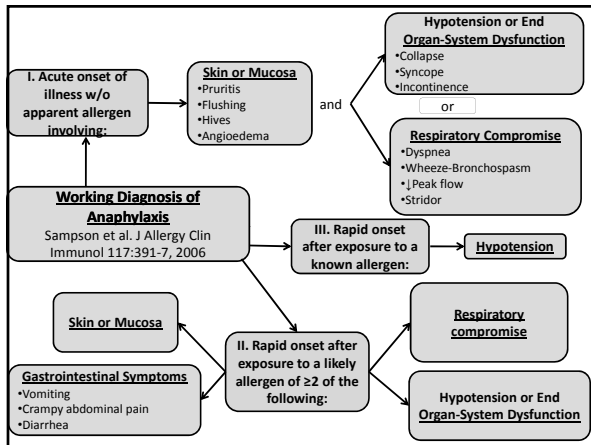
24 y/o to OR for elective cholecystectomy, PCN allergy hx. During anesthesia induction: BP ↓ 120/60 to 60/30 & P ↑ 75 to 120, improved over ~30 min with iv fluids & epinephrine.

50 y/o male with osteoporosis, vertebral fx & flushing spells. When 20 y/o systemic anaphylaxis to wasp sting.

35 y/o M with prior urticaria response after an insect sting. DM, enalapril. Likelihood of systemic anaphylactic shock to a future insect sting?

Definition of Systemic Anaphylaxis

Systemic anaphylaxis is a form of immediate hypersensitivity arising when mast cells and/or basophils are provoked to secrete mediators with potent vasoactive and smooth muscle contractile activities that evoke a systemic response.

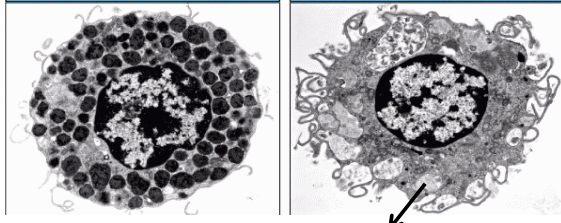


Differential Diagnosis of Systemic Anaphylaxis

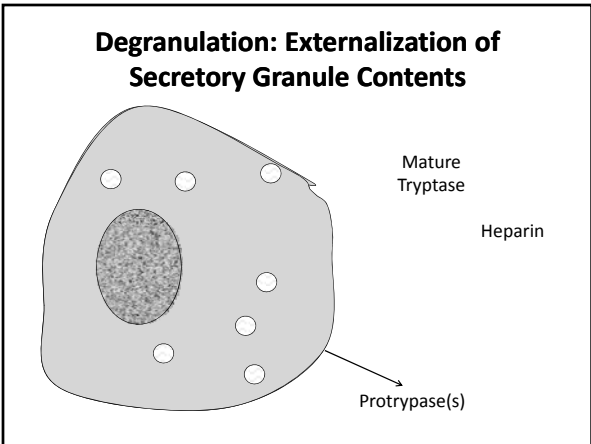
- Pulmonary/Cardiogenic Shock**
- Flushing disorders** (carcinoid syndrome, VIPoma)
- Vasovagal, Panic attacks, Vocal cord dysfunction**
- Hereditary/Acquired Angioedema** (bradykinin)
- Contact system activation** (bradykinin, CHSO₄ contaminant)
- Complement activation** (C3a & C5a)
- Scombroidosis** (histamine)
- Other shock syndromes** (septic)
- Systemic mastocytosis** (anaphylaxis)

Can a laboratory test provide objectivity to the clinical diagnosis of systemic anaphylaxis?

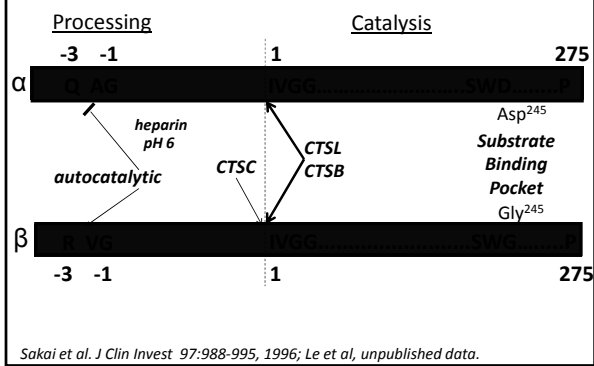
Resting Mast Cell **Activated Mast Cell**



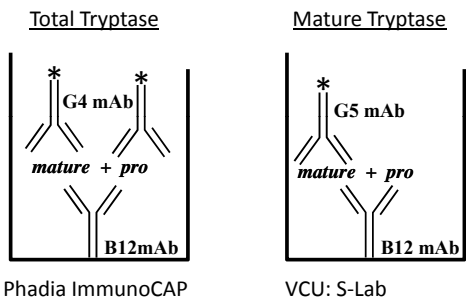
Preformed Granule Mediators:
histamine, heparin, **tryptase**, chymase, carboxypeptidase A3
Newly-Generated Lipids, Cytokines, Chemokines:
PGD₂, LTC₄, PAF (PAF acetyl hydrolase), S1P, IL-4/13



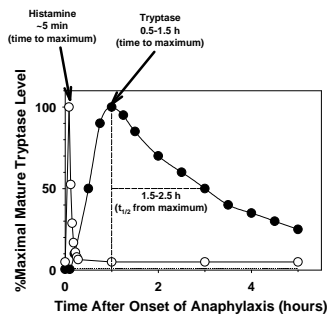
Two Key Differences Between α - & β - Tryptases



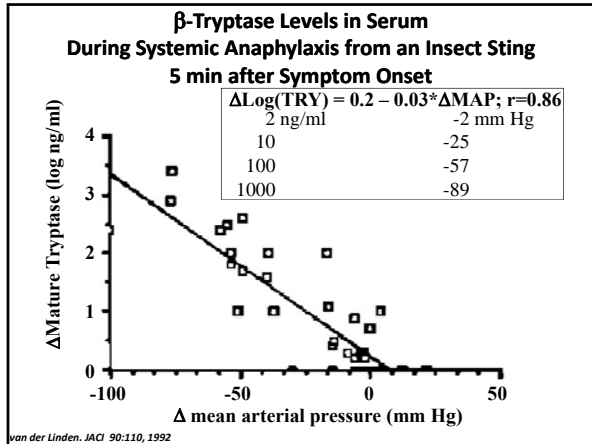
Immunoassays for Total (pro + mature) & Mature Tryptases

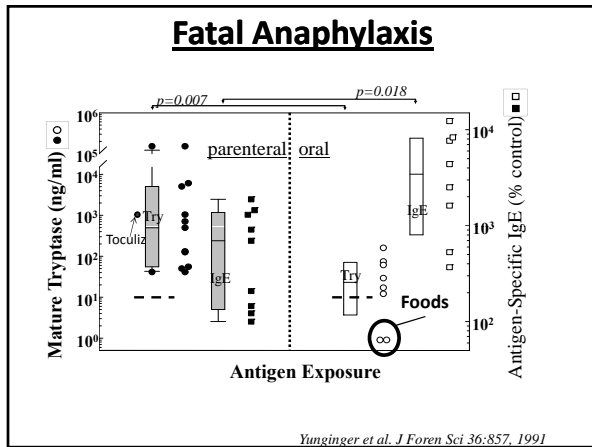


Mature Tryptase & Histamine Levels in Plasma During Insect Sting-Induced Systemic Anaphylaxis



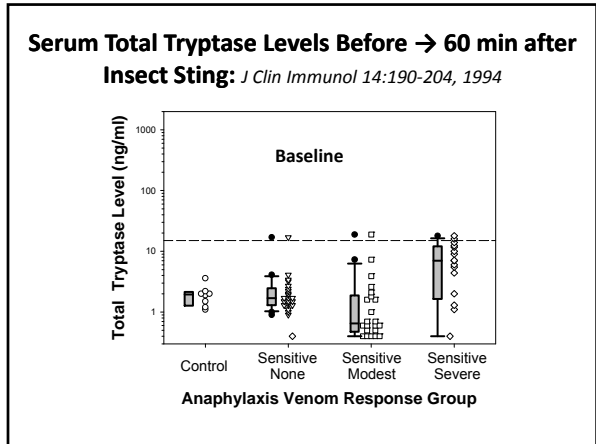
J Clin Invest 83:1551, 1989





Anaphylaxis without elevated tryptase?

1. Local mast cell-mediated angioedema (laryngeal).
2. Mast cells with less tryptase (MC_T v MC_{TC}).
3. Mast cells further from circulation (mucosal v perivascular).
4. Early (mast cell) v late (basophil/eosinophil) phase.
5. Non-mast cell-mediated (basophils).



Characteristics of the Total Tryptase & Mature Tryptase Immunoassays (ng/ml)

Tryptase Type	Mature Tryptase	Total Tryptase
	mature	pro + mature
Normal Serum Baseline	<1	1 – 15 (11.4)
Systemic Anaphylaxis (acute)	>1	↑

Case 1

56 y/o stung by an insect, underlying HBP (HCTZ, lisinopril), c/o dizziness, dyspnea and chest pain. ER: MI

Acute:

- EKG: Inferior MI
- Troponin: elevated
- Tryptase: mature=6 ng/ml; total=15 ng/ml
- venom IgE skin test: negative

Baseline (1 month later):

- Tryptase: mature tryptase <1; total tryptase =5
- venom IgE skin test: positive

Acute elevations in mature and total tryptase ~ diagnosis of systemic anaphylaxis to venom, which precipitated the MI.

Case 2

24 y/o to OR for elective cholecystectomy with PCN allergy hx. Received fentanyl, lidocaine, midazolam, propofol, vancomycin, rocuronium prior to surgery → BP(P) from 120/60 (75) to 60/30(120), improved over ~30 min with iv fluids & epinephrine and procedure cancelled.

Acute tryptase: total = 13; mature =5.3
Allergy skin test negative to lidocaine, rocuronium, propofol
Vancomycin (1 g) infused over 5 min

*High peak [vancomycin] directly activates mast cells
~severe Red-Man Syndrome*

Does the serum total tryptase level reflect:

- (1) The burden of mast cells in tissues
- &
- (2) The effect of cytoreductive therapy?

Characteristics of the Total Tryptase & Mature Tryptase Immunoassays (ng/ml)

Tryptase Type	Mature Tryptase	Total Tryptase
	mature	pro + mature
Normal Serum Baseline	<1	1 – 15 (11.4)
Systemic Anaphylaxis (acute)	>1	↑
Systemic Mastocytosis (non-acute)	±↑ RATIO: Total/Mature > 20	≥20*

*WHO minor criterion

Diagnosis of Systemic Mastocytosis

Major Criterion MC Granulomas (BM; >15 MC)
<p style="text-align: center;">Minor Criteria</p> <ol style="list-style-type: none"> 1. Abnormal MC morphology (>25% spindle-shaped) 2. Activating <i>KIT</i> mutation (e.g., D816V) 3. CD25⁺ or CD2⁺ MC 4. Baseline serum total tryptase >20 ng/ml (>11.4 insect sting anaphylaxis)
<p>Diagnosis</p> <p>1 major + 1 minor ≥3 minor</p>

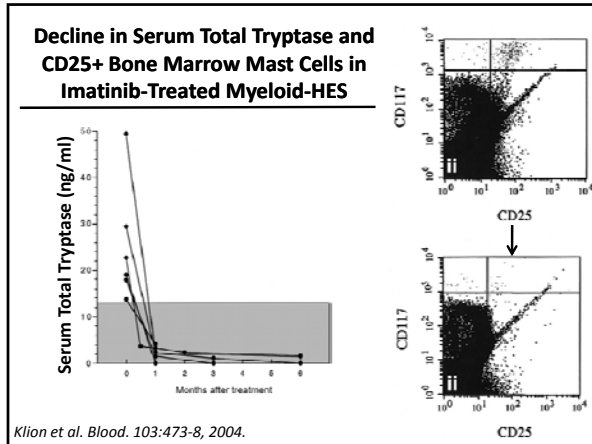
Systemic Mastocytosis

Urticaria
Pigmentosa Bone Marrow



Differential Diagnosis of Elevated Total Tryptase Level in Serum

1. Systemic mastocytosis
2. Mast Cell Activation Syndrome
3. Hypereosinophilic syndrome: FIP1L1-PDGFR α
4. Acute Myelocytic Leukemia (~30%)
5. Myelodysplastic syndromes
6. SCF administration
7. End-stage kidney disease
8. ?Normal variant
9. ?Transient mastocytosis



Case 3

50 y/o male with osteoporosis, vertebral fx & flushing spells.
When 20 y/o systemic anaphylaxis to wasp sting.

Cortisol, PTH, TSH, VS, Pi, creat, Ca WNL.
Baseline serum tryptase: 29 ng/ml
BM Bx: MC granulomas, CD25+ spindle-shaped MCs

Osteoporosis/vertebral fx may be a presenting manifestation of systemic mastocytosis

Systemic mastocytosis:
osteoporosis (30%)[40% vertebral fx], osteosclerosis (10%)
Osteoporosis: 1-2.5% systemic mastocytosis

Is an elevated serum total tryptase level an indicator for risk of severe systemic anaphylaxis?

Mast cell clonality in patients with systemic reactions to insect stings & ↑serum baseline total tryptase levels (sBT)

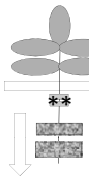
Bonadonna et al. J Allergy Clin Immunol 123:680-6, 2009

3-year prospective study → 44/379 (12%) systemic reactors
sBT >11.4 ng/mL

BM bx 30/34 (88%) ~ clonal mast cell disorder (D816V Kit);
systemic mastocytosis (21/34) ; MCAS (9/34)
What % with sBT<11.4 have clonal mast cells?

1. Consider mast cell clonality: insect sting SA & sBT > 11.4 → BM bx
2. 12% of systemic reactors → 88% mast cell clonality
(Epidemiology: 0.8-5% incidence systemic reactions)
3. sBT >11.4 ng/mL → OR=6 severe anaphylactic reaction

Implications of Constitutively Activated D816V Kit Tyrosine Kinase



Functionally:

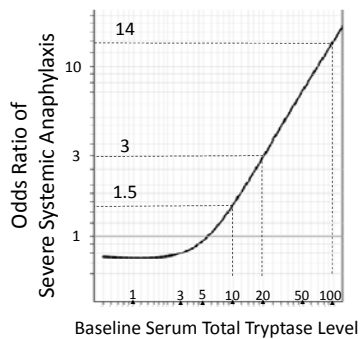
1. Primes mast cell activation
2. Increases mast cell survival
3. Increases mast cell accumulation

Practically:

1. Minor criterion for diagnosis of systemic mastocytosis.
2. Presence indicates mast cell clonality.
3. Anaphylaxis to insect venom stings & IT, ?other allergens
4. Predisposes to spontaneous/primary MCAS

Odds ratio for severe systemic anaphylaxis to insect sting ~ baseline serum total tryptase level

Ruëff et al. JACI 124:1047-54, 2009



Case 4

35 y/o M with prior urticaria response after an insect sting. DM, enalapril. Likelihood of systemic anaphylactic shock to a future insect sting?

Clinical Feature	OR
Male	1.7
ACE-inhibitor	2.2
Prior systemic reaction	4.7
Tryptase = 30	6.0

The risk for a severe anaphylactic reaction to a future insect sting is substantial; venom immunotherapy and an action plan (Trendelenburg/Epipen) to a future sting are indicated.

Diagnosis of Mast Cell Activation Syndrome

1. Typical clinical signs and symptoms
 2. Clinically significant increase in serum total tryptase:
 >(baseline + 20% of baseline + 2 ng/ml)*
 ≤4 h after onset
 3. Response of clinical symptoms to HR1 ± HR2 blockers or cromolyn
- *1.0 → 1.0 + 0.2 + 2 → >3.2 ng/ml
 10 → 10 + 2 + 2 → >14 ng/ml
 20 → 20 + 4 + 2 → >26 ng/ml

Valent P et al. Definitions, criteria, and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol, 2011 in press.

Concluding Comments

Levels of serum tryptase can reflect

1. Mast cell activation during anaphylaxis
 2. Mast cell number (mastocytosis and M-HES)
 3. Risk of anaphylaxis severity to insect stings and IT
- ...thereby providing diagnostic and therapeutic guidance.

Contributors	
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