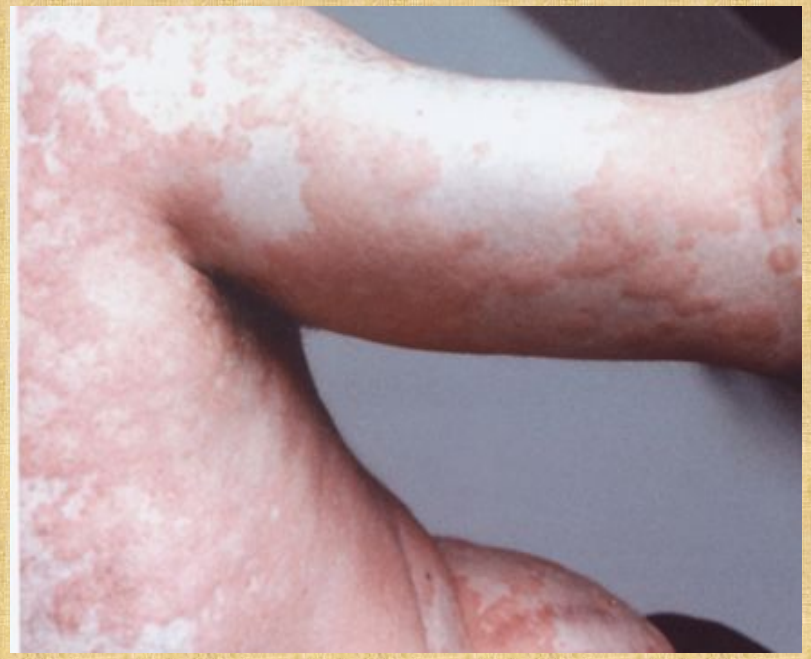
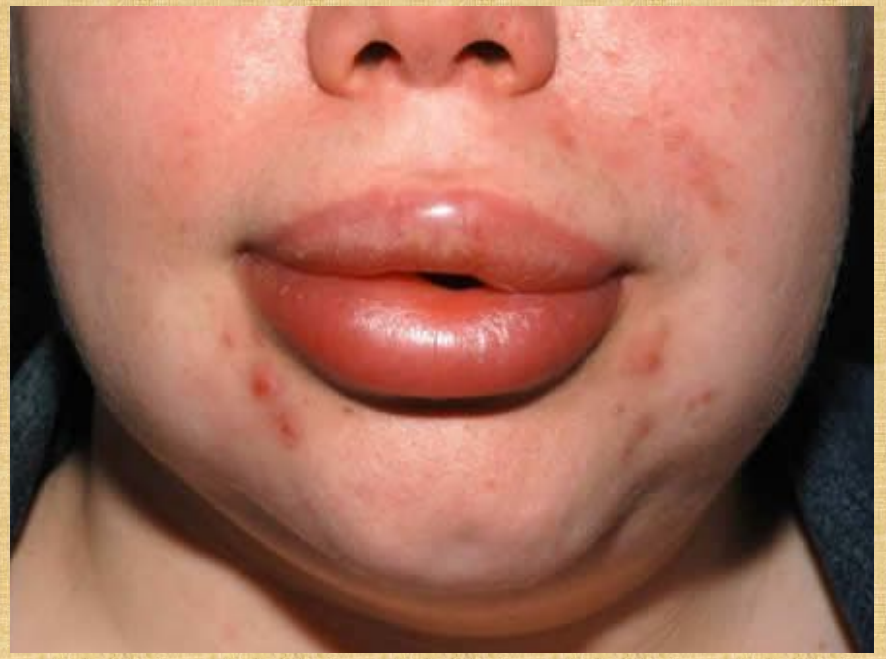
Chronic Spontaneous Urticaria Beyond Omalizumab





Disclosure

I have No financial disclosure or conflicts of interest with materials presented.

Objectives

- Review the nomenclature, classification, diagnosis and treatment options in the management of chronic spontaneous urticaria (CSU)
- Be aware of CSU mimickers

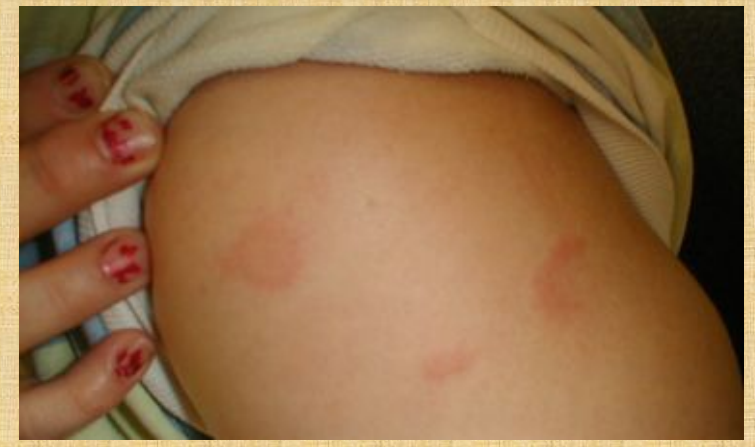
- Urticaria is characterized by the development of wheals (hives), angioedema, or both.

  - Acute Urticaria is defined as lasting <6 weeks

  - Chronic Urticaria is defined as lasting >6 weeks

Urticaria is Characterized By

- Central swelling of various size surrounded by erythema
- Severe pruritus (hallmark of urticaria)
- Lesions are of a transient and fleeting nature (≤24 hours)
- No scarring of the skin
- Can be associated with angioedema



Urticaria *Does Not* Present With

Fever

Joint pain

Blisters

Scarring lesions

Petechia

Purpura

Weight loss

Lesions lasting >24 hours

Pathophysiology of Urticaria

Degranulation of mast cells and basophils and resultant release of

Histamine
Prostaglandin metabolites
Leukotrienes

Platelet activating factor
Other proinflammatory mediators

Chronic Urticaria

- Symptoms continuously or intermittently (daily or almost daily) for ≥ 6 weeks
- More common in adults
- Female/male = 2:1
- No increased incidence in atopics

The EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy. 2022;Mar 77(3):734-66

Phenotypes of Chronic Urticaria/Angioedema

- Urticaria-predominant in 50% of patients
- Urticaria and angioedema in 40% of patients
- Mainly angioedema in 10%

The EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy. 2022;Mar 77(3):734-66

In 2017, isolated spontaneous angioedema without urticaria was included in the definition of CSU for the first time

CSU Laboratory Evaluation

- Limited set of labs: Usually CBC with diff, CRP/ESR, TSH/fT4, thyroid autoantibodies; others may be of use given the appropriate scenario:

Interleukin 1β serum (Schnitzler Syndrome, CAPS, and FCAS 2)

D-Dimer: When elevated, associated with prompt response to Xolair

Prothrombin fragment 1+2

PTH, with calcium, phosphorous, creatinine

Asero R, et al. Elevated baseline D-dimer plasma levels are associated with a prompt response to omalizumab in patients with severe CSU. J Allergy Clin Immunol Pract 2017;5(6):1740-1742

Phenotypes of Chronic Urticaria

Chronic Spontaneous Urticaria (CSU) (no identifiable eliciting factor)

- Previous terminology: Chronic idiopathic urticaria

Chronic Inducible Urticaria (CIndU)

- Subtype of urticaria defined as having a specific environmental stimulus
- Can be seen in association with chronic spontaneous urticaria
- Previous terminology: Physical urticaria

CIndU - Physical Urticarias

- Symptomatic Dermatographism
- Cold/Heat Urticaria
- Delayed Pressure Urticaria
- Solar Urticaria
- Vibratory Urticaria

Maurer M. et al. How to Approach Inducible Urticaria. J Allergy Clin Immunol Pract 2018;6:1119-30

CIndU - Nonphysical Urticarias

- Cholinergic Urticaria
- Contact Urticaria
- Aquagenic Urticaria

Maurer M. et al. How to Approach Inducible Urticaria. J Allergy Clin Immunol Pract 2018;6:1119-30

CIndU

- present in about a third of CSU patients
- is associated with worse disease control with second-generation antihistamines than chronic spontaneous urticaria alone.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Classical Urticaria

Features	Accompanying Symptoms	Laboratory Results	Skin Biopsy	Response to Treatment
Circumscribed, raised, erythematous plaques, often with central pallor intensely itchy. Pruritus symptoms often seem most severe at night	*Angioedema in minority of patients*	*No specific abnormalities*	*Dermal edema, blood vessel dilatation, and a mild perivascular infiltrate predominantly consisting of monocytes and CD4+ lymphocytes*	*Good response to antihistamines. Good response to corticosteroids*

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases (J Allergy Clin Immunol Pract 2018;6:1162-70)

Mimickers of Classical Urticaria

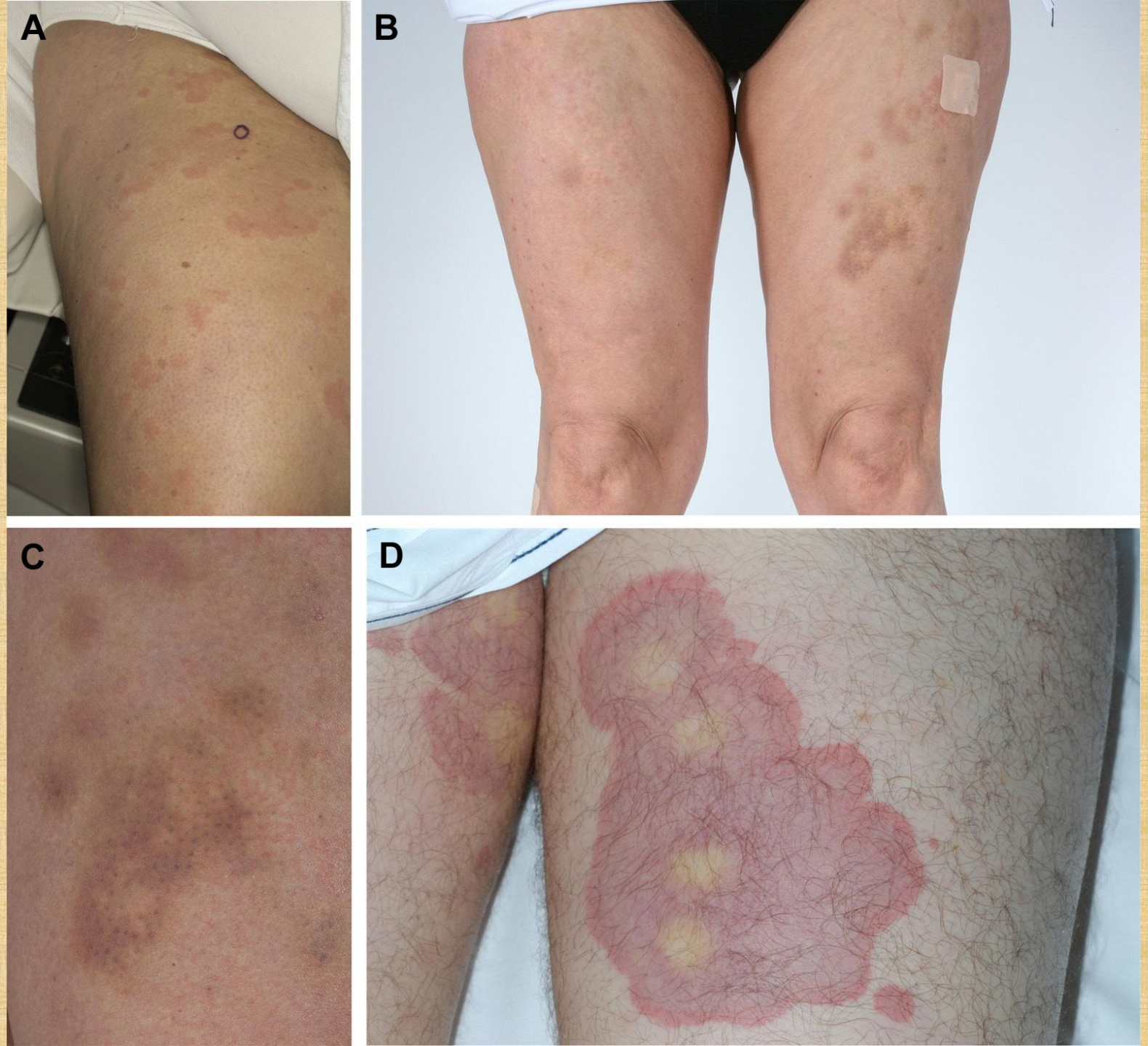
- Urticarial Vasculitis
- Schnitzler Syndrome
- Cryopyrin Associated Periodic Syndromes (CAPS)
- Familial Cold Autoinflammatory Syndrome 2 (FCAS2)

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases (J Allergy Clin Immunol Pract 2018;6:1162-70)

Urticarial Vasculitis

Features	Accompanying Symptoms	Laboratory Results	Skin Biopsy	Response to Treatment
Painful and itching urticarial plaques often last > 24 h and may be accompanied by signs of leukocytoclastic vasculitis; residual dusky pigmentation at site of plaques; burning, bruising, scarring	*May be associated with concurrent angioedema, purpura*	*Hypocomplementemia (complement studies [total complement, C3, C4], C1q levels); may be associated with anti-C1q antibody*	*Both signs of urticaria (dermal edema) and vasculitis,*	*Variable response to antihistamines, hydroxychloroquine, colchicine, corticosteroids, immunosuppressive medications (azathioprine, mycophenolate mofetil, or cyclophosphamide, rituximab)*

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases (J Allergy Clin Immunol Pract 2018;6:1162-70)


A
B
C
D

Schnitzler Syndrome

Features	Accompanying Symptoms	Laboratory Results	Skin Biopsy	Response to Treatment
Chronic recurrent urticarial rash on trunk and upper extremities. Nonpruriginous. Persists between 4 and 36 h	*Fever, arthralgias, hepatosplenomegaly, lymphadenopathy*	*Monoclonal gammopathy, increased inflammatory parameters*	*Heterogeneous findings: neutrophilic urticaria is most common, spongiotic dermatitis, leukocytoclastic vasculitis in 25% of patients*	*No response to antihistamines, partial response to high dose corticosteroids, rapid and complete response to anti-IL-1 therapy*

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases (J Allergy Clin Immunol Pract 2018;6:1162-70)

Cryopyrin Associated Periodic Syndromes (CAPS)

Features	Accompanying Symptoms	Laboratory Results	Skin Biopsy	Response to Treatment
Daily, nonpruriginous urticarial rash on trunk extremities and face. Exacerbated by exposure to cold	*Fever, arthritis/arthralgia, sensorineural hearing loss, aseptic meningitis, type AA amyloidosis*	*Increased inflammatory Parameters*	*Predominantly neutrophilic, perieccrine, and perivascular infiltrates throughout the dermis. There is no evidence of vasculopathy or vasculitis*	*No response to antihistamines, limited/no response to corticosteroids, rapid and complete response to anti-IL-1 therapy*

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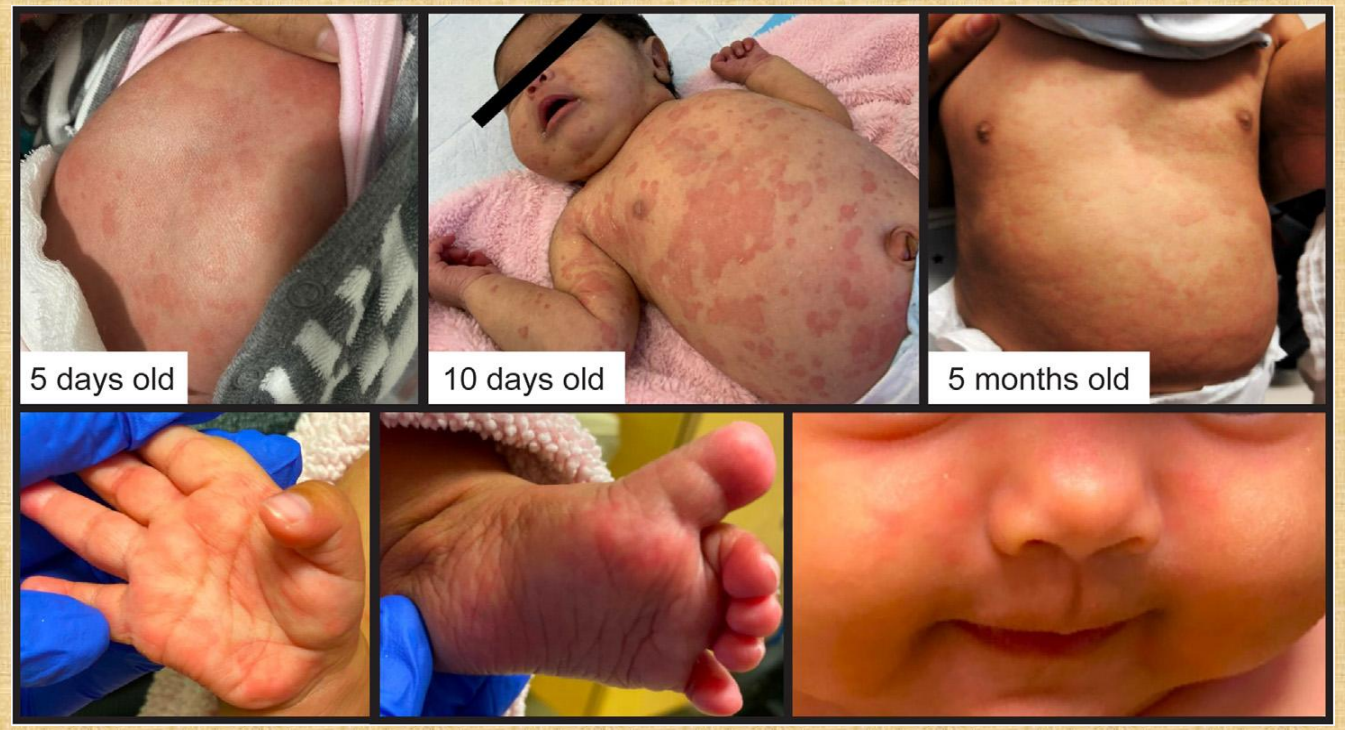
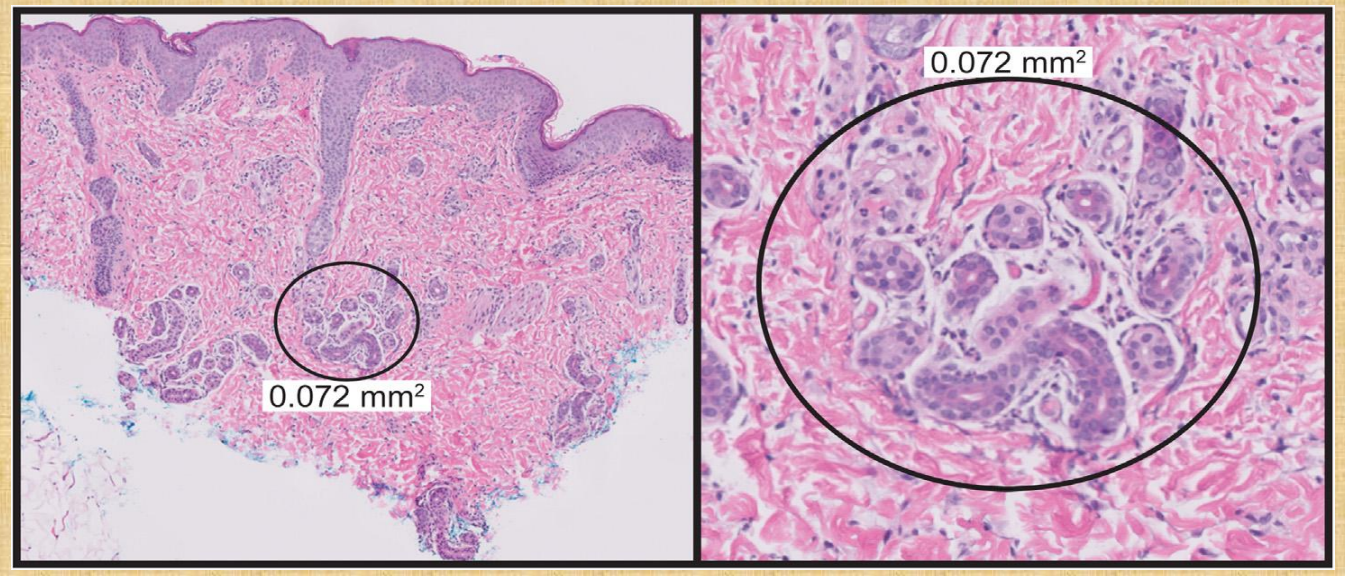

5 days old
10 days old
5 months old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Familial Cold Autoinflammatory Syndrome 2 (FCAS2)

Features	Accompanying Symptoms	Laboratory Results	Skin Biopsy	Response to Treatment
Recurrent urticarial rash lasting 5 to 10 d. Triggered by exposure to cold	*Fever, headache, arthralgia, sensorineural hearing loss*	*Increased inflammatory parameters during attacks*	*Not reported*	*Response to antihistamines and low-dose corticosteroids in some, rapid response to anti-IL-1 therapy*

Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases (J Allergy Clin Immunol Pract 2018;6:1162-70)

CSU FACTS

- At least a quarter of patients with CSU have uncontrolled disease despite up-dosing of second-generation antihistamines
- 32% of second-generation antihistamine non-responders or partial responders are also non-responders or partial responders to omalizumab.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

WHY?

CSU pathogenesis is complex with interplay between autoimmunity, complement, coagulation, and inflammation

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Emerging chronic spontaneous urticaria endotypes mediated by mast cell-activating autoantibodies

A. Autoimmune chronic spontaneous urticaria (type IIb autoimmunity) mediated by IgG autoantibodies

B. Autoallergic chronic spontaneous urticaria mediated by IgE autoantibodies

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Autoimmunity or Autoreactive IgE

- IgG may react with the IgE receptor (30-45%)
- IgG may react with IgE (5-10%)
  - Complement activation
  - Further mast cell activation via C5a

Type IIb autoimmunity mediated by IgG autoantibodies

- present in 8–40% of patients with chronic spontaneous urticaria
- linked to high disease activity, autoimmune comorbidities (eg, autoimmune thyroid disease)
- no, partial, or slow response to second-generation antihistamines and omalizumab
- good response to ciclosporine

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

IgE auto antibody mechanism(s)

- IgE to autoallergens (eg, IgE-anti-thyroperoxidase and IgE-anti-IL-24

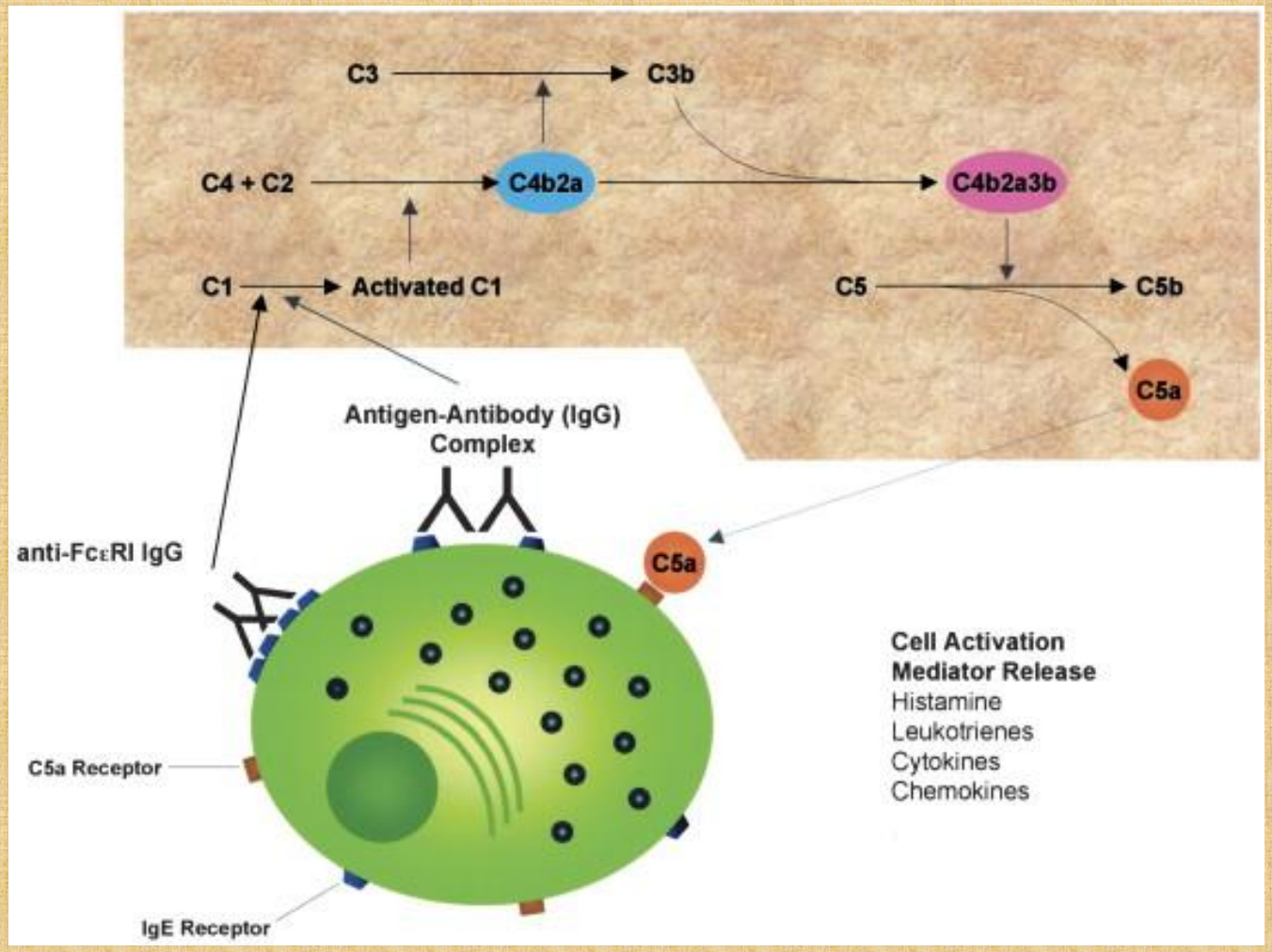
- Autoallergic chronic spontaneous urticaria is present in over 50% of patients with chronic spontaneous urticaria

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Hyper-Release Phenotype Skin Mast Cells in CSU

- React to stimuli that activate the Mas-related G-protein-coupled receptor X2 (MRGPRX2)
- Ligands include VIP, substance P, drugs (e.g. atracurium)

Fig 8



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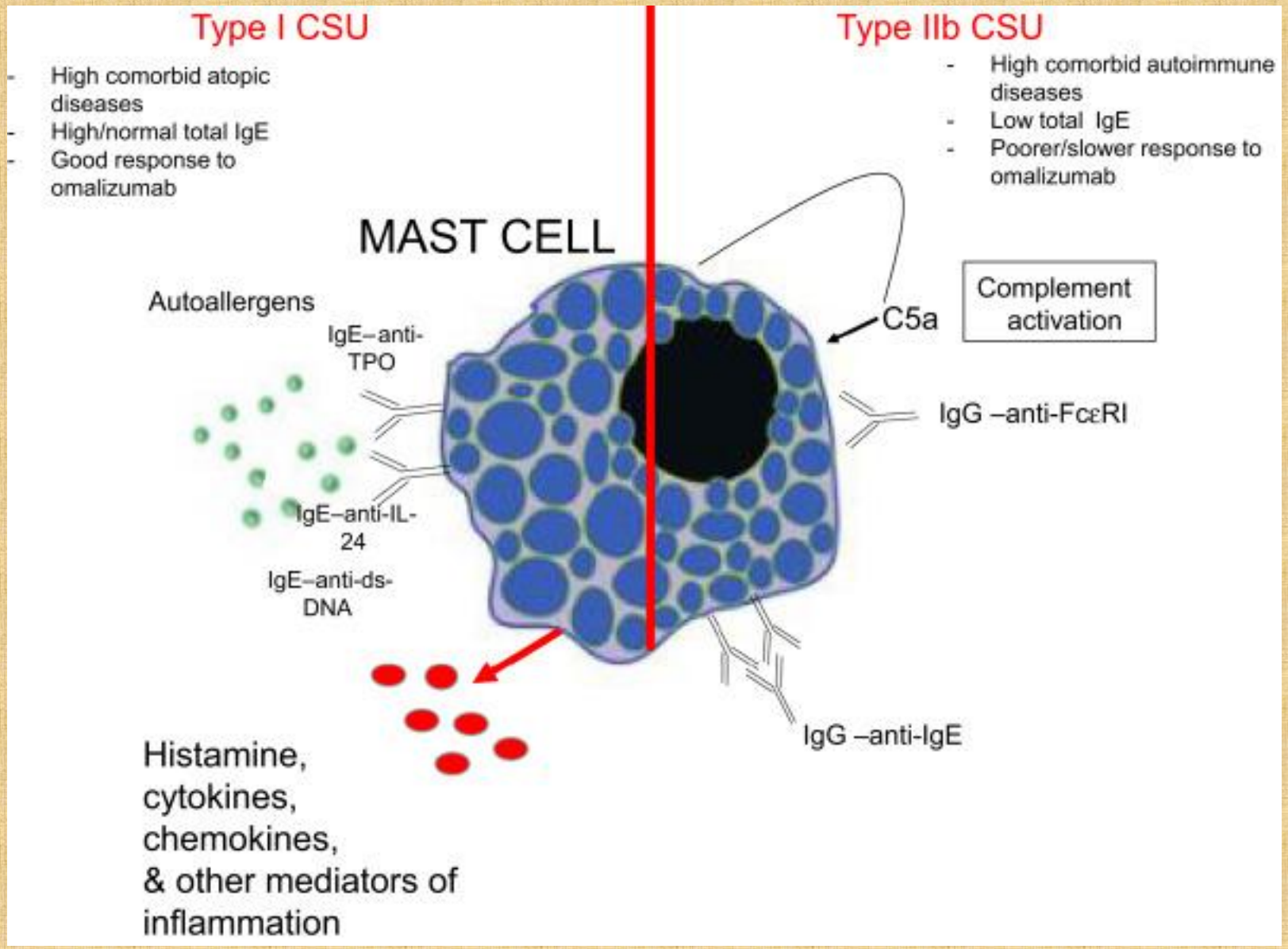


Asero R et al. Chronic Spontaneous Urticaria: The Role and Relevance of Autoimmunity, and Autoallergy. J Allergy Clin Immunol Practice 2023;11:2302-9

Recent studies suggest that patients who have IgG and IgE autoantibodies to the same autoantigen might more often be late or insufficient responders to omalizumab, as compared with patients with only one class of autoantibodies.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Biologic Markers and Response to Omalizumab

No or slow response

- positive autologous serum skin test (ASST)
- low serum total IgE
- low FcεRI expression on basophils
- Eosinopenia
- positive basophil activation test or basophil histamine release assay

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Biologic Markers and Response to Omalizumab

High serum concentrations of total IgE are associated with a **complete/early response to treatment with omalizumab**.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

And Now For

CSU : “Beyond Omalizumab”

Cyclosporine – A Disease

A short course (ie, median of 5 months) of ciclosporine can induce a *long-term remission*, which continues even after drug cessation, probably via downregulating T cell-dependent autoantibody formation by B cells, raising the possibility of a disease modifying effect.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Cyclosporine
Severe But Reversible Side Effects

57% of patients with chronic spontaneous urticaria treated with low to moderate doses of ciclosporine had one or more adverse events, such as arterial hypertension, elevation of creatine levels and gastrointestinal symptoms (eg, abdominal pain)

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Novel Treatments Under Development

- Anti-IgE
- Bruton Tyrosine Kinase (BTK) Inhibitors
- Anti-IL-4Rα
- Mast Cell Depletion
- MRGPRX2 inhibitors
- JAK inhibitors

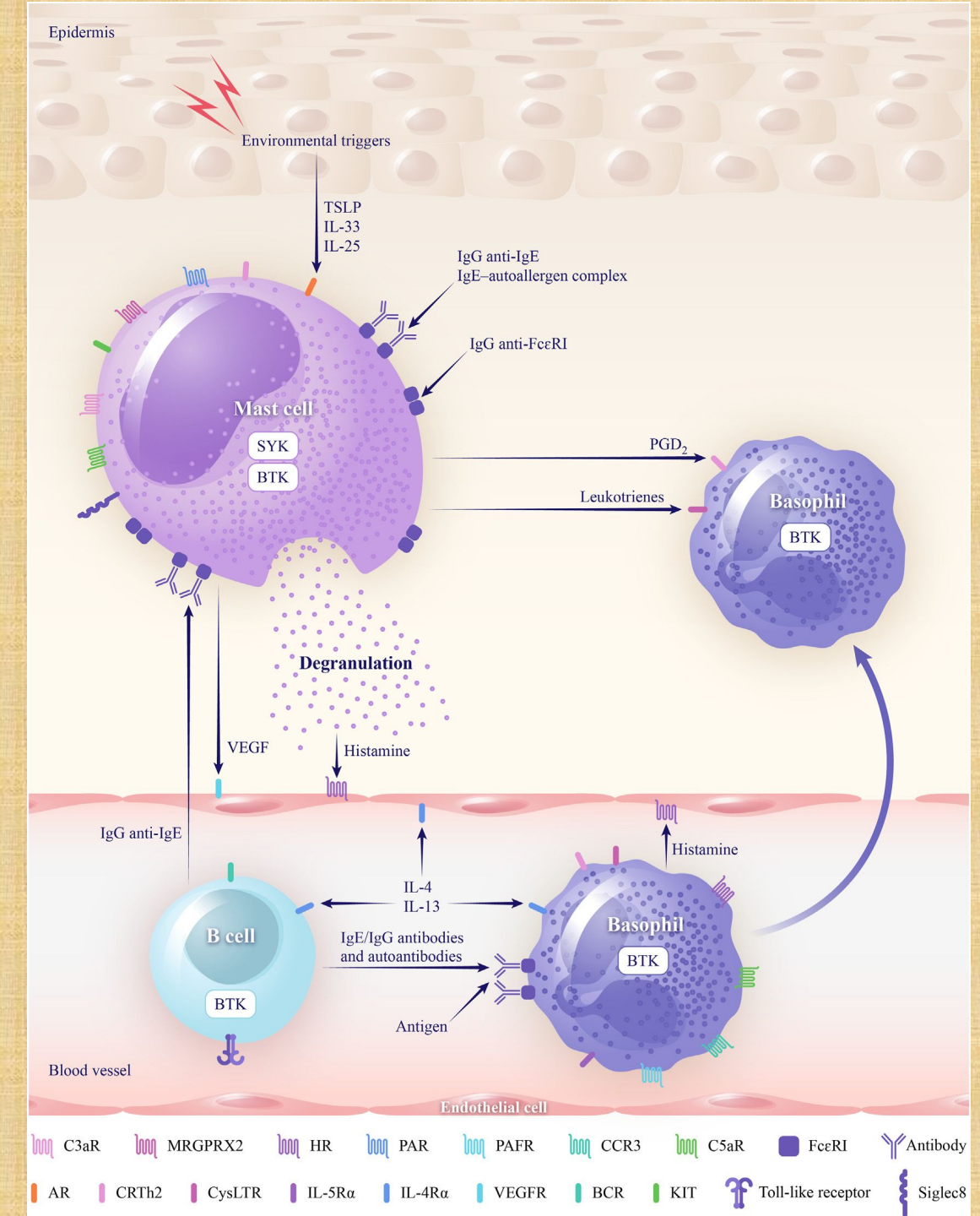
Anti-IgE

- Several omalizumab biosimilars are in development
- Can be useful in CSU with IgE antibodies to allergens/autoallergens
- Can be useful in CSU with IgE-mediated comorbidities
- May be less effective in autoimmune CSU phenotype

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Bruton’s tyrosine kinase (BTK)

A signalling molecule for FcεRI-mediated mast cell activation and B-cell receptor-mediated antibody production



Bernstein JA, et al. BTK Signaling – a crucial link in the pathophysiology of chronic spontaneous urticaria. J Allergy Clin Immunol 2024;153: 1229-40

Remibrutinib

A promising BTK inhibitor in development, has the potential to be a new treatment option for patients with antihistamine-resistant chronic spontaneous urticaria, probably independently of a chronic spontaneous urticaria endotype

Anti-IL-4Rα
Dupilumab, a Disease Modifier?

Several studies have recently shown patients with CSU treated for comorbidities including chronic rhinosinusitis with nasal polyps, and atopic dermatitis who were refractory to antihistamine therapy and prolonged therapy with omalizumab (300-600 mg monthly) treated with dupilumab had a reduction in their UAS7 to 0 which remained as such as long as 14-22 months after dupilumab withdrawal.

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

Mast Cell Depletion
Anti-KIT mAbs

- Barzolvolimab, an anti-KIT mAb is currently under investigation and looks promising
- Anti-KIT mAb therapy may benefit patients with chronic urticaria independent of phenotype

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

MRGPRX2 Inhibitors

- A mast cell receptor associated with IgE-independent activation of mast cells via multiple ligands
- The number of MRGPRX2-positive skin mast cells has been shown to be significantly higher in patients with severe chronic spontaneous urticaria than in control participants
- Two potent, highly selective small molecule antagonists of MRGPRX2 are currently in trials for chronic spontaneous urticaria

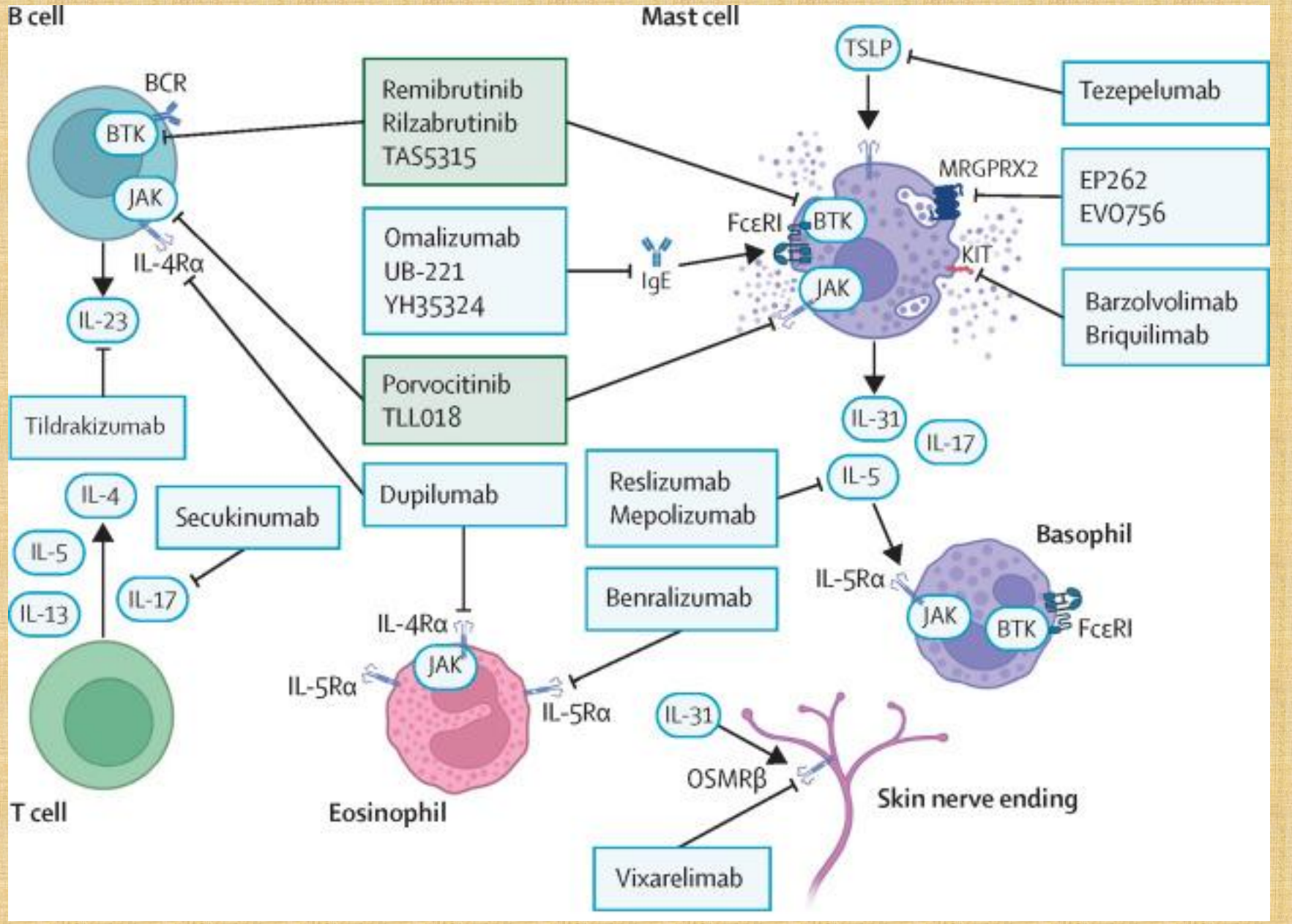
Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet

JAK Inhibitors

Several molecules currently under study

- Ruxolitinib (JAK1/2 inhibitor)
- Tofacitinib (JAK1/3 inhibitor)
- Povorcitinib (JAK1inhibitor)

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404



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Most Likely Drugs to Come to Market in the Next 1-2 Years

- Remibrutinib (BTK inhibitor)
- Dupilumab (can be considered as a second-line therapy alternative to omalizumab)

Zuberbier Torsten, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives in personalized treatment. Lancet 2024;404:393-404

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Asero R et al. Chronic Spontaneous Urticaria: The Role and Relevance of Autoimmunity, and Autoallergy. J Allergy Clin Immunol Practice 2023;11:2302-9

Laboratory tests and CSU features linked to long disease duration

- *Elevated IgG anti-TPO*
- *High CSU severity/activity*

Metz M. The diagnostic workup in Chronic Spontaneous Urticaria - What to Test and Why. J Allergy Immunology Pract 2021;9:2274-83

CSU parameters or biomarkers linked to poor response to treatment with sgAHs

- *Presence of concomitant CIndU*
- *ASST positivity*
- *High D-dimer*
- *High UAS*
- *High CRP*
- *Previous corticosteroid treatment*
- *Low blood basophil and eosinophil counts*

Metz M. The diagnostic workup in Chronic Spontaneous Urticaria - What to Test and Why. J Allergy Immunology Pract 2021;9:2274-83

CSU parameters or biomarkers linked to poor response to omalizumab treatment

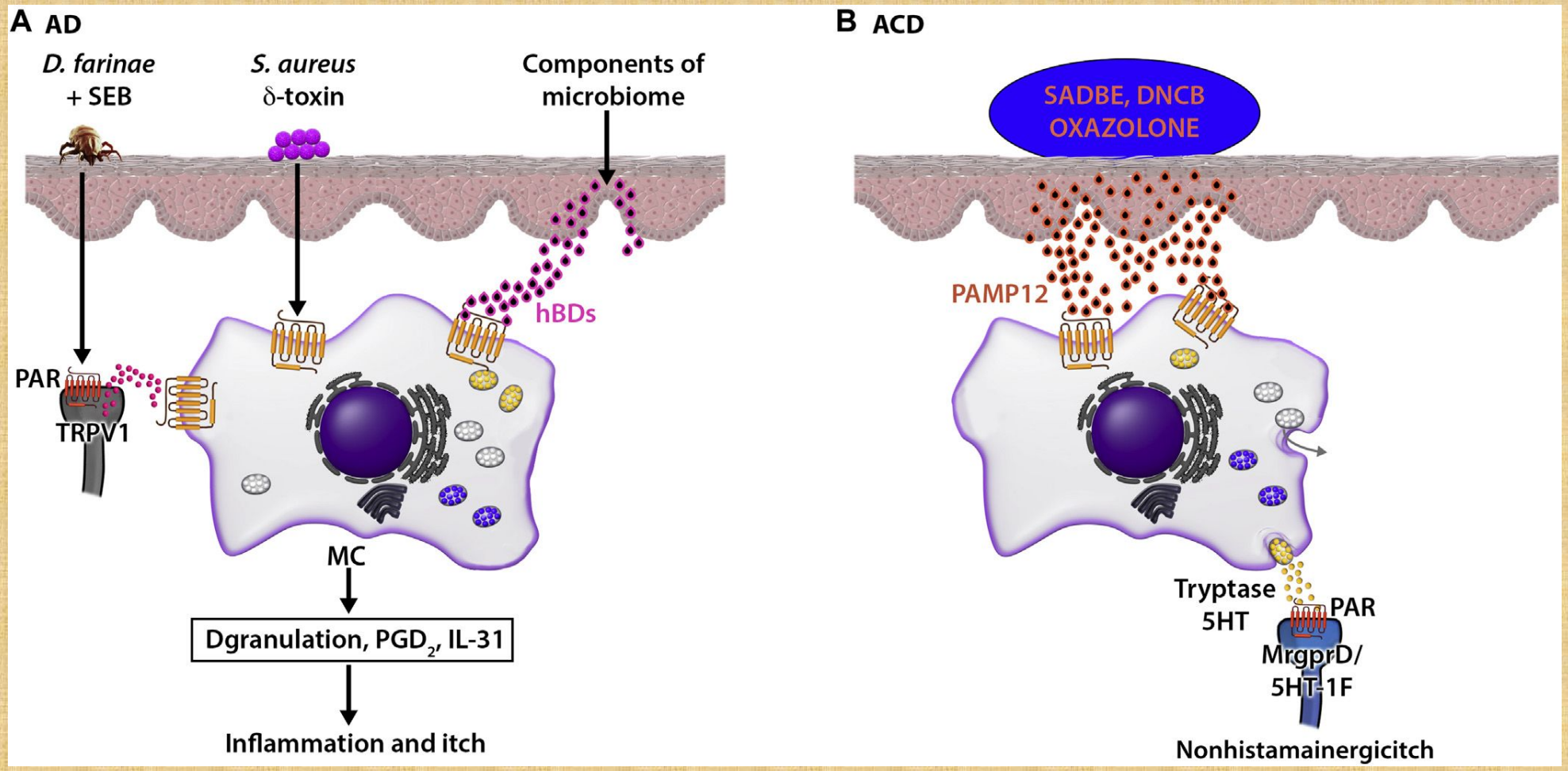
- *Low total IgE*
- *Positive BHRA*
- *History of previous immunosuppressive treatment*
- *Low basophil FcεRI expression*

Metz M. The diagnostic workup in Chronic Spontaneous Urticaria - What to Test and Why. J Allergy Immunology Pract 2021;9:2274-83

CSU parameters or biomarkers linked to good response to cyclosporine treatment

- *Low total IgE*
- *Positive BHRA*

Metz M. The diagnostic workup in Chronic Spontaneous Urticaria - What to Test and Why. J Allergy Immunology Pract 2021;9:2274-83



Roy S, et al. Multifaceted MRGPRX2: New insight into the role of mast cells in health and disease. J Allergy Clin Immunol 2021;149:293-308

Type IIb autoimmunity mediated by IgG autoantibodies

- IgG to FcεRI and IgE (ie, IgG-anti- FcεRI and IgG-anti-IgE)

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