

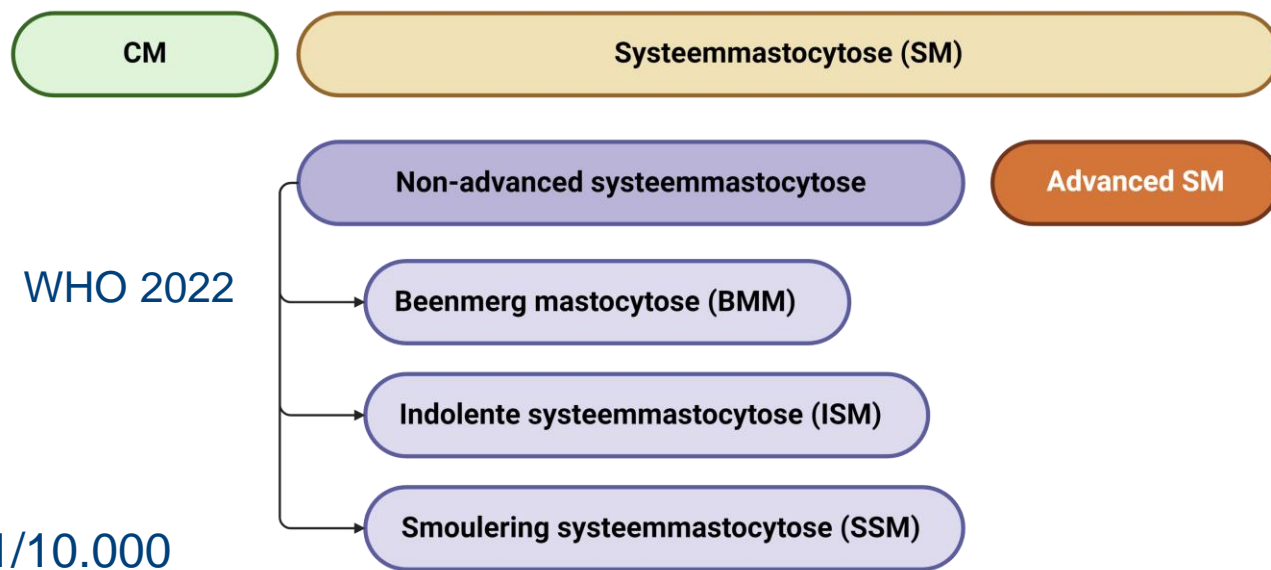
De verschillende gezichten van indolente systeemmastocytose: Symptomen, diagnostiek en behandeling van mediator release

Prof. dr. Christine Breynaert
IAL – Allergie & Klinische Immunologie, UZ Leuven

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Systemmastocytose

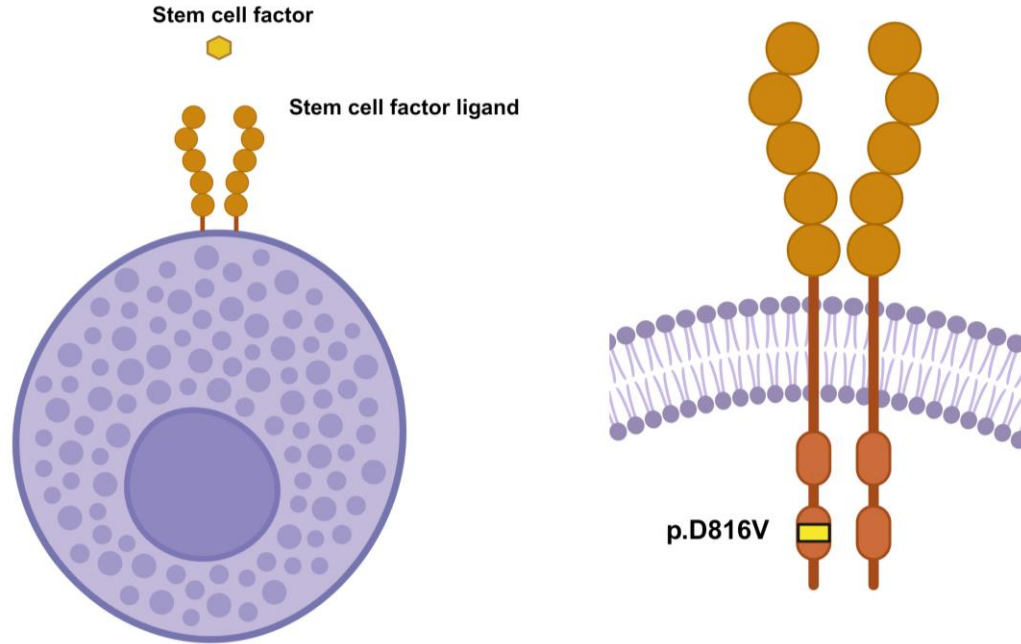
- Abnormale proliferatie van clonale mastcellen in **extracutane** organen (beenmerg, milt, lever, GI,...)



Prevalentie: 1/10.000

Systememastocytose: *KIT* p.D816V

> 95%: Gain-of-function mutatie in *KIT* (type III tyrosine kinase receptor)





Symptomen

Non-advanced systemic mastocytosis

Mediator release

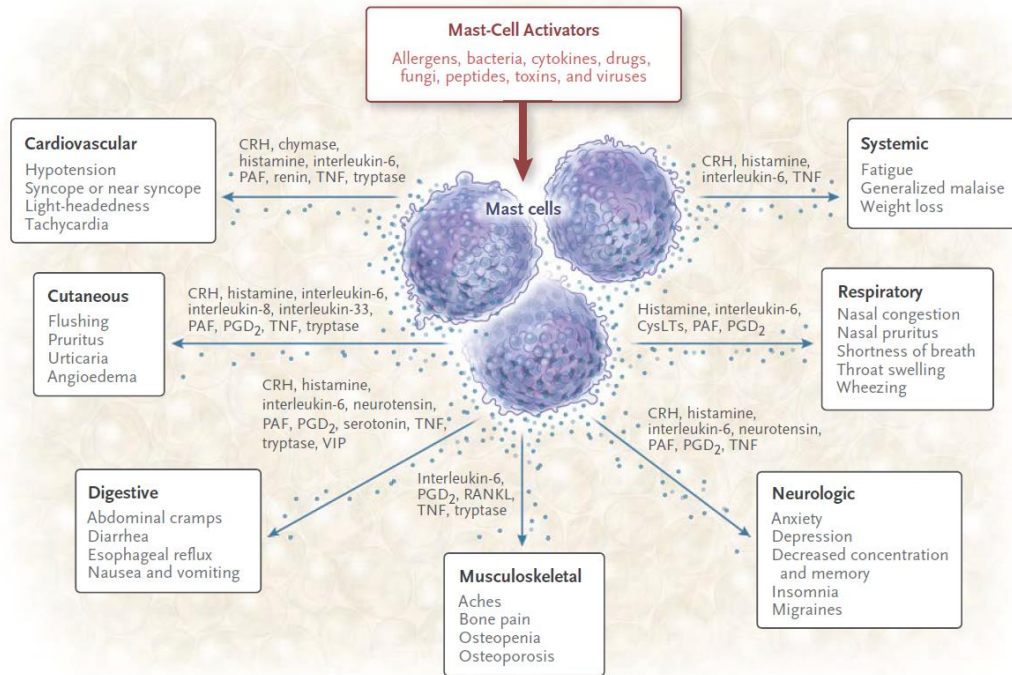


Table 1. Conditions That Can Mimic Mast-Cell Disorders.

Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)*
Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia
Parathyroid tumor
Pheochromocytoma
Carcinoid syndrome

Digestive conditions

Adverse reaction to food*
Eosinophilic esophagitis*
Eosinophilic gastroenteritis*
Gastroesophageal reflux disease
Gluten enteropathy
Irritable bowel syndrome
Vasoactive intestinal peptide-secreting tumor

Immunologic conditions

Autoinflammatory disorders such as deficiency of interleukin-1-receptor antagonist*
Familial hyper-IgE syndrome
Vasculitis*

Neurologic and psychiatric conditions

Anxiety
Chronic fatigue syndrome
Depression
Headaches
Mixed organic brain syndrome
Somatization disorder
Autonomic dysfunction
Multiple sclerosis

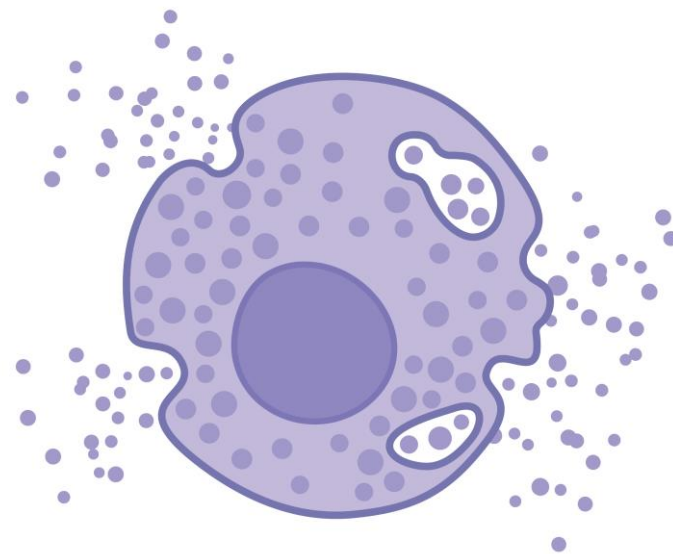
Skin conditions

Angioedema*
Atopic dermatitis*
Chronic urticaria*
Scleroderma*

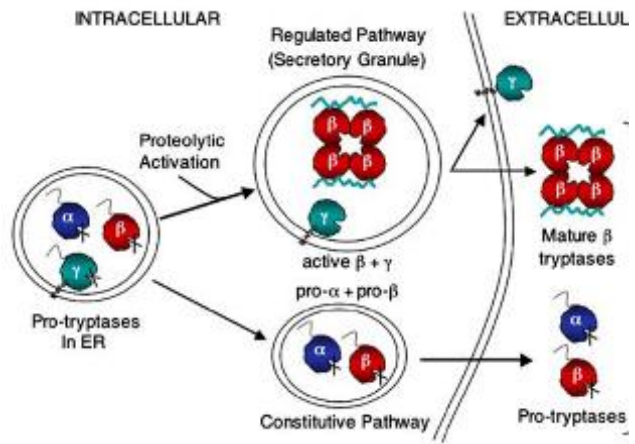
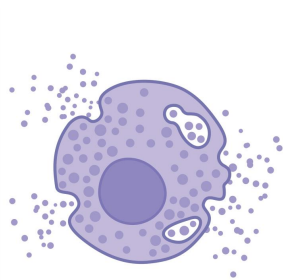


Majeure symptomen van SM

1. Verhoogd basaal tryptase
2. Anafylaxie
3. Huidletsels
4. Gastro-intestinale symptomen
5. Botziekten



1. Basaal tryptase (BST)



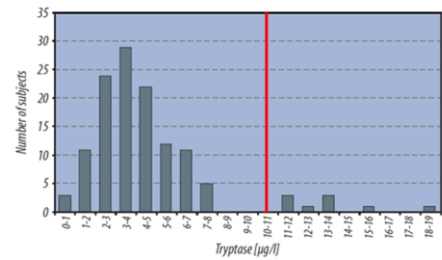
Acuut tryptase

Basaal tryptase

Totaal tryptase



N = 126
 Mean = 3,8 $\mu\text{g/L}$
 95th percentile = 11,4 $\mu\text{g/L}$



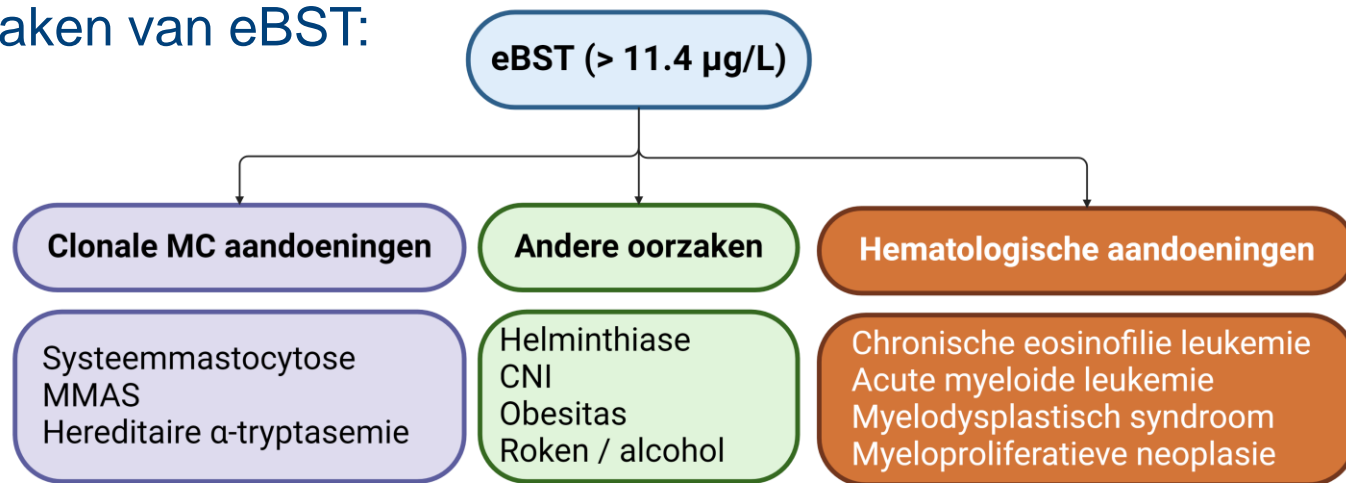
Verhoogd basaal tryptase > 11,4 $\mu\text{g/L}$



Verhoogd basaal tryptase (eBST)

- **Basaal tryptase > 20 µg/L**: minor criterium voor diagnose van SM

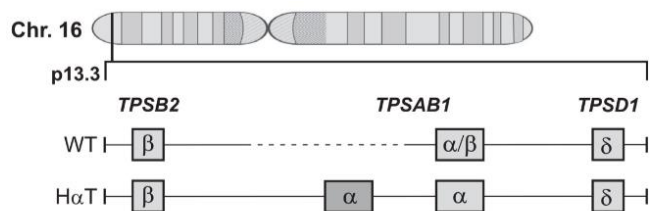
- Andere oorzaken van eBST:



- Een normaal BST sluit systeemmastocytose **NIET** uit!

Hereditaire α -tryptasemie (HaT)

- Prevalentie in gewone bevolking: 5%
- **Basaal tryptase > 8 μ g/L**
- **Autosomaal dominant**
- Mono-allelische multiplicatie van *TPSAB1*
- Observationeel onderzoek: **associatie met ernstige HVA** (hemodynamische weerslag)
- Modulator/versterkende factor voor de ernst van mastcel activatie bij mastocytose en/of anafylaxie

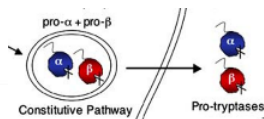


Haplotypes

| Non-HaT: | HaT: |
|---------------------|-----------------------------------|
| $\alpha\beta$ 42% | $\alpha\alpha\beta$ 2.1% |
| $\beta\beta$ 53% | $\alpha\alpha\beta\beta$ * |
| $-\beta$ * | $\alpha\alpha\alpha\beta$ 0.3% |
| $\beta\beta\beta$ * | $\alpha\alpha\alpha\alpha\beta$ * |

Genotypes

| Non-HaT: | HaT: |
|---------------------------------|---|
| $\beta\beta/\beta\beta$ 35% | $\alpha\alpha\beta/\beta\beta$ 2.2% |
| $\alpha\beta/\beta\beta$ 38% | $\alpha\alpha\beta/\alpha\beta$ 1.7% |
| $\alpha\beta/\alpha\beta$ 22% | $\alpha\alpha\beta\beta/\beta\beta$ * |
| $\alpha\beta/\beta-$ * | $\alpha\alpha\beta\beta/\alpha\beta$ * |
| $\beta\beta/\beta-$ * | $\alpha\alpha\beta/\alpha\alpha\beta$ 0.2% |
| $\beta\beta\beta/\beta\beta$ * | $\alpha\alpha\alpha\beta/\beta\beta$ 0.4% |
| $\beta\beta\beta/\alpha\beta$ * | $\alpha\alpha\alpha\beta/\alpha\beta$ 0.2% |
| | $\alpha\alpha\alpha\beta/\alpha\alpha\beta$ * |
| | $\alpha\alpha\alpha\alpha\beta/\beta\beta$ * |
| | $\alpha\alpha\alpha\alpha\beta/\alpha\beta$ * |



2. Anafylaxie

Definitie: ernstige levensbedreigende systemische overgevoeligheidsreactie van ≥ 2 orgaansystemen

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)

| | | | |
|--|---|---|--|
| | AND AT LEAST ONE OF THE FOLLOWING: | | |
| | | Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia) | Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence) |

OR 2 Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours)

| | | | |
|---|---|--|---|
| | | | |
| Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula) | Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia) | Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence) | Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting) |

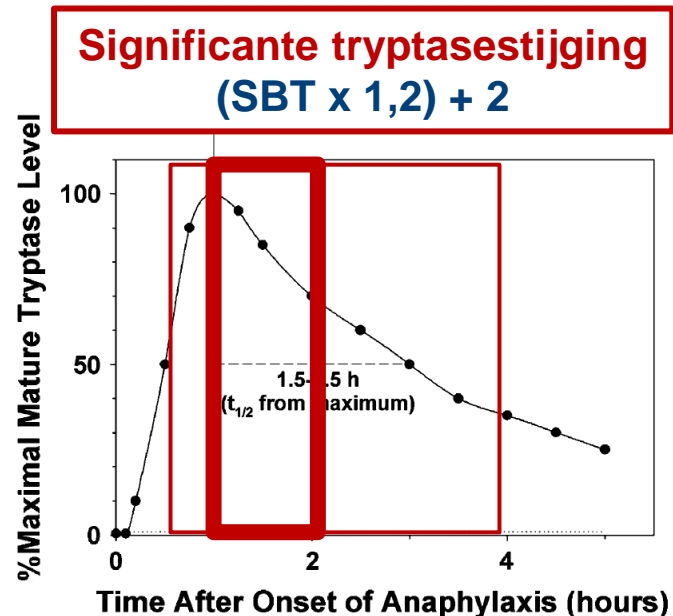
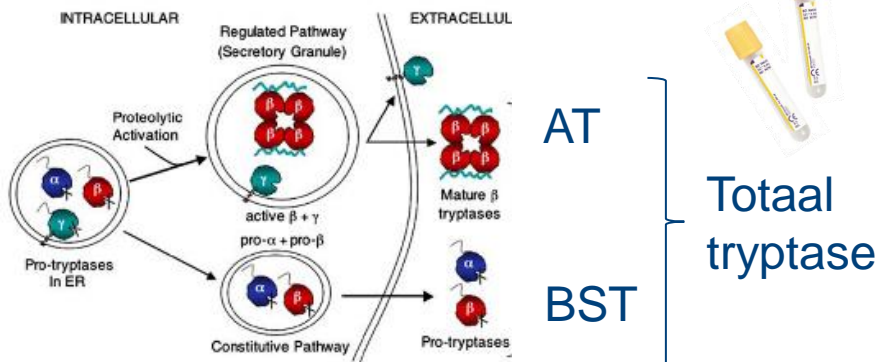
OR 3 Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours)

| | |
|--|--|
| Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP *** | Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline |
|--|--|



Significante tryptasestijging

- Bewijs voor mastcel degranulatie



Atypische syncopes, stereotiepe reacties: acute tryptasebepaling!



Anafylaxie

Lifetime risk 1,6% - Prevalentie 0,3%
(incidentie 5/100 000 pers jaren)

- **Prevalentie van anafylaxie bij SM 100x** hoger ivm gewone bevolking

Cumulatieve prevalentie 22% - 43% - 49%

Anafylaxie = symptoom dat meestal leidt tot diagnose

CAVE aspecifieke mastceldegranulatie

- **Hymenoptera sting:** meest frequente oorzaak van anafylaxie bij VW met SM (22-53%)



- Prevalentie van SM bij patiënten met **ernstige insectengif allergie** is significant hoger ivm de gewone populatie



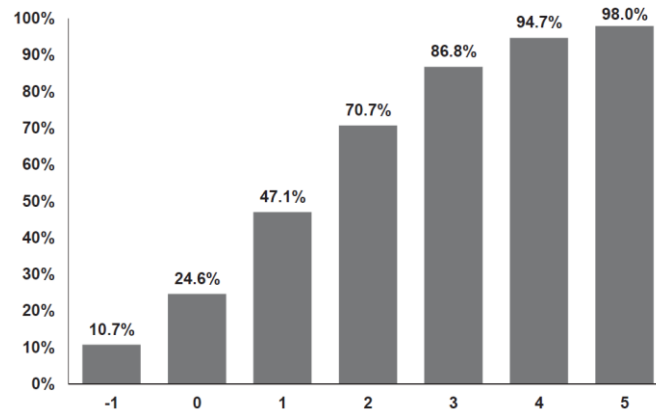
3. Cutane mastocytose

- **Volwassenen** met ontstaan van cutane mastocytose hebben (bijna) **ALTIJD** een onderliggende systeemmastocytose.
- Bij herkennen van letsels: snellere diagnose (en behandeling)
- ECNM register: 944/1145 VW patiënten met MIS diagnose van SM

TABLE II. Risk score for SM in patients with MIS

| Parameter | Score |
|---|-------|
| Tryptase (ng/mL) | |
| <10.0 | -1 |
| ≥10.0 and <15.0 | 0 |
| ≥15.0 and <20.0 | 1 |
| ≥20.0 | 3 |
| Bone symptoms or osteoporosis | 1 |
| Constitutional or cardiovascular symptoms | 1 |

-1 to 0 low, 1-2 intermediate and 3-5 high risk



4. Gastro-intestinale symptomen

- Reflux, braken, abdominale krampen, diarree tot colitis
- Vaak aanvalsgewijs / langere periode
- Uitgebreide endoscopie met biopsies op alle niveau's voor tryptase / KIT kleuringen door ervaren patholoog

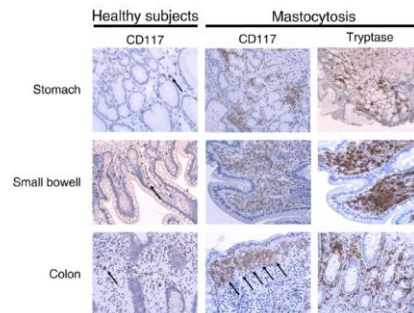
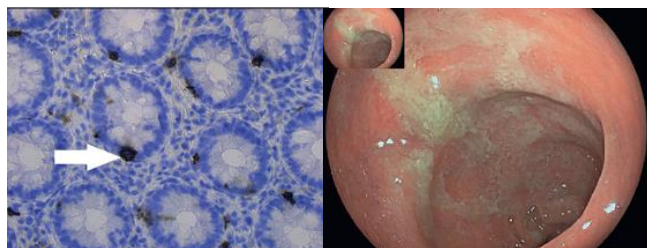


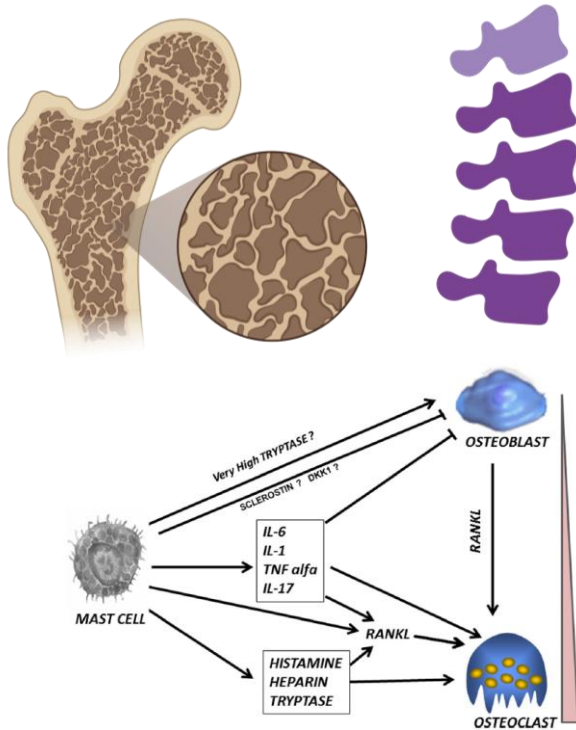
FIG 2. Examples of MC infiltration of the gastrointestinal tract. Biopsy specimens of the stomach, small bowel, and colon from healthy subjects and patients with mastocytosis undergoing immunohistochemistry with anti-CD117 antibody (Gx200) and anti-tryptase antibody (Gx100 for stomach biopsy specimens and Gx200 for small bowel and colon biopsy specimens) are shown. Black arrows show MCs.

TABLE II. Gastrointestinal symptoms and history of patients with mastocytosis and matched controls

| | Patients with mastocytosis (n = 83) | Control subjects (n = 83) | P value |
|--|-------------------------------------|---------------------------|---------|
| Age on study (y), mean (SD) | 52.0 (12.9) | 52.0 (12.7) | .99 |
| Male sex, no. (%) | 24 (28.9) | 24 (28.9) | 1 |
| Medical history, no. (%) | | | |
| Crohn disease | 0 | 0 | 1 |
| Ulcerative colitis | 1 (1.2) | 2 (2.4) | 1 |
| Celiac disease | 1 (1.2) | 0 | .5 |
| Gastric ulcer | 6 (7.4) | 2 (2.4) | .13 |
| Duodenal ulcer | 5 (6.2) | 0 | .02 |
| Gastric or duodenal ulcer | 9 (11.4) | 2 (2.4) | .02 |
| Colorectal cancer | 1 (1.2) | 0 | .5 |
| Gastrointestinal symptoms | | | |
| Any gastrointestinal symptom,* no. (%) | 49 (59.0) | 16 (19.3) | <.0001 |
| Bloating score, mean (SD) | 4.2 (3.3) | 1.7 (2.4) | <.0001 |
| Bloating score >5, no. (%) | 26 (33.3) | 6 (7.2) | <.0001 |
| Abdominal pain score, mean (SD) | 3.6 (3.1) | 1.0 (1.8) | <.0001 |
| Abdominal pain score >5, no. (%) | 21 (27.3) | 4 (4.8) | <.0001 |
| Nausea score, mean (SD) | 3.3 (10.5) | 0.1 (0.5) | <.0001 |
| Nausea score ≥1, no. (%) | 18 (23.4) | 7 (8.4) | .009 |
| Vomiting score, mean (SD) | 0.3 (1.2) | 0.04 (0.24) | .11 |
| Vomiting score ≥1, no. (%) | 6 (7.8) | 2 (2.4) | .16 |
| Diarrhea score, mean (SD) | 6.2 (9.4) | 0.3 (1.6) | <.0001 |
| Diarrhea score ≥5, no. (%) | 27 (33.8) | 1 (1.2) | <.0001 |
| Blood in stool, no. (%) | 14 (18.7) | 18 (21.7) | .6 |
| Gastrointestinal endoscopy, no. (%) | | | |
| Upper gastrointestinal endoscopy | 42 (55.3) | 13 (15.7) | <.0001 |
| Colonoscopy | 43 (51.8) | 14 (17.1) | <.0001 |

*A bloating score of greater than 5, an abdominal pain score of greater than 5, a nausea score of 1 or greater, a vomiting score of 1 or greater, or a diarrhea score of 5 or greater.

5. Osteopenie / osteoporose / fracturen



- Vroegtijdige osteoporose of indeukingsfracturen bij (jonge) personen!
- Onverklaarbare/familiale osteoporose
- Spectrum: **osteoporose**, focale lytische of sclerotische botletsels, osteosclerose, botpijnen
- Mechanisme: grotendeels ongekend



Diagnostiek

Non-advanced systemic mastocytosis

Hoeksteen van diagnose: BM-BB biopsie

Diagnose van systeemmastocytose

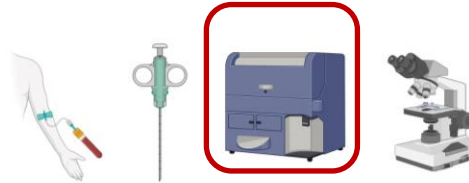
Major criterium

Multifocale dense infiltraten van mastcellen (≥ 15 MC/aggregaat) in BM-BB en/of extra-cutaan orgaan



Minor criteria

1. BST > 20 $\mu\text{g/L}$ (bij HaT: aanpassing BST)
2. p.D816V KIT mutatie (of andere)
3. $\geq 25\%$ spoelvormige mastcellen
4. CD2 en/of CD25 en/of CD30 expressie



Vierledige diagnostiek

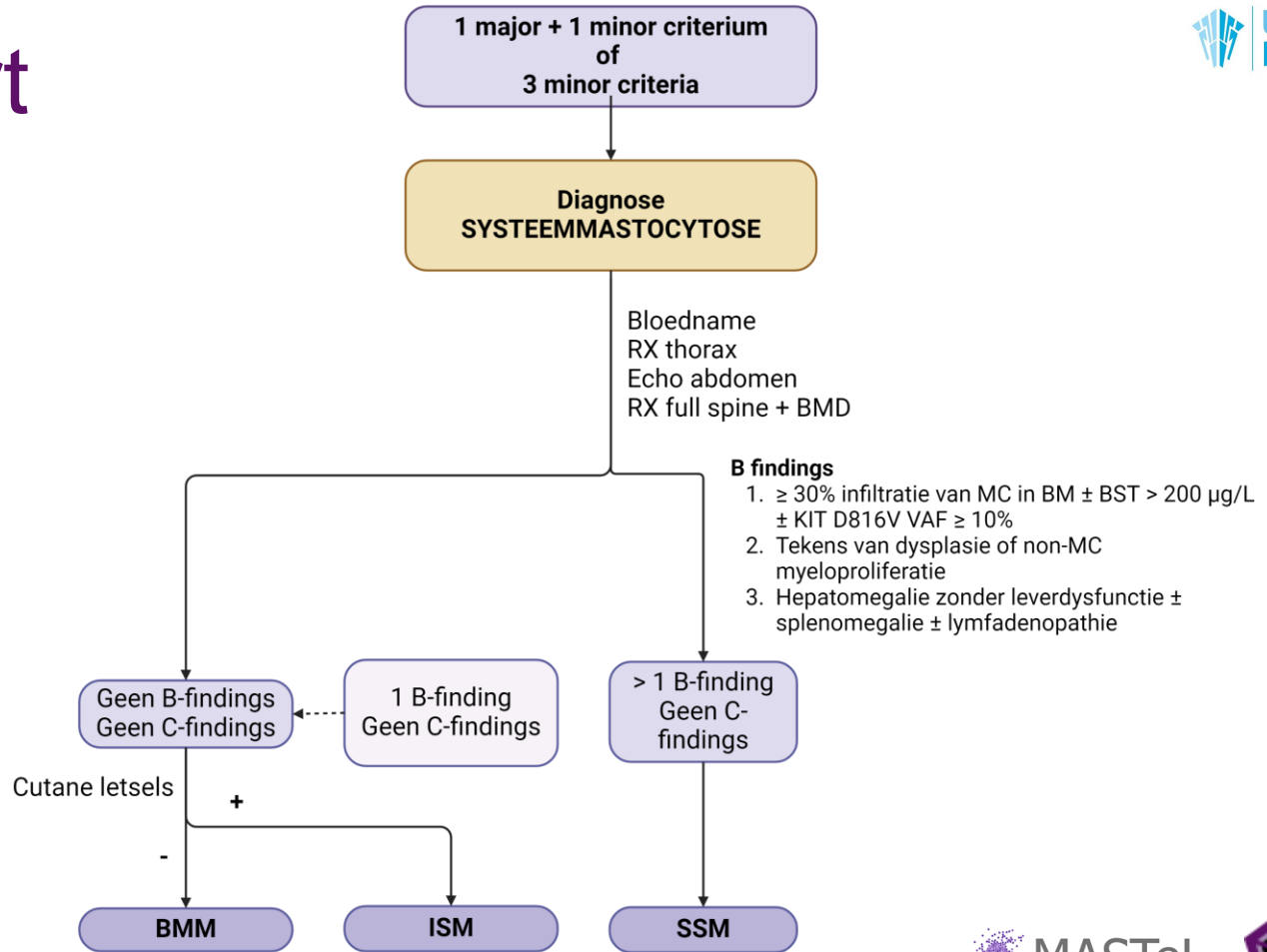
1. Cytologie
2. Immuunfenotypering
3. APO
4. Moleculair onderzoek

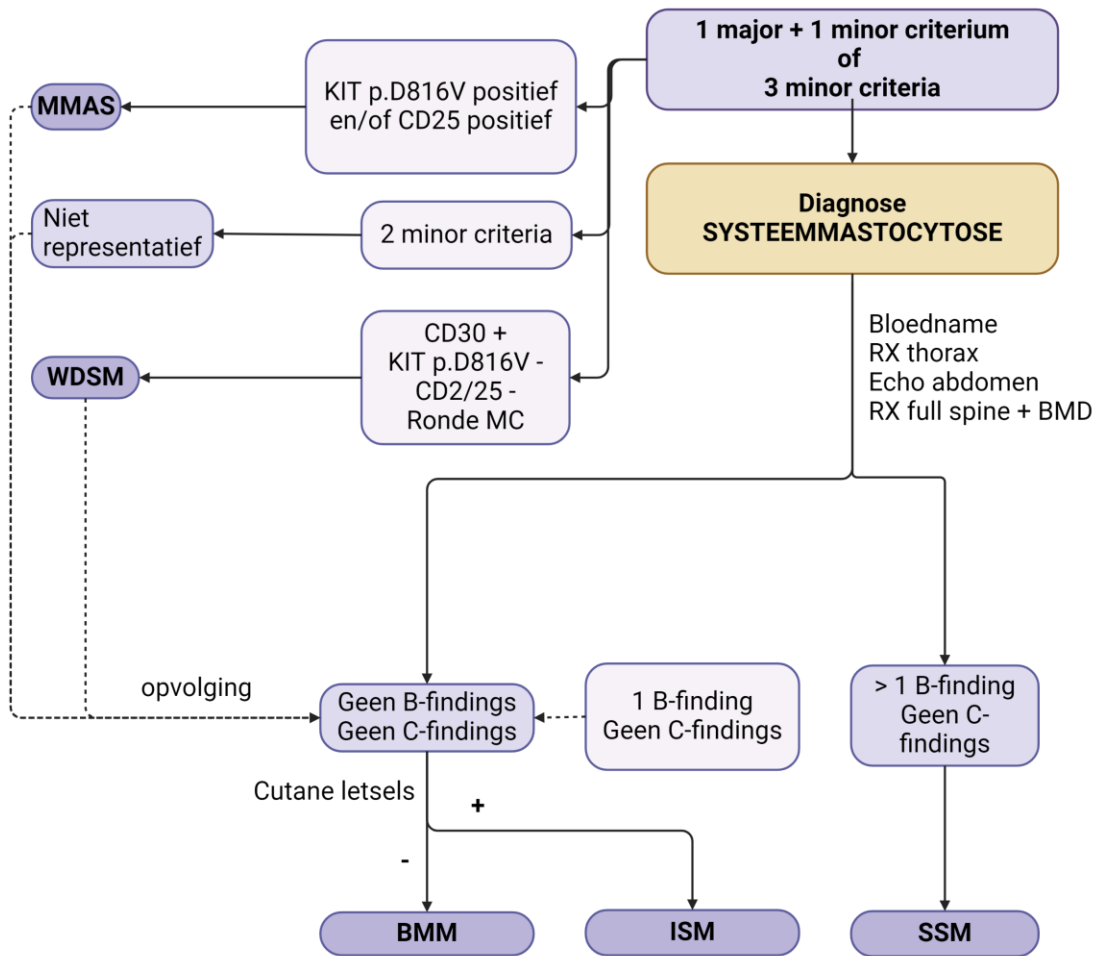
Diagnose: tenminste

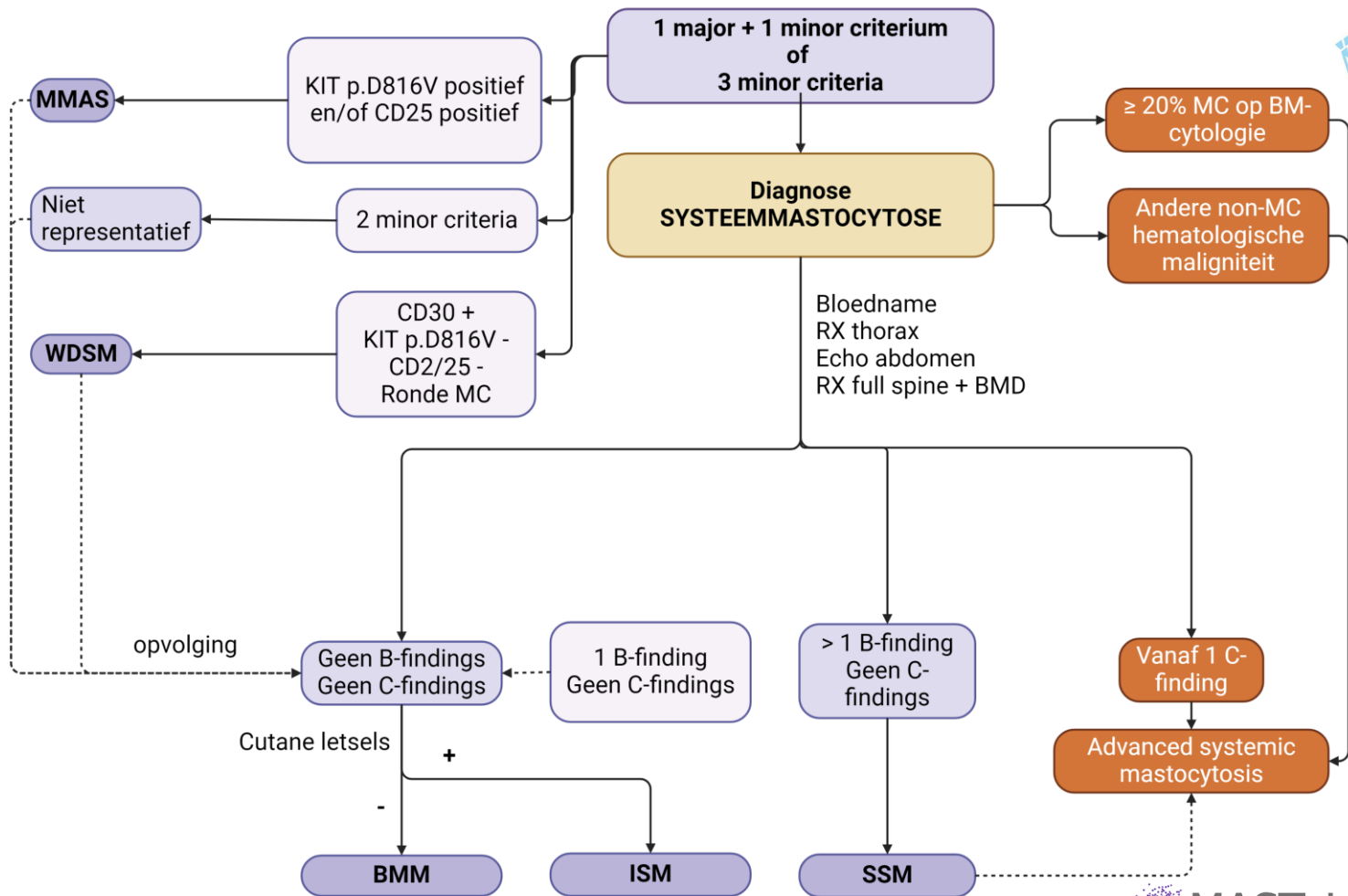
- 1 major + 1 minor criterium
- 3 minor criteria

Diagnose SM in afwezigheid van eBST en/of p.D816V KIT!

Flowchart





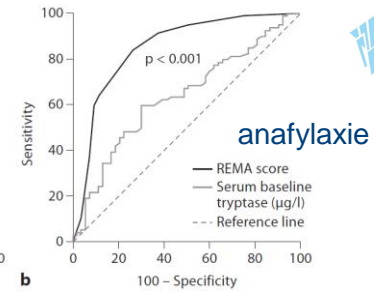
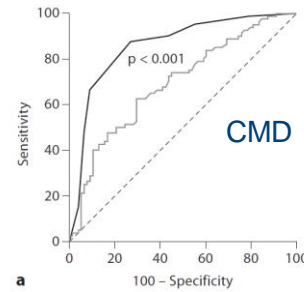


When to marrow?

NICAS (idiopathic anaphylaxis)

| A. Mast cell activation symptom scores-NICAS | | |
|--|-----------------------|-------|
| 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 KIT p.D816V | Negative | -1 |
| | Positive | +3 |

Total score ≥ 2 is predictief voor clonal mast cell disease (CMD)



REMA-score

| Variable | Score |
|---|-------|
| Gender | |
| Male | +1 |
| Female | -1 |
| Clinical symptoms | |
| Absence of urticaria, pruritus and angioedema | +1 |
| Urticaria, pruritus and/or angioedema | -2 |
| Presyncope and/or syncope | +3 |
| Tryptase ¹ | |
| <15 ng/ml | -1 |
| >25 ng/ml | +2 |

Sterke klinische verdenking voor SM



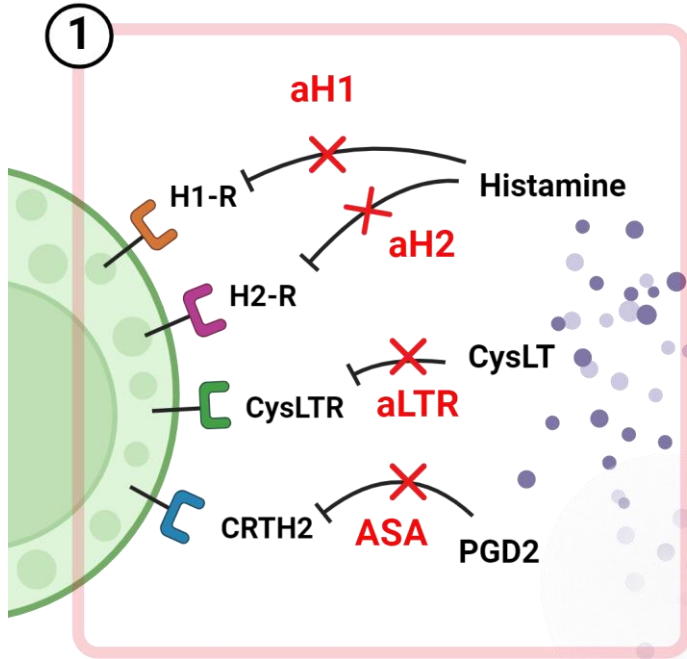
- Cutane mastocytose bij VW
- Ernstige anafylaxie **zonder** urticaria of angio-oedeem (insectengif!)
- Bij insectengif allergie: recidief anafylaxie na staken immunotherapie
- Recidiverende anafylaxie eci of op verschillende culprits (medicatie, insect, jodiumhoudend contrast, voeding,...)
- Vroegtijdige osteoporose of indeukingsfracturen
- Recidiverende (ernstige) stereotiepe reacties met mastcel mediator release (flushing, diarree, hypotensie, bronchospasme, BWZ-verlies)



Behandeling

Non-advanced systemic mastocytosis

1. Anti-mediator therapie



Anti-mediator therapie

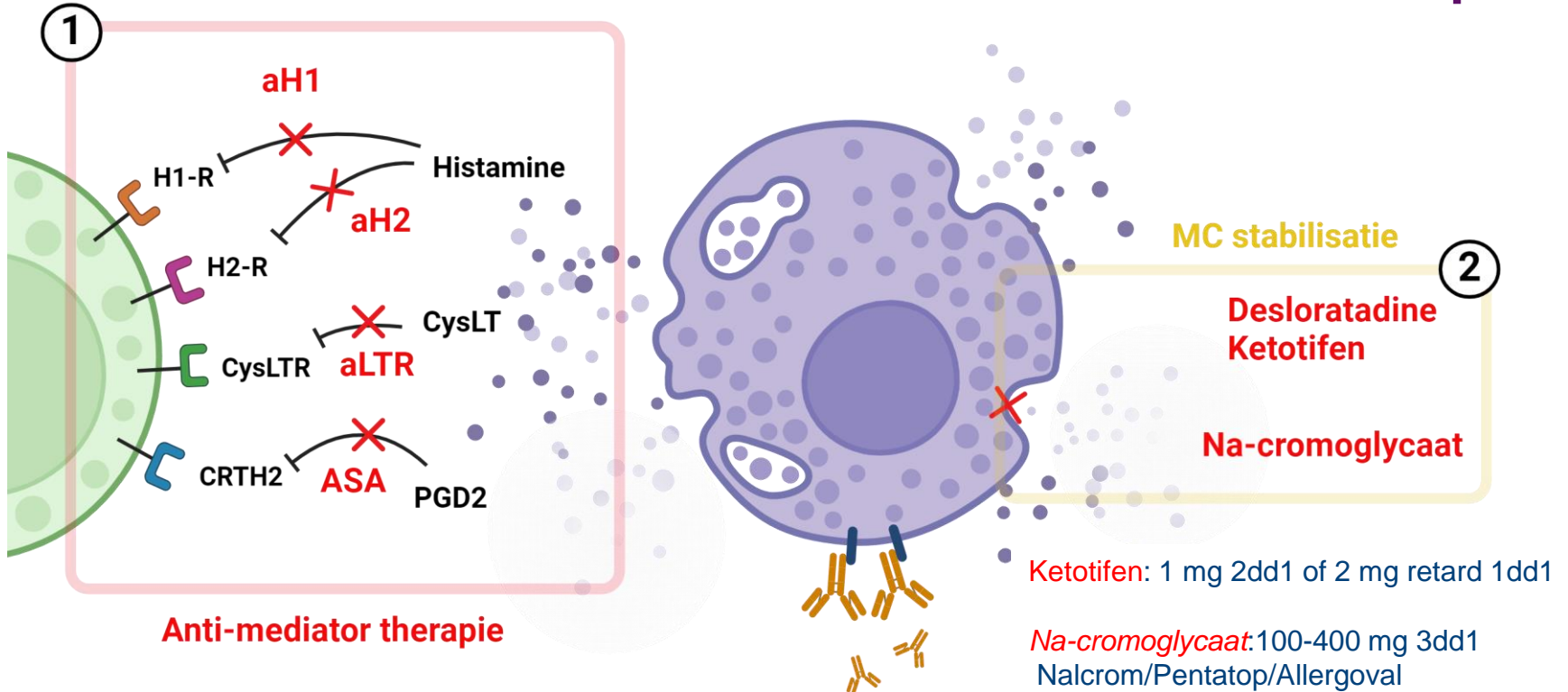
aH1: nieuwe generatie tot 4dd
ebastine
bilastine

aLTR: montelukast 10 mg 1-2dd1

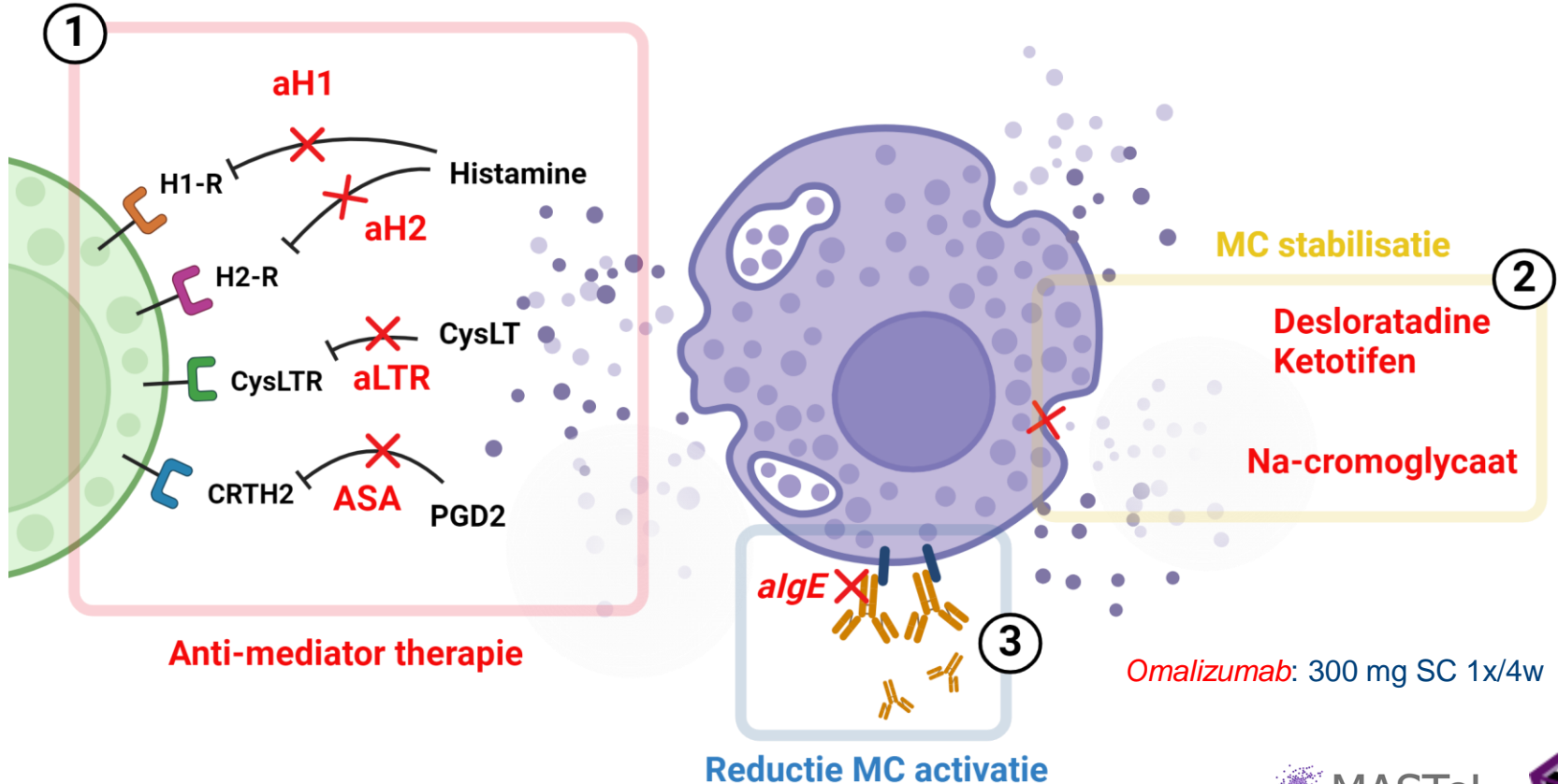
aH2: famotidine 20-40 mg 2dd1

Aspirine: CAVE anafylaxie

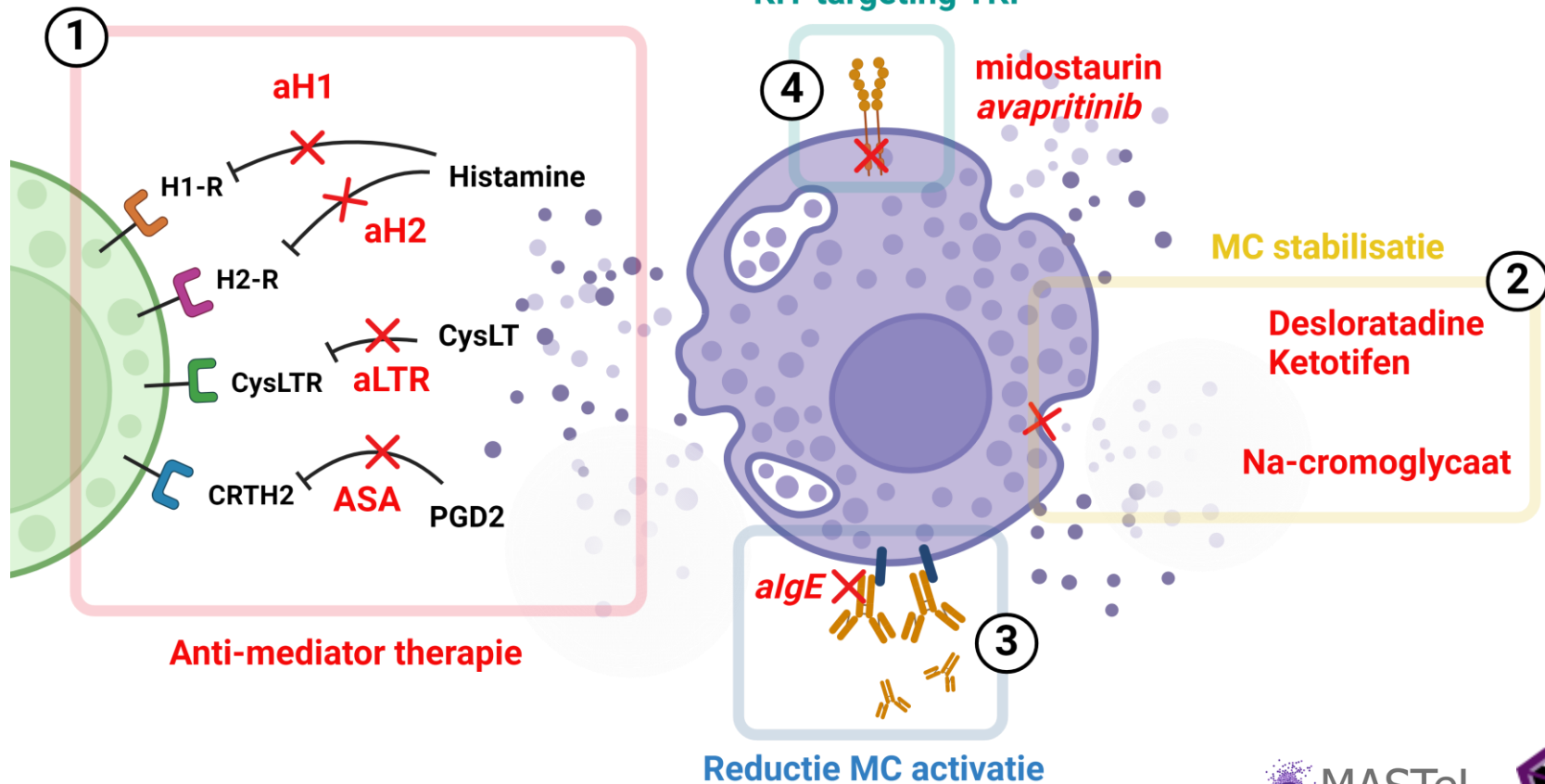
2. Mastcelstabiliserende therapie



3.Reductie mastcel activatie



4. Mastcel reductie



Preventie en educatie

- Preventie van **anafylaxie**: rescue-medicatie stand-by + educatie

- Adrenaline auto-injector 0,3 mg IM
- Ebastine 20 mg smelttabletten: 40 mg SL



- In geval van **insectengif allergie**: VIT levenslang, kort interval

- Preventie van **osteoporose/indeukingsfracturen**:
actieve screening + tijdig instellen van calcium/vitamine D
supplementen en antiresorptieve therapie (bisfosfanaten – denosumab,
ev. Teriparatide)

CAVE specifieke mastceldegranulatie

- Medicatie: curares (voorkeur suxamethonium, cisatracurium), bepaalde opiaten (voorkeur remi-/su-/fentanyl), aspirine en NSAIDs, β -blokkers
- Jodiumhoudende contrastmiddelen
- Insectengif (wespen-, bijen-, en hommeligif), en –speeksel (daas!)

- H1- (en H2- zo beschikbaar) antihistaminica en/of montelukast en/of ketotifen als onderhoudsbehandeling
- Rescuemedicatie: Adrenaline auto injector (Epipen® / Jext® 0.3 mg) en Ebastine 20 mg smelttabletten stand-by



PREMEDICATIE bij geplande onderzoeken, operaties, etc.: van dag -2 tot dag +2

- Levocetirizine 5 mg/Ebastine 20 mg/Bilastine 20 mg 2x1 pd
 - Montelukast 10 mg 2x1 pd
 - Medrol 8 mg 1x1 pd (dag -1 en dag 0) bij operaties/contrasttoediening
 - (Anxiolyticum pre-procedure te overwegen)
-



