Mast cells and Disease

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Consultant Immunologist

UHB and UHCW

Declarations

- Chairing meetings and sponsorship- Biocryst

Objectives

- Mast cell biology
- Symptoms associated with mast cell disorders-anaphylaxis

- Mast cell diseases-
  - Presentation
  - Investigation
  - Treatment

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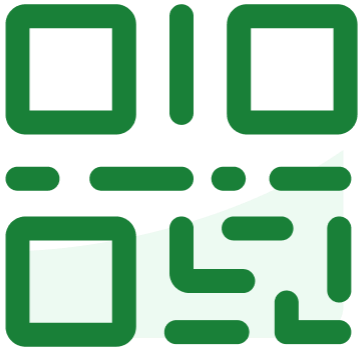

Join at slido.com
#4006328

ⓘ Start presenting to display the joining instructions on this slide.

Patients presents having vomited this?
They ask what is the cause.
What do you tell them?

A. Peptic ulcer
B. Cancer
C. Varices
D. Oesophgeal tear

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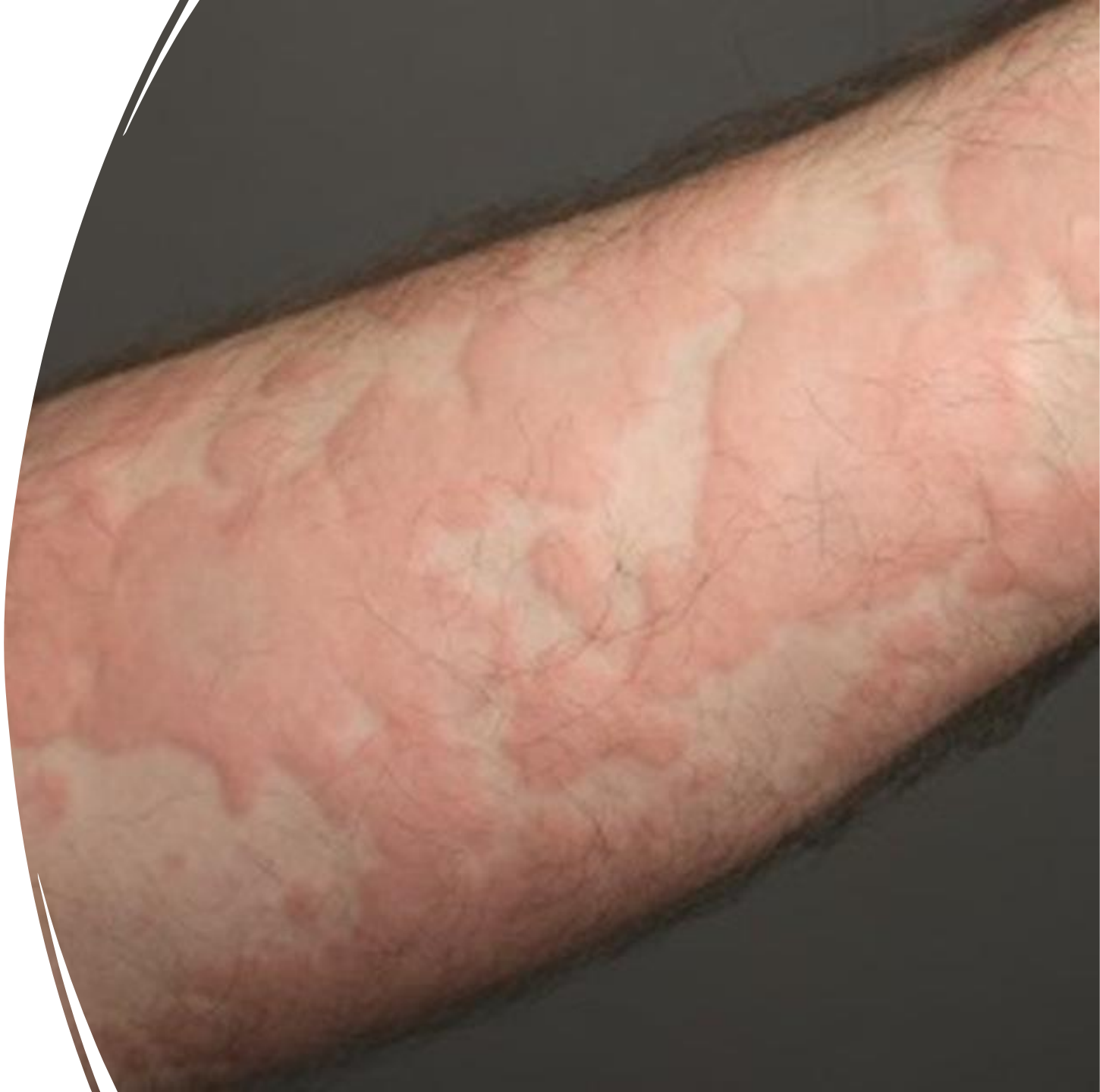
Patients presents having vomited this? They ask what is the cause. What do you tell them?

ⓘ Start presenting to display the poll results on this slide.

Patients presents with this rash with no other symptoms? They ask what is the cause. What do you tell them?

A. Allergic reaction
B. Anaphylaxis
C. Spontaneous urticaria
D. Urticarial vasculitis



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Patients presents with this rash with no other symptoms? They ask what is the cause. What do you tell them?

ⓘ Start presenting to display the poll results on this slide.

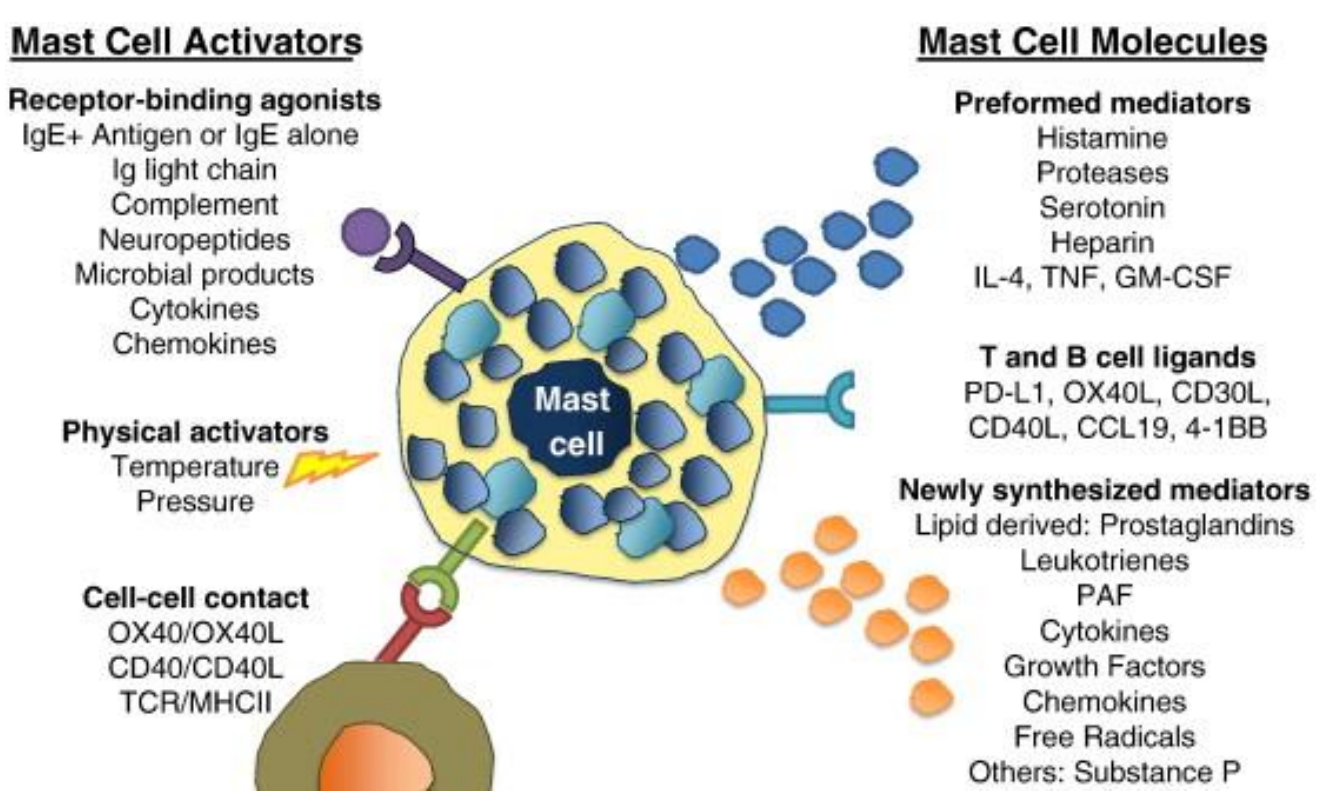
What are mast cells

- Myeloid lineage cells involved in IgE-mediated and non-IgE mediated immunological responses
  - Vasodilation, angiogenesis, vascular homeostasis
  - Allergy, asthma, anaphylaxis, malignancy, mastocytosis
- Some similarities to basophils
- Found in mucosal and epithelial tissues
  - Widely distributed in different sites
  - More abundant in skin, lung, GI tract
- Involved in innate and adaptive immune responses

Development

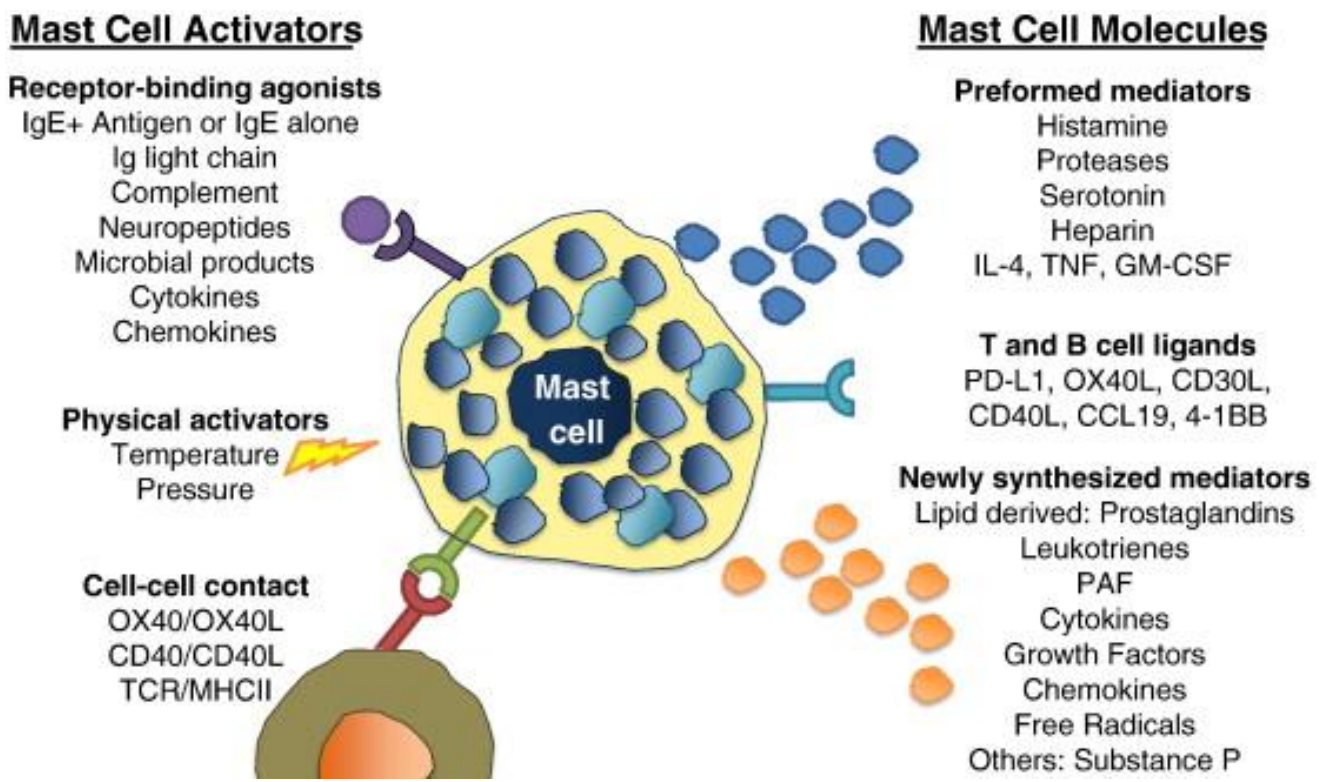
- Bone marrow derived from stem cells
- Stem cell factor (SCF) is *essential* for development and survival
- Kit (CD117) is a transmembrane tyrosine kinase receptor for SCF
- Migrate to peripheral tissues
- Very few in peripheral blood

Activation

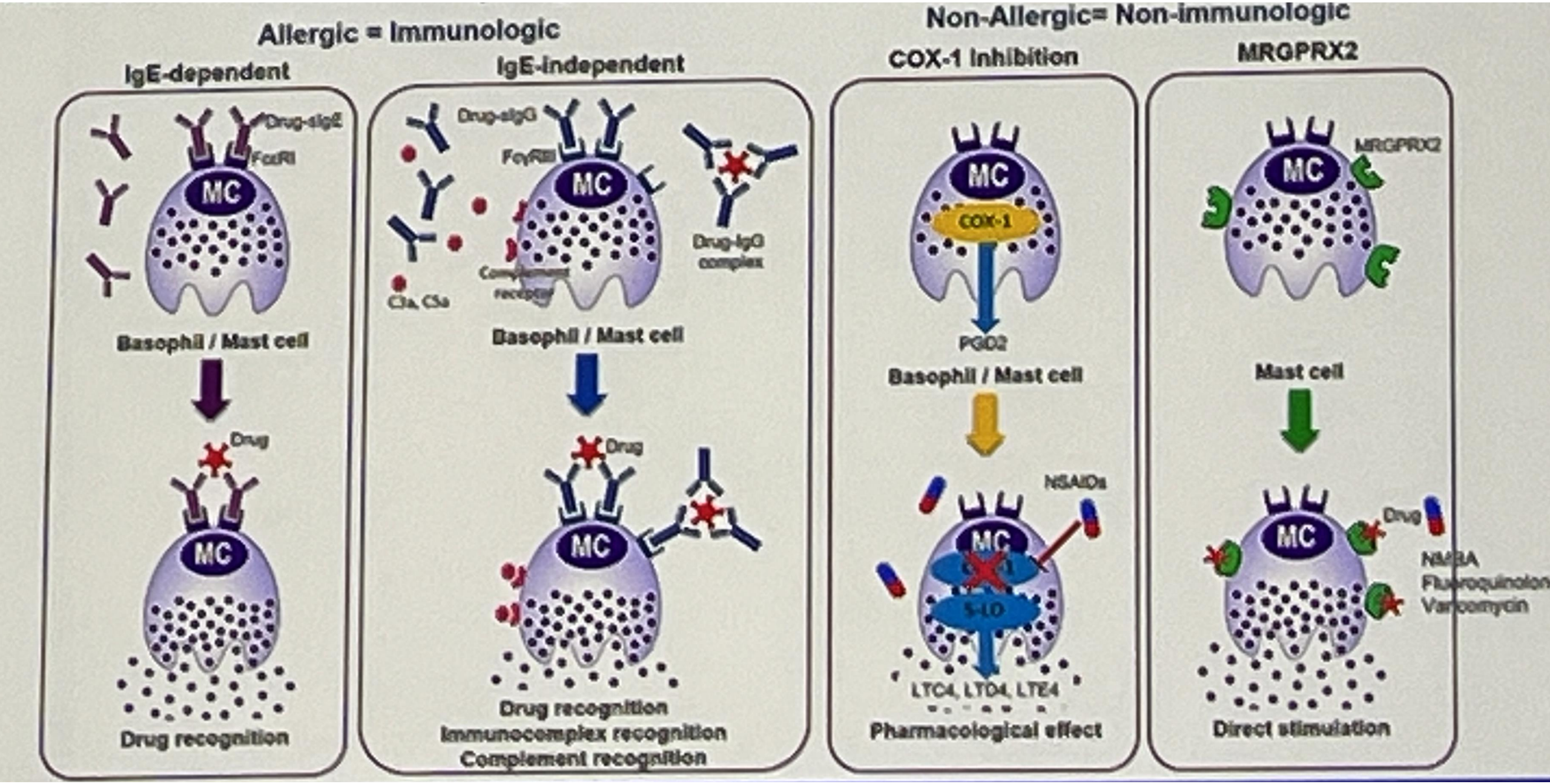


- Activation through surface receptors
  - **High affinity IgE Fc receptors (FcεRI)**
  - Low affinity IgG receptor (FCγRII)
  - MRGPRX2 receptor
  - Complement receptors
  - TLR receptors
  - Drug receptors e.g. PAF, Opioid
  - T-cells
  - Physical stimuli

Function



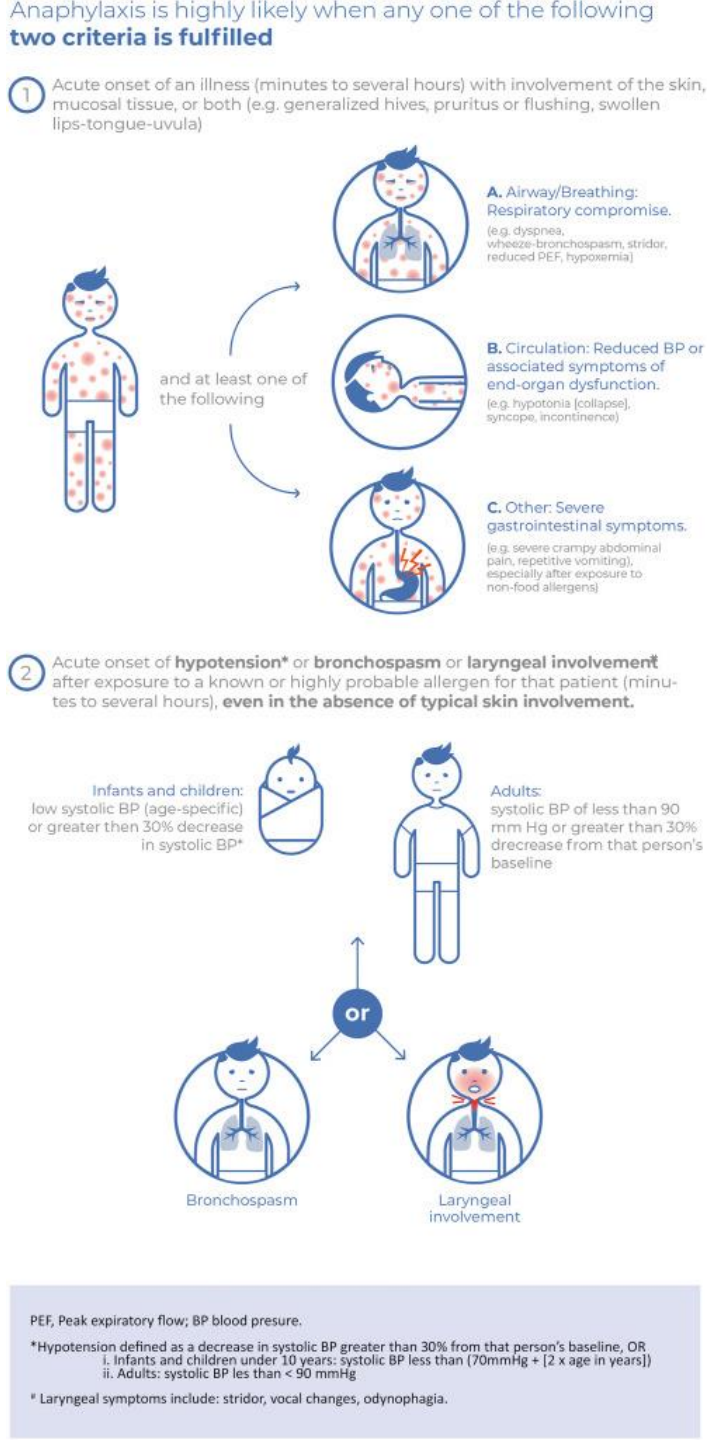
- Preformed mediators
  - Seconds
    - Tryptase, etc
- Newly synthesised mediators
  - <15mins
    - Leukotrienes
    - Prostaglandins
  - > 3 hours
    - Cytokines
    - Chemokines


Allergic = Immunologic
Non-Allergic= Non-immunologic
IgE-dependent
IgE-independent
COX-1 Inhibition
MRGPRX2
Drug-sIgE
FcεRI
MC
Basophil / Mast cell
Drug
Drug recognition
Drug-sIgG
FcγRIII
Complement receptor
C3a, C5a
Drug-IgG complex
Basophil / Mast cell
Drug
Drug recognition
Immunocomplex recognition
Complement recognition
COX-1
PGD2
Basophil / Mast cell
NSAIDs
5-LO
LTC4, LTD4, LTE4
Pharmacological effect
MRGPRX2
Mast cell
Drug
NMBA
Fluoroquinolon
Vancomycin
Direct stimulation

Clinical manifestations

- Excessive release of mast cell mediators
  - Urticaria
  - Flushing
  - Angioedema
  - Shortness of breath
  - Rhinitis
  - Palpitations
  - Nausea
  - Diarrhoea
  - Hypotension
  - Lethargy and fatigue
  - Brain fog, difficulty concentrating
- Anaphylaxis

World Allergy Organisation Criteria for Anaphlaxis



Causes of anaphylaxis

- Insect stings
- Drugs
- Foods
- Latex

- Idiopathic-IA (30-60% in adults, 10 % in children)

- Note atypical allergens omega-5-gliadin and alpha-gal allergy

Adrenaline autoinjector training

Use of Adrenaline Autoinjectors in Adults

Mild symptoms (very common)

- Itchy skin, rash, tickly throat, facial swelling, lip swelling, mild tongue swelling

Treatment: Use antihistamines (chlorphenamine 4-8mg or acrivastine 8mg or cetirizine 10-20mg) as directed

SEEK MEDICAL HELP IF YOUR SYMPTOMS PERSIST OR GET WORSE

Severe symptoms - TRY TO REMAIN CALM- DON'T PANIC

- **A**IRWAY COMPROMISE- *swelling in the throat, tongue or upper airways (tightening of the throat, hoarse voice, difficulty swallowing)*
- **B**REATHING DIFFICULTY-*sudden onset wheezing, breathing difficulty, noisy breathing*
- **C**IRCULATION COMPROMISE- *dizziness, feeling faint, sudden sleepiness, tiredness, confusion, pale clammy skin, loss of consciousness*

1. If you have Airway compromise or breathing difficulty sit on the floor with your back supported by a wall.

2. If you have circulation compromise lie flat with your legs elevated. Lie on your side if you feel sick or if you are vomiting.

Treatment: make sure you have your adrenaline autoinjector and phone

1. **If you experience any of the severe symptoms use your adrenaline auto-injector as directed below without delay- hold the device firmly in a clenched fist in the dominant hand.**
2. **The autoinjector should be administered, even if in doubt**

Emerade (300 or 500)

- Remove white shield from the end
- Press the opened end firmly into thigh
- Hold in place for a full 5 seconds
- Massage injection site for a few seconds

www.emerade-bausch.co.uk

Epipen

- Remove blue safety cap
- Hold pen 10cm away from thigh
- Jab orange tip into thigh at right angles to the leg and press hard into thigh
- Hold in place for a full 3 seconds

www.epipen.co.uk

Jext

- Remove yellow safety cap
- Place black tip onto side of thigh, at right angles to the leg
- Press hard into thigh until you hear the pen click
- Hold in place for a full 10 seconds then massage injection site for a full 10 seconds

www.jext.co.uk

3. If you have a blue inhaler, use it if you feel wheezy or feel tight in your chest

4. Dial 999 immediately. Tell the operator this is anaphylaxis (anna-fill-axis). If you are unable to speak, press 55 on your phone.

5. A second adrenaline auto-injector can be used if symptoms do not improve 5 minutes after the first injection. This should be given into the other thigh.

Please visit the relevant website for further information e.g. obtaining trainer pens, expiry alert service and videos.

Further management

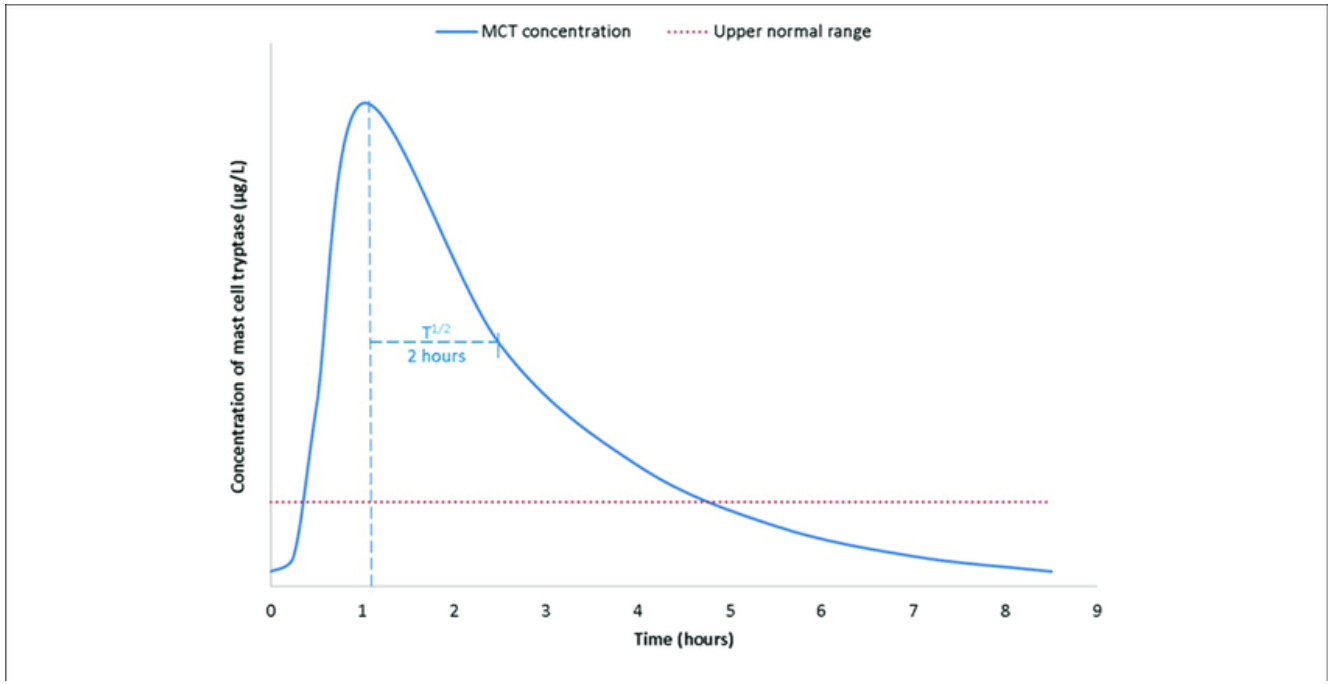
- Strict allergen avoidance
- Immunotherapy
- Medic Alert Bracelet
- Regular antihistamines for IA

Mast cell disorders

Primary	Secondary	Idiopathic/Spontaneous
Mastocytosis- systemic or cutaneous (anaphylaxis)	Allergic disease (anaphylaxis)	Anaphylaxis
Monoclonal mast cell activation disorder (anaphylaxis)	Mast cell activation with chronic inflammatory or neoplastic disorder	Angioedema
	Physical urticarias	Urticaria
	Chronic autoimmune urticarias	Mast cell activation syndrome

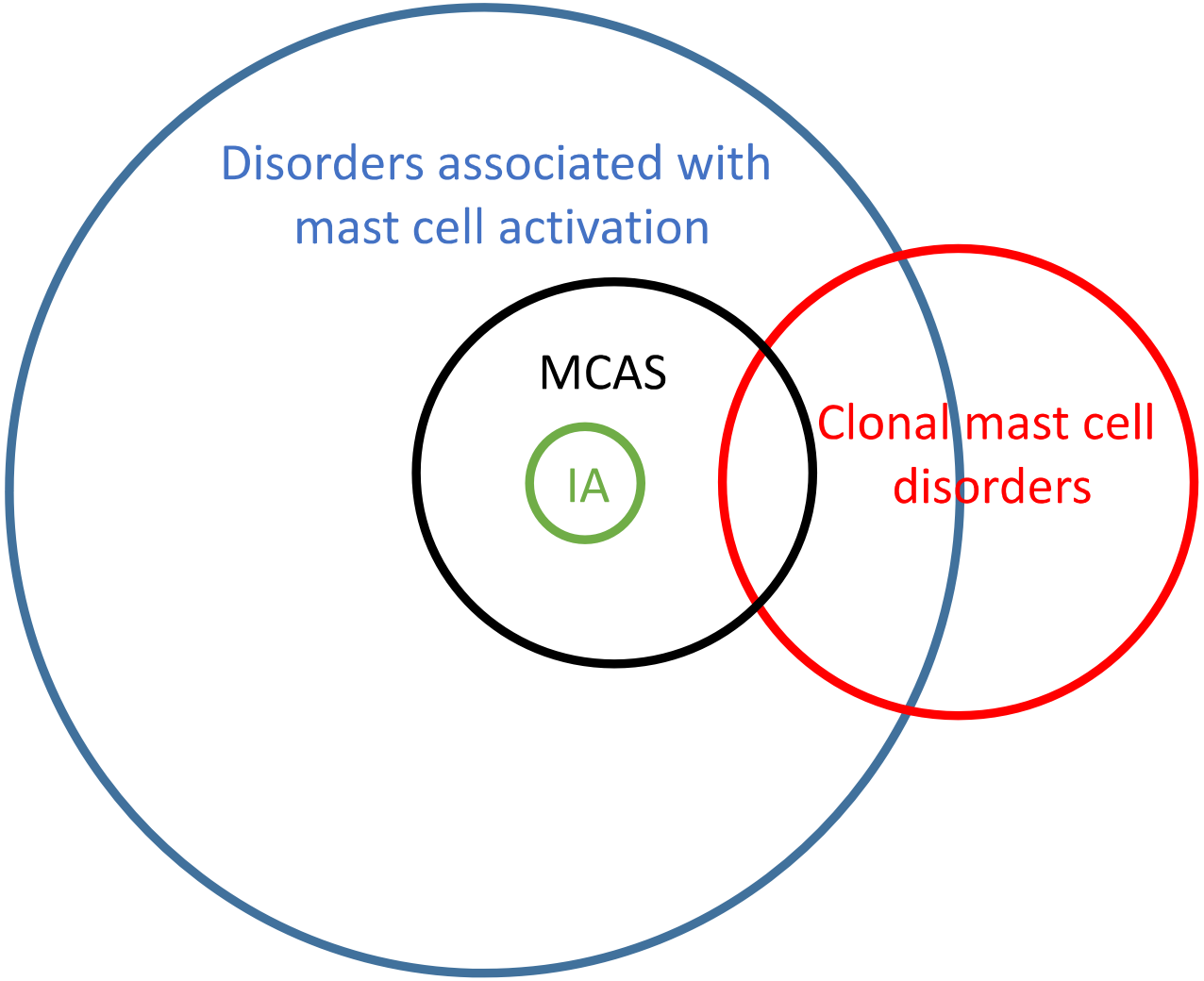
Investigations

1. Serum tryptase
2. Urine methyl histamine
3. Urinary prostaglandin D_2
4. Urinary leukotriene E_4
5. Specific IgE



Mast cell activation is confirmed if:
Baseline is ≥20 % of the individual's own baseline tryptase + 2 mvg/L.

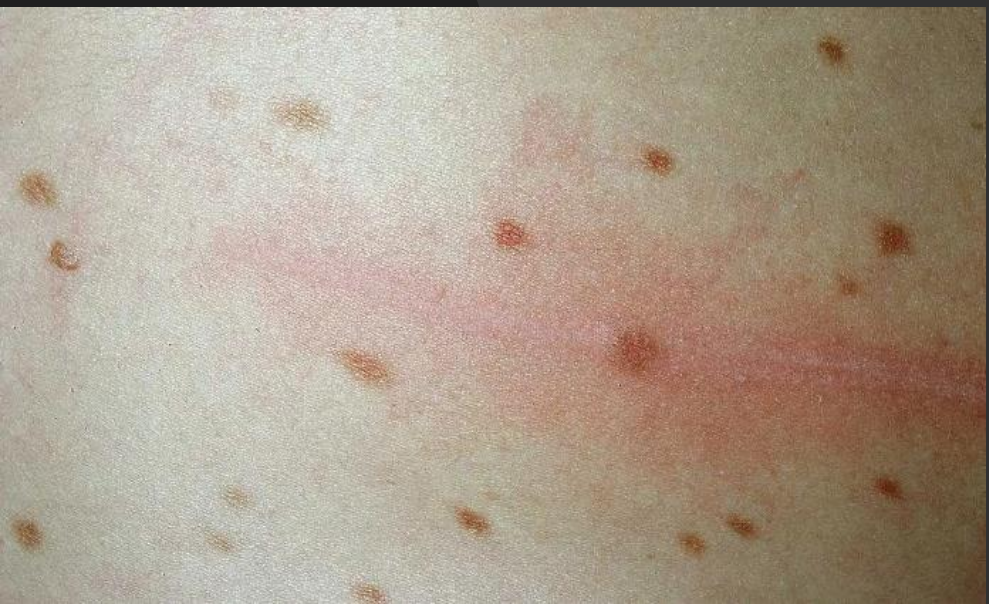
Relationship between disorders of mast cell activation and clonal mast cell disorders



Clonal mast cell disorders

- Refers to a group of disorders characterised by excessive mast cell accumulation in one or multiple tissues.
- Mastocytosis is subdivided into two groups of disorders
- Cutaneous mastocytosis (CM) describes forms of mastocytosis that are limited to the skin.
  - Mainly affects children
- Systemic mastocytosis (SM) describes forms of mastocytosis in which pathologic mast cells infiltrate multiple extracutaneous organs, with or without skin involvement.
  - Mainly affects adults
- Monoclonal mast cell activation syndrome- tryptase <20 mcg/L with clonal mast cells

Skin involvement



- Most manifestations are explained by excess production of mast cell mediators
- Risk of anaphylaxis especially with hymenoptera stings and some medication

- Skin is involved in almost all cases
  - 90% usually present with hyperpigmented skin lesions or urticaria pigmentosa
  - An urticarial reaction is elicited after rubbing or stroking referred to as Darier’s sign
  - In children lesions tend to be well demarcated and may form nodules or plaques
  - In adults lesions may become confluent

Other organ involvement

- 80% of adults with SM show focal or diffuse collections of mast cells in the bone marrow
- Patients can also have an associated neoplastic disorder
- Bone involvement is observed in around 30% of patients with osteoporosis, osteopenia, sclerosis or cystic lesions. In severe disease fractures may occur
- Splenic and hepatic involvement is reported in 24-54% of cases
  - Severe liver disease is usually associated with aggressive disease
- Neuropsychiatric problems, such as altered cognitive or emotional function has also been reported

Diagnosis

- 1 major and 1 minor or 3 minor criteria

- Major criteria
  - **Histology/immunohistochemistry:** Multifocal dense infiltrates of mast cells (MCs) (> 15 MCs in aggregate) in tryptase stained biopsy sections of the bone marrow or other extracutaneous organ
    - Maybe the only criteria in CM
- Minor criteria
  - **Cytology:** More than 25% of MCs in bone marrow or other extracutaneous organ(s) show abnormal morphology (i.e. are atypical MC type 1 or are spindle–shaped MCs) in multifocal lesions in histologic examination
  - **Genetics:** KIT mutation at codon D816V in extracutaneous organ(s) (in most cases bone marrow cells are examined) (>90%)
  - **Immunophenotyping:** KIT(CD117)+MCs in bone marrow show aberrant expression of any of the following CD2, CD25, CD30*
  - **Serology:** Serum total tryptase > 20 ng/mL (persistent)

Prognosis

- Children mostly present with cutaneous mastocytosis, which resolves by adulthood in ~70% of cases
- Most adults fall into the indolent SM category and disease is relatively stable
- Evolution tends to occur in those which high numbers of neoplastic mast cells and when KIT mutation is detected in multiple cell lineages
- Non-indolent cases tend to have poor prognosis with some experiencing rapid progression
- Large numbers of neoplastic mast cells are observed in aggressive mastocytosis or mast cell leukaemia, survival in the latter is general <1 year

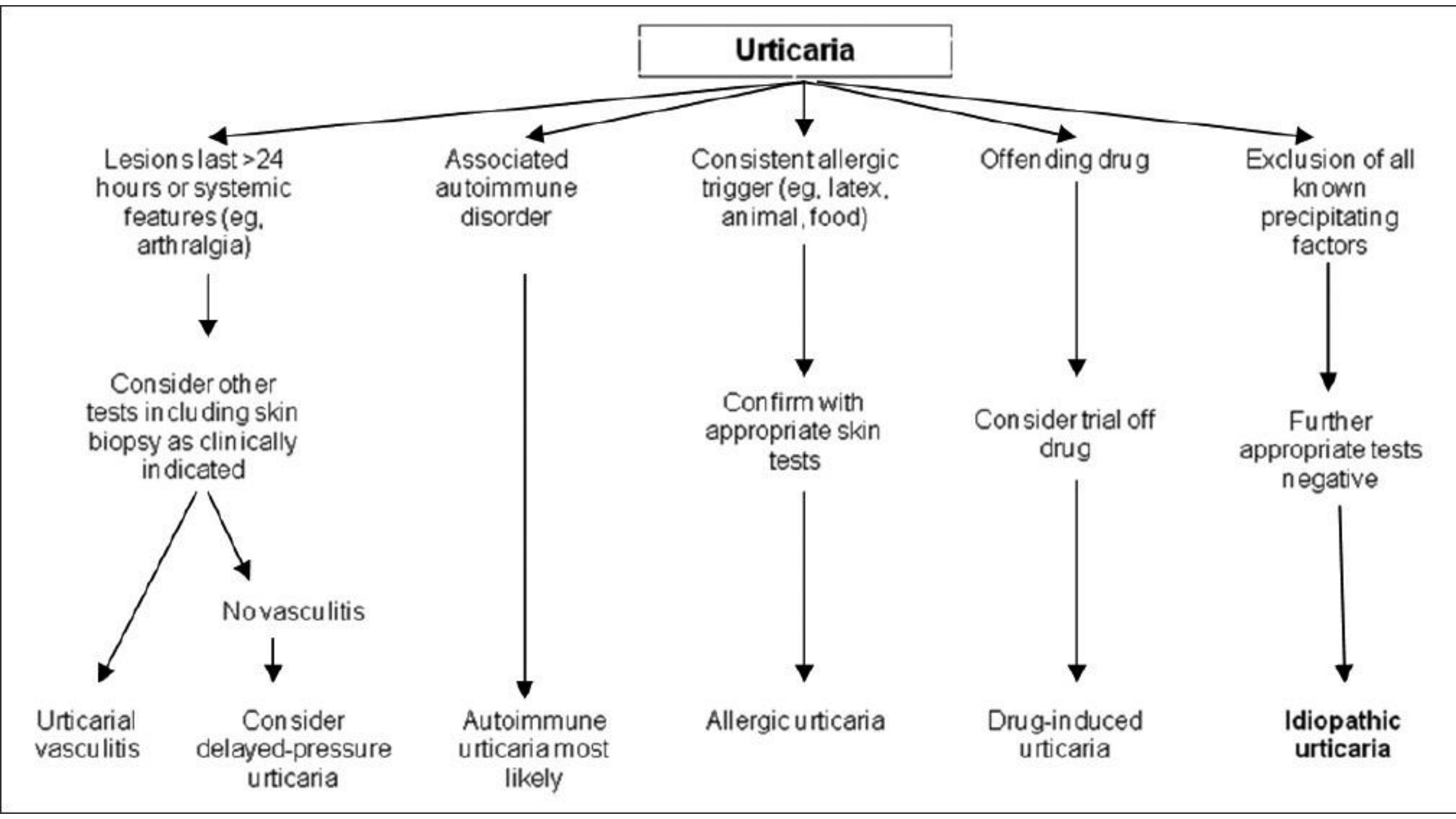
Treatment

1. Avoidance of triggers
   - Allergens
   - Environmental

2. Drugs
   - Non-aggressive disease/ symptom directed treatment
     - Anti-histamines
     - Leukotriene receptor antagonists
     - Adrenaline
     - Glucocorticoids
     - UV radiation

   - Aggressive disease / mast cell directed treatment
     - Chemotherapy
     - Cladribine
     - Imatinib (for those with KIT mutations other than D816)
     - Stem cell transplant

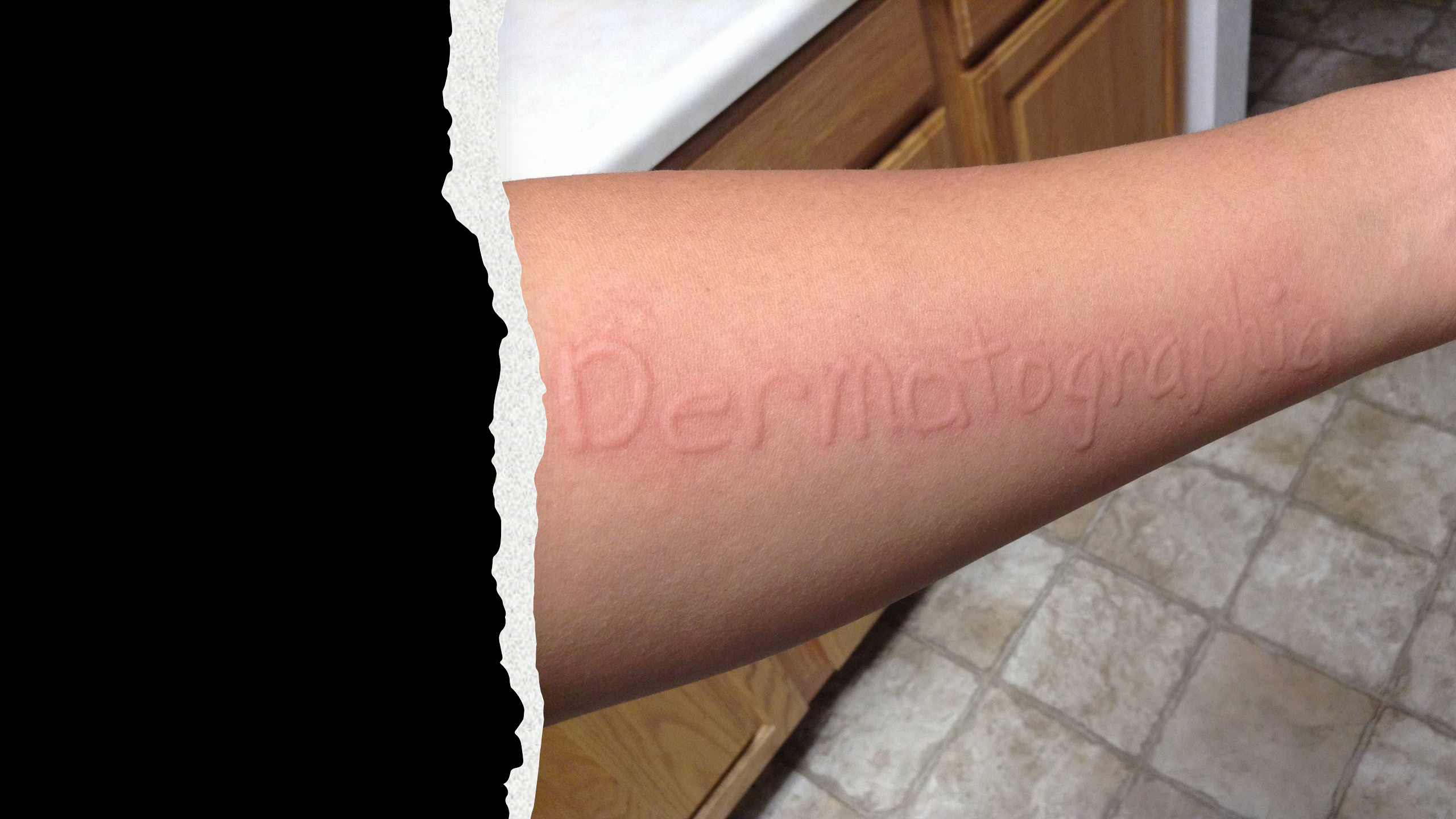
- Alternative tyrosine kinase inhibitors in phase I and II clinical trials

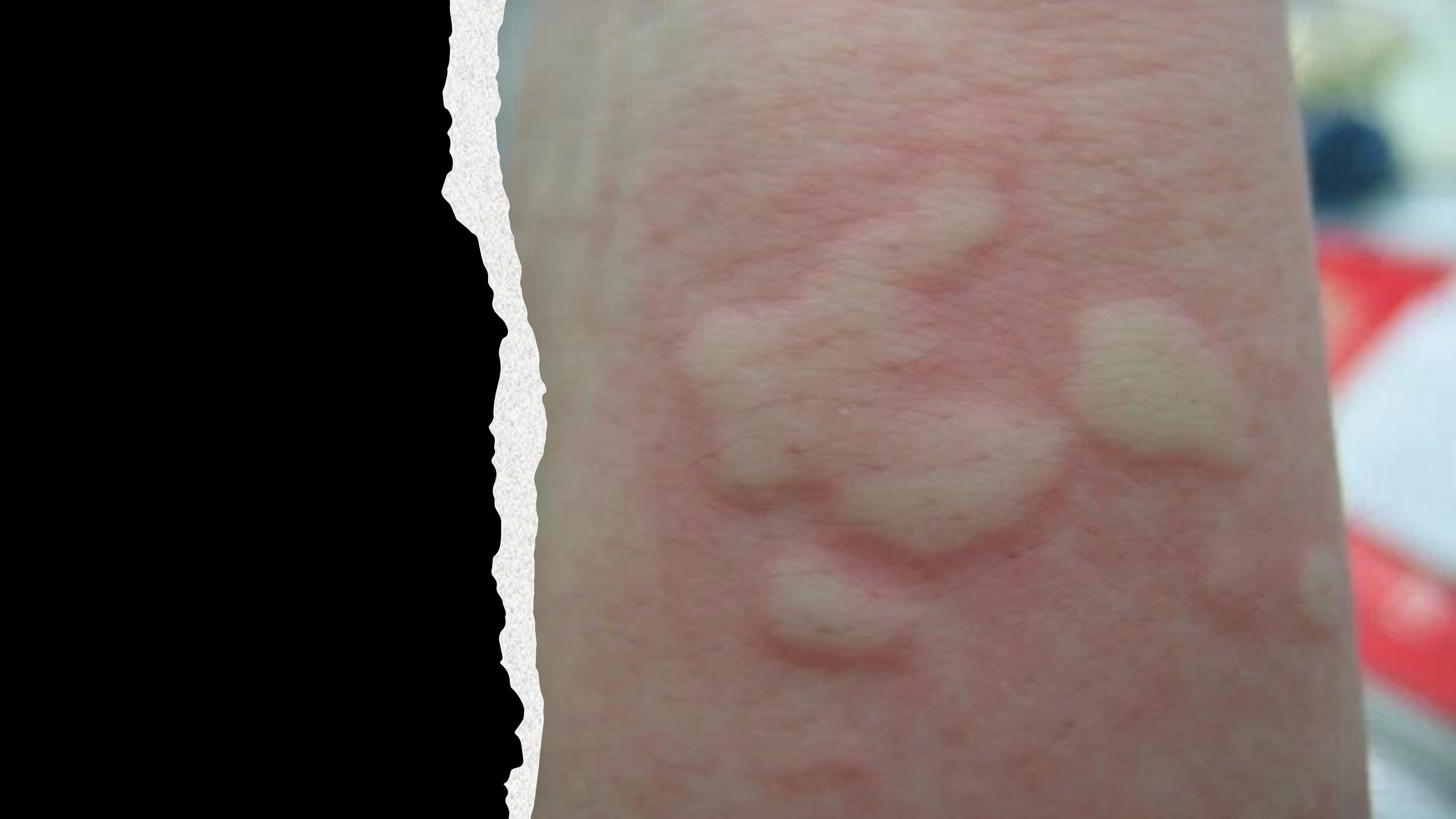

Urticaria
Lesions last >24 hours or systemic features (eg, arthralgia)
Associated autoimmune disorder
Consistent allergic trigger (eg, latex, animal, food)
Offending drug
Exclusion of all known precipitating factors
Consider other tests including skin biopsy as clinically indicated
No vasculitis
Confirm with appropriate skin tests
Consider trial off drug
Further appropriate tests negative
Urticarial vasculitis
Consider delayed-pressure urticaria
Autoimmune urticaria most likely
Allergic urticaria
Drug-induced urticaria
Idiopathic urticaria

SKIN PRICK TEST 1

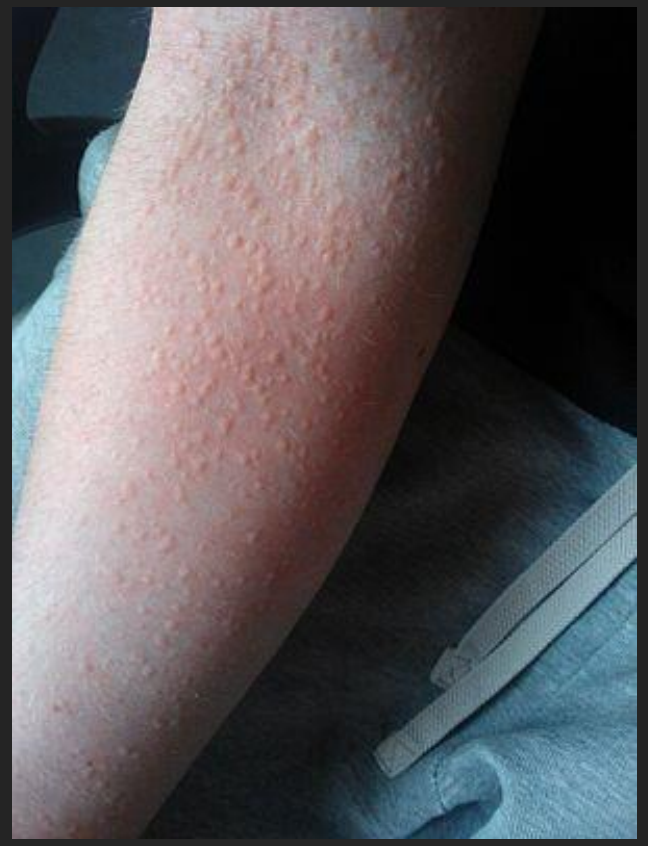
SKIN TESTS

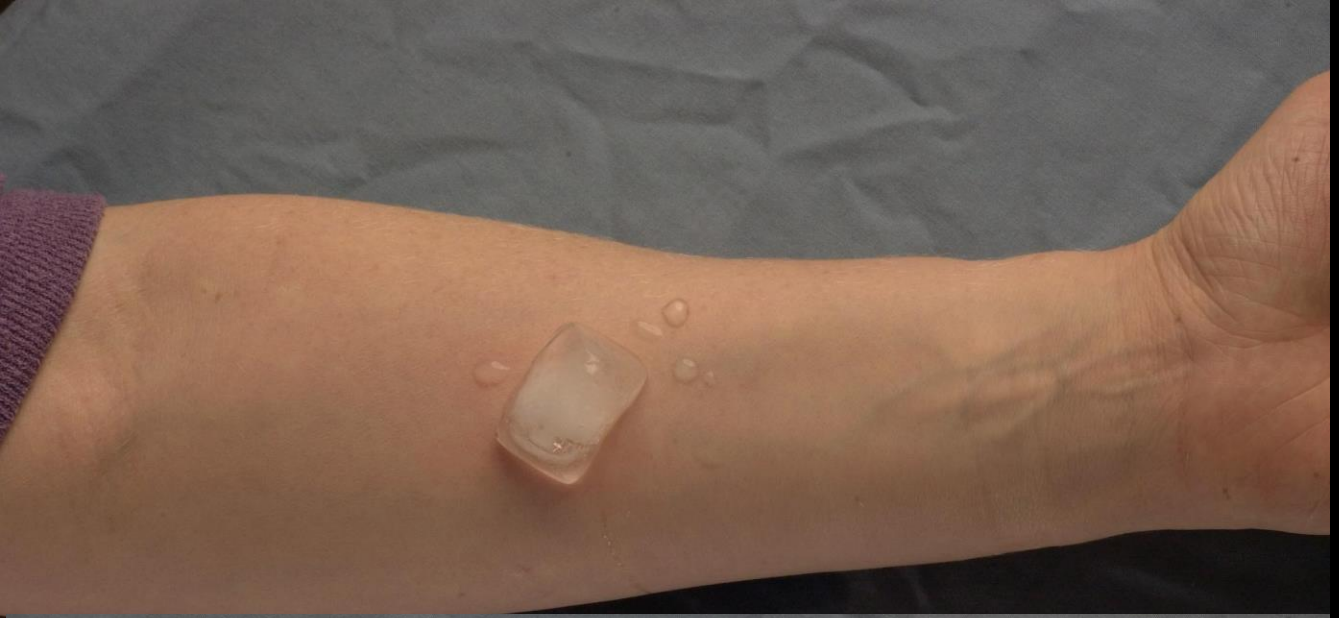

Histamine
Feather
Cat
Dog
Horse
Sheep Wool
Negative Control
Plane Pollen
Birch Pollen
Grass Pollen
Daisy Pollen
Alternaria (mould)

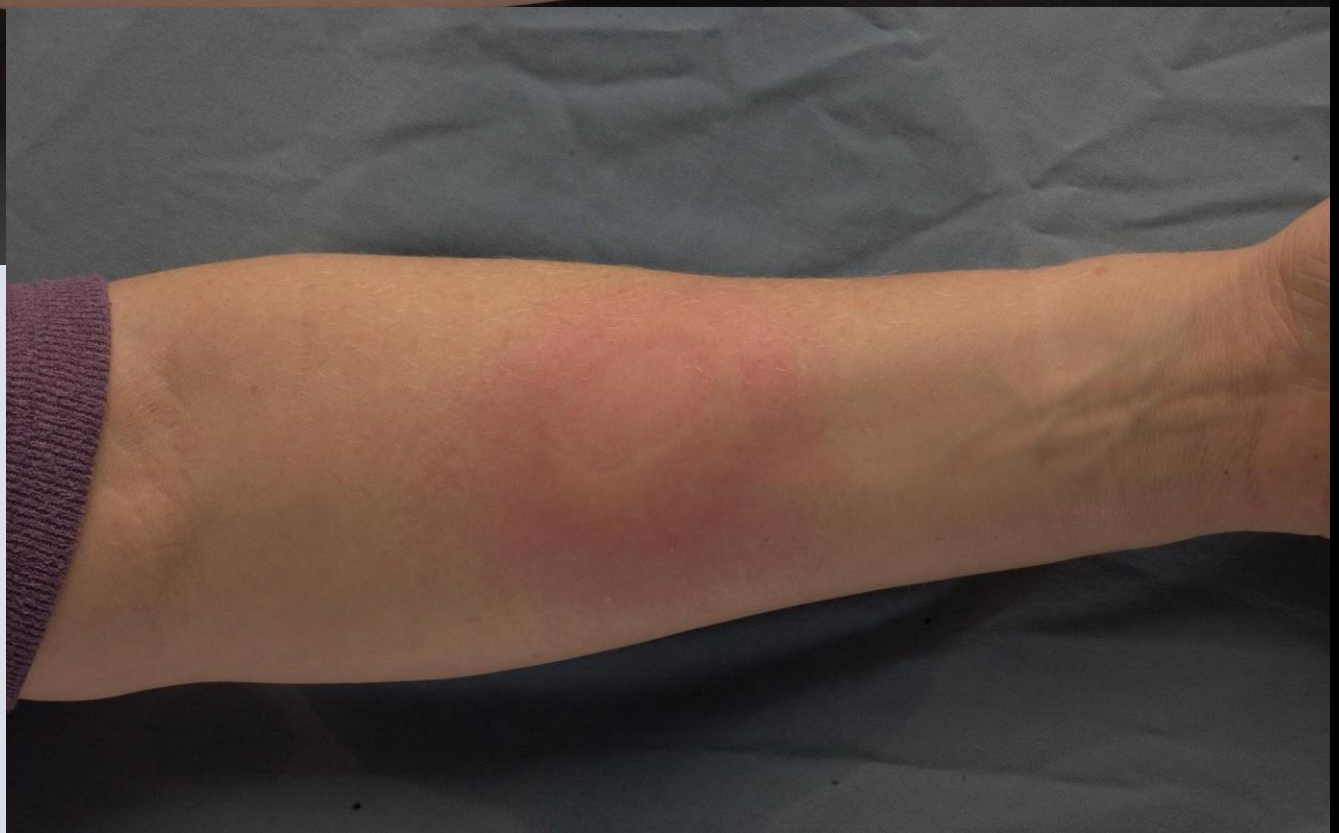

Dermatographia



CHOLINERGIC URTICARIA



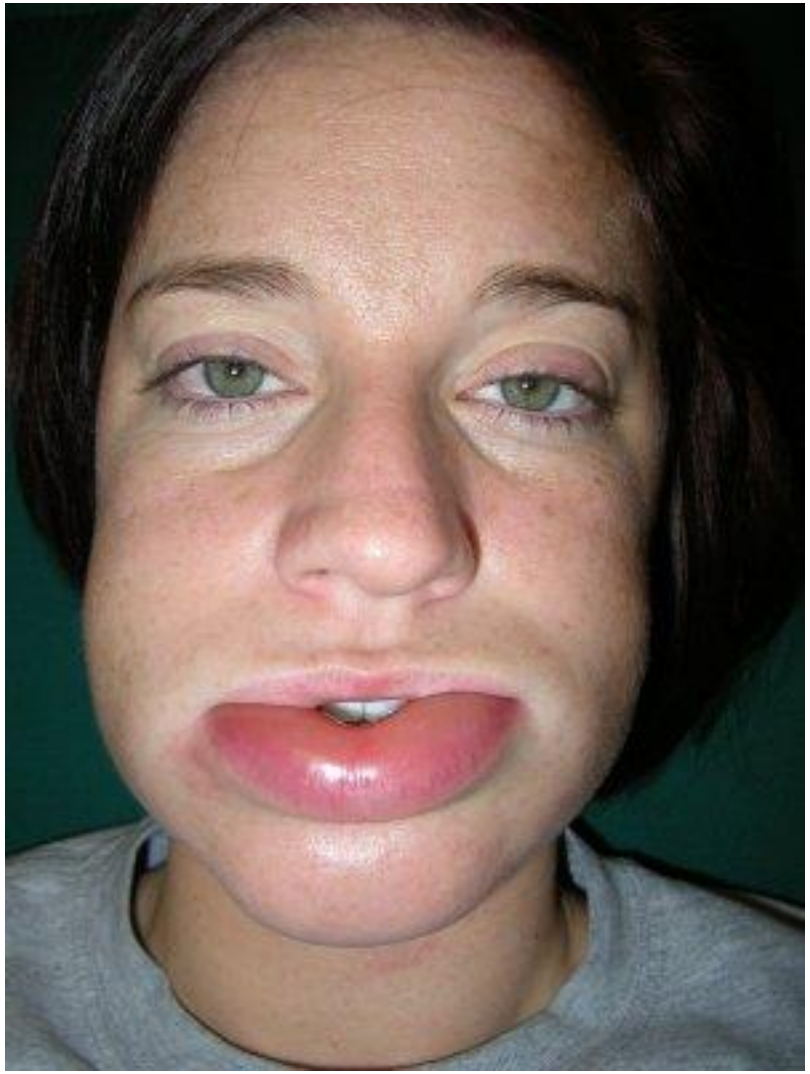


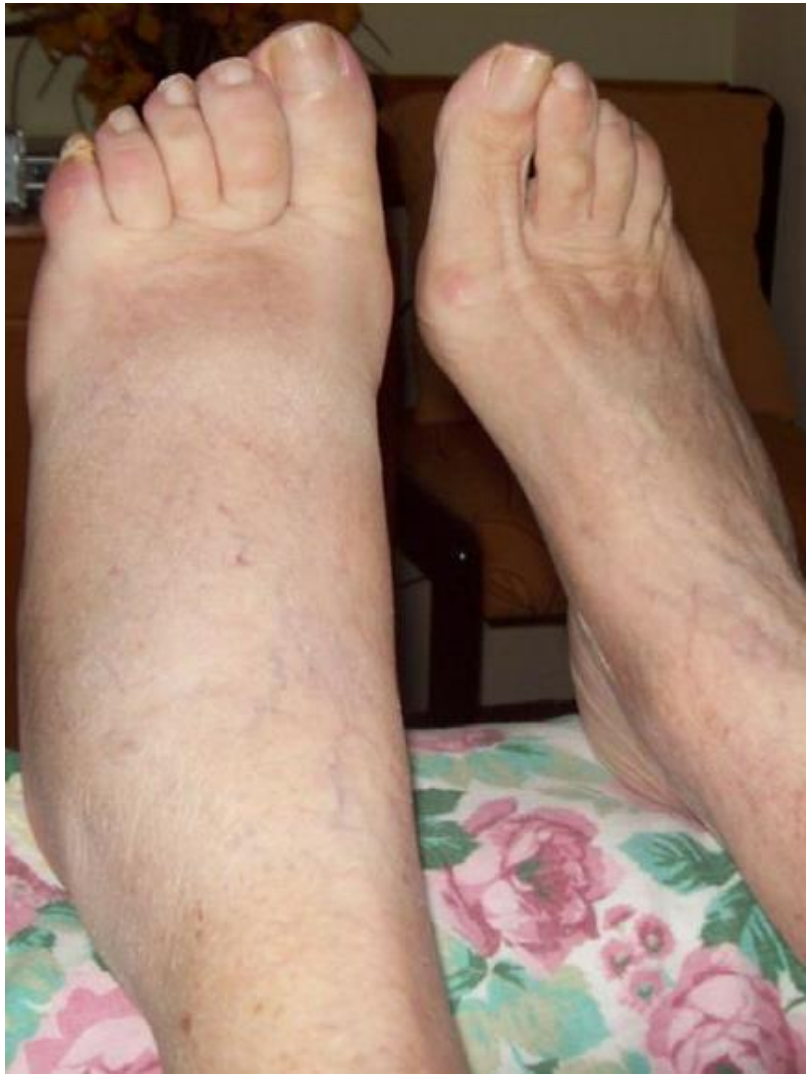


COLD URTICARIA

- Cold exposed parts:
  URTICARIA
- Swimming: hypotension and death
- Cold drink: pharyngeal oedema
- Onset 2-5 minutes
- Duration 1-2 hours
- IgE dependant (also IgM and IgG)
- Antihistamines (Cyproheptadine)

ANGIOEDEMA





MANAGEMENT

- High dose/combination antihistamines
- H_1 and H_2
- Add in montelukast
- Trial of either:-
  - Omalizumab- anti-IgE therapy- very effective
  - Immune suppression- e.g. ciclosporin
- Isolated angioedema consider C1 esterase inhibitor deficiency, ACE inhibition induced symptoms

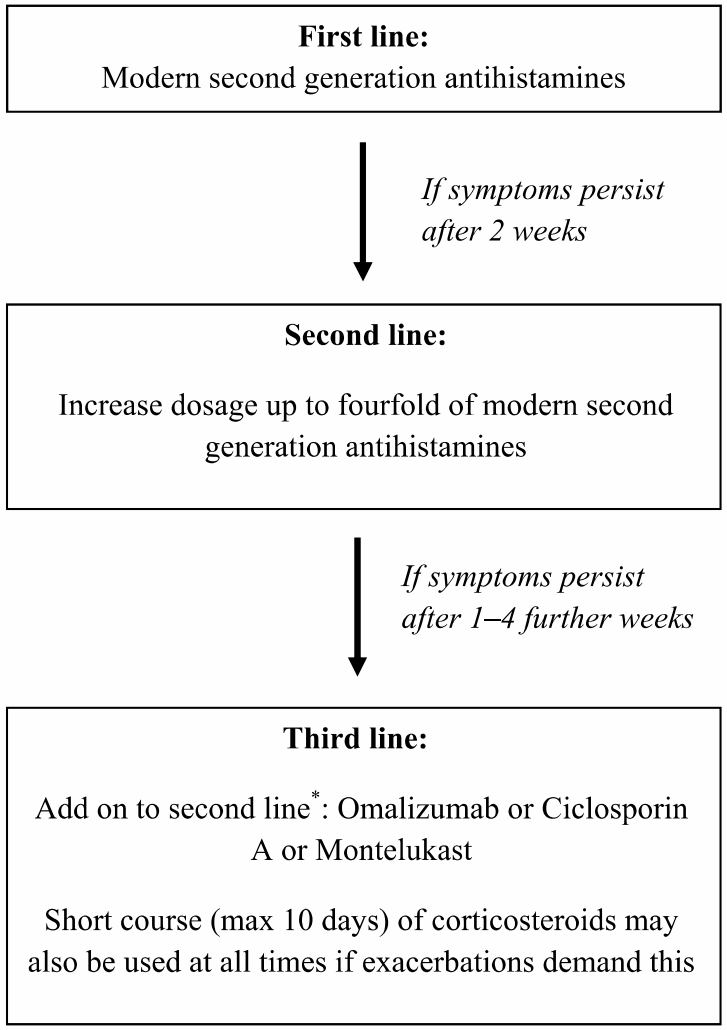
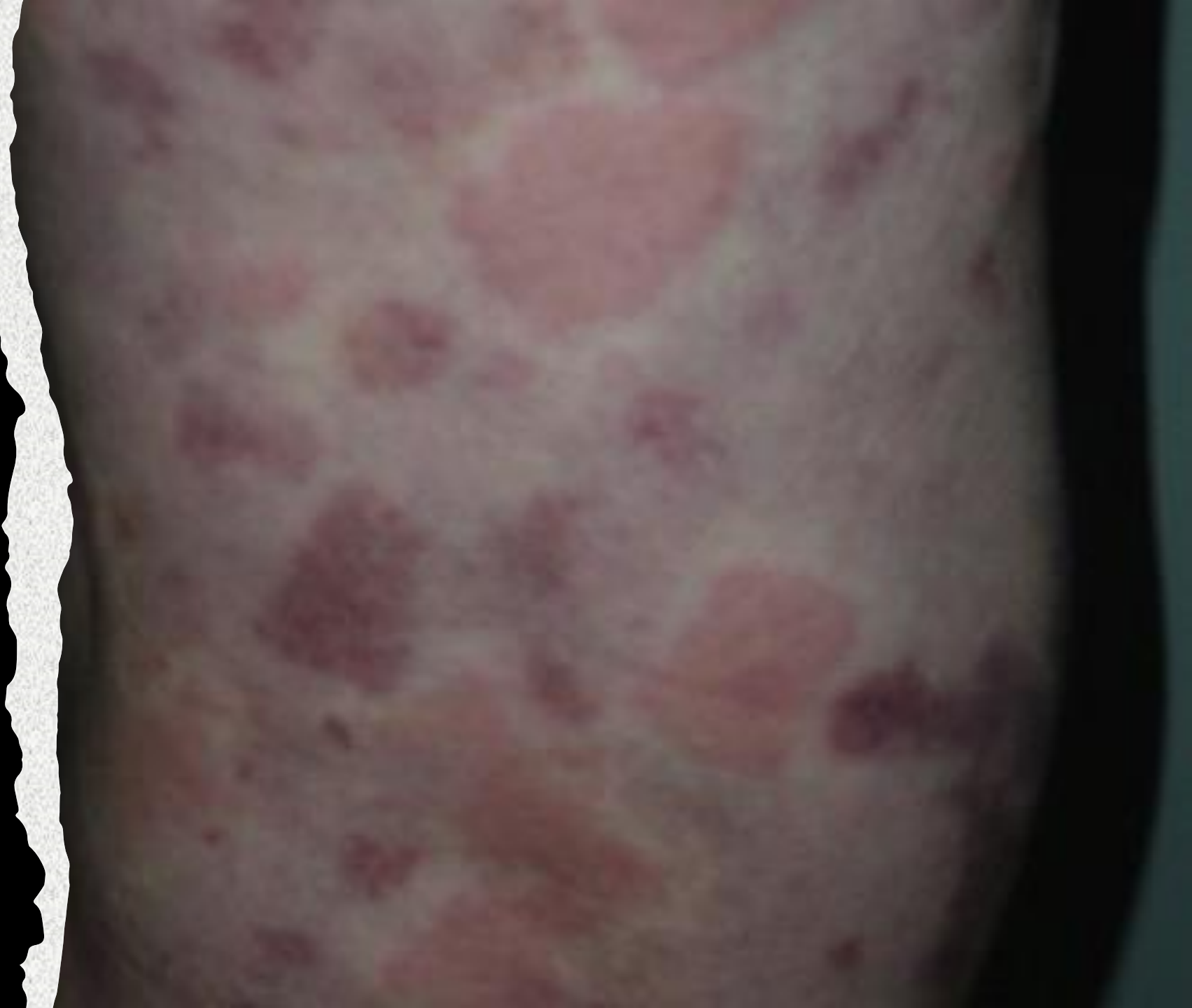


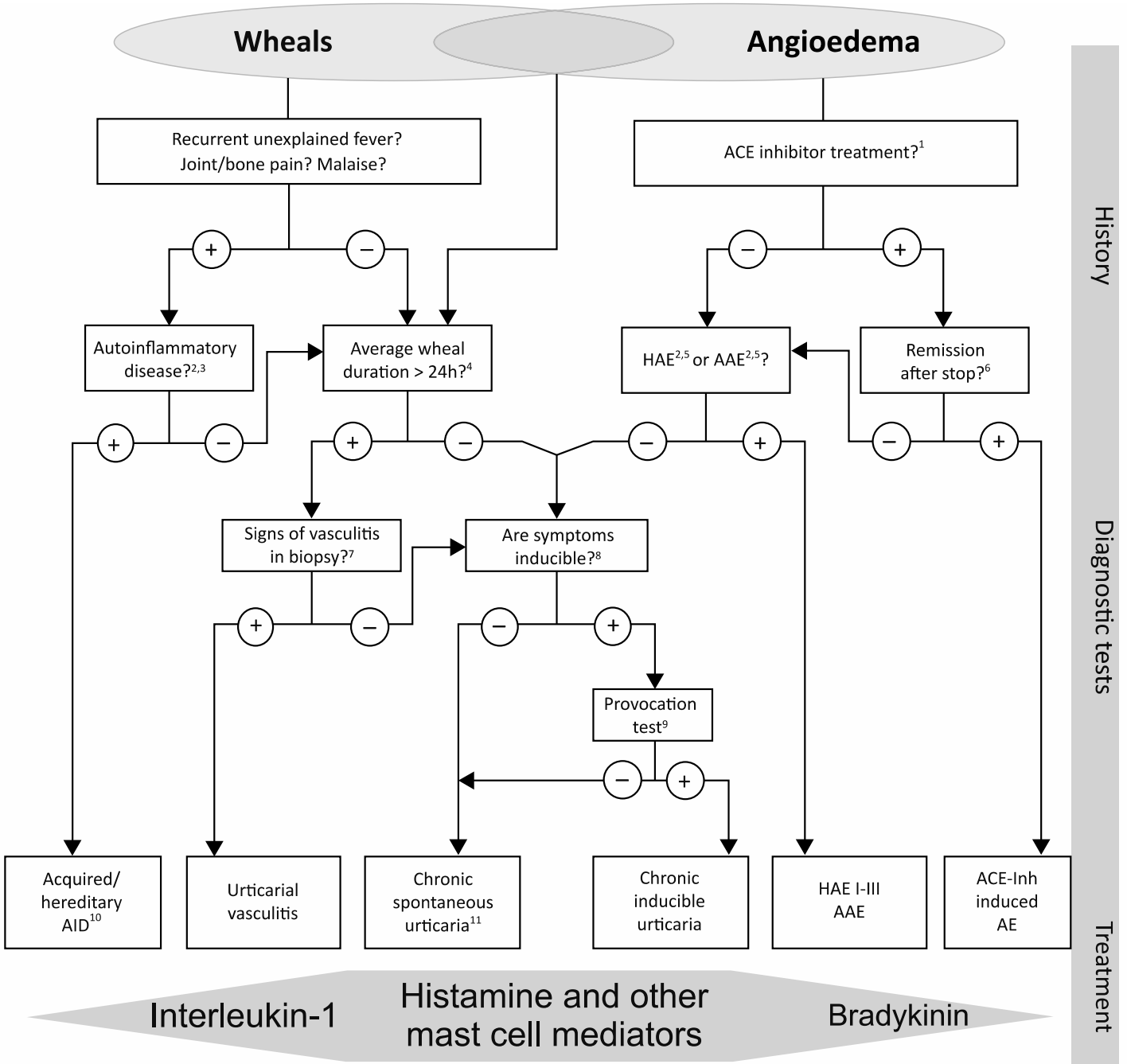
Table 4 The UAS7 for assessing disease activity in CSU

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6 for each day is summarized over one week (maximum 42).

Urticarial vasculitis
May respond to Antihistamines
May need other therapies




Wheals
Angioedema
Recurrent unexplained fever? Joint/bone pain? Malaise?
ACE inhibitor treatment?[1]
Autoinflammatory disease?[2,3]
Average wheal duration > 24h?[4]
HAE[2,5] or AAE[2,5]?
Remission after stop?[6]
Signs of vasculitis in biopsy?[7]
Are symptoms inducible?[8]
Provocation test[9]
Acquired/ hereditary AID[10]
Urticarial vasculitis
Chronic spontaneous urticaria[11]
Chronic inducible urticaria
HAE I-III AAE
ACE-Inh induced AE
Interleukin-1
Histamine and other mast cell mediators
Bradykinin
History
Diagnostic tests
Treatment

Proposed criteria for MCAS- all 3 must be present

1. Episodic multisystem symptoms consistent with mast cell activation
2. Appropriate response to medications targeting mast cell activation
3. Documented increase in validated markers of mast cell activation systemically (ie, either in serum or urine) during a symptomatic period compared with the patient's baseline values*

*Documentation of a single meaningful increase (see text) in tryptase level is sufficient, whereas it is recommended to document at least 2 measurements of increased levels of other markers.

Clinical manifestations

- Excessive release of mast cell mediators
  - Urticaria
  - Flushing
  - Angioedema
  - Shortness of breath
  - Rhinitis
  - Palpitations
  - Nausea
  - Diarrhoea
  - Hypotension
  - Lethargy and fatigue
  - Brain fog, difficulty concentrating
- Anaphylaxis

Comparison of IA and MCAS

Feature	Idiopathic anaphylaxis	Mast cell activation syndrome
Symptoms occur in well-defined episodes	Yes	Yes
Increased markers of mast cell activation during episodes	Yes (but absence of laboratory confirmation does not exclude the diagnosis if the patient meets the clinical definition of anaphylaxis)	Yes (required for diagnosis)
Positive response to mast cell–targeting medications	Yes	Yes
Presence of respiratory compromise or hypotension during episodes	+	+/−
Might be associated with clonal (mastocytosis or MMAS), IgE-mediated, or non–IgE-mediated trigger of mast cell activation	−	+

- ? Difference from spontaneous/idiopathic urticaria and IA

ORIGINAL RESEARCH

Mast Cell Activation Disorder and Postural Orthostatic Tachycardia Syndrome: A Clinical Association

555 Prevalence of Symptoms of Mast Cell Activation in Patients with Postural Orthostatic Tachycardia Syndrome and Hypermobile Ehlers-Danlos Syndrome

CONCLUSIONS: Symptoms of mast cell activation were present in patients with confirmed diagnoses of POTS alone; with hEDS alone, and both POTS and hEDS. The most dominant manifestations recurring were cutaneous and gastrointestinal. The use of H1 and H2 blockers and mast cell stabilizers were associated with reduction in these symptoms.

MANAGEMENT

- High dose/combination antihistamines
- H_1 and H_2
- Add in montelukast
- Trial of either:-
  - Omalizumab- anti-IgE therapy- very effective
  - Immune suppression- e.g. ciclosporin

Hereditary alpha tryptasaemia

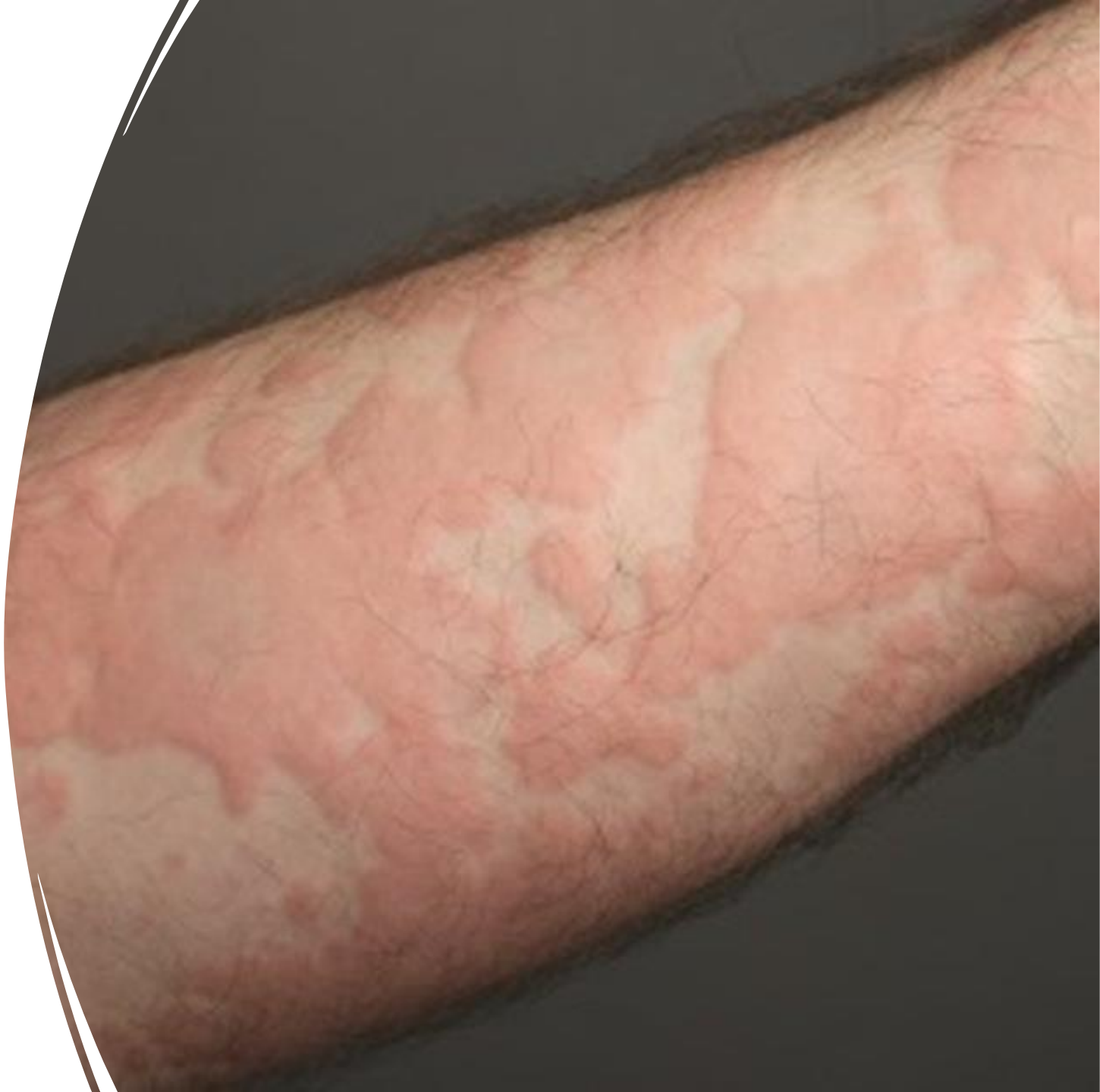
- Common autosomal dominant genetic trait
- Discovered in 2016
- 6% population in UK
- Increased *TPSAB1* gene copy number encoding alpha (a)-tryptase
- Elevated baseline serum tryptase levels
- Not associated with increased risk of mast cell activation
- When occurs may be more severe

Patients presents with this rash with no other symptoms?
They ask what is the cause.
What do you tell them?

A. Allergic reaction- if history is consistent with this
B. Anaphylaxis- No
C. Spontaneous urticaria- possible
D. Urticarial vasculitis-if lesions are suggestive

May need referral.

Don’t tell them “they are allergic”



Summary

- Diseases range from mild to malignancy
- Symptoms are associated with excessive mast cell mediators
- Blocking the mediators treats symptoms
- Reserve the word allergy for the appropriate clinical presentation

- Serial tryptase testing is very useful in anaphylaxis
- Provide training and information when prescribing AAIs

Thank you for listening

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