

# Chronic Spontaneous Urticaria: Seeking New Paradigms

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## Relevant Disclosures

Investigator: AbbVie (IIT fund and medication)

# Outline

1. Definition of Chronic Spontaneous Urticaria
2. Immunopathogenesis
3. Severity Scoring and Clinically available testing
4. Current Paradigm
5. Improving clinical practice

Which of these is a hive (urticaria): photos removed

A

B

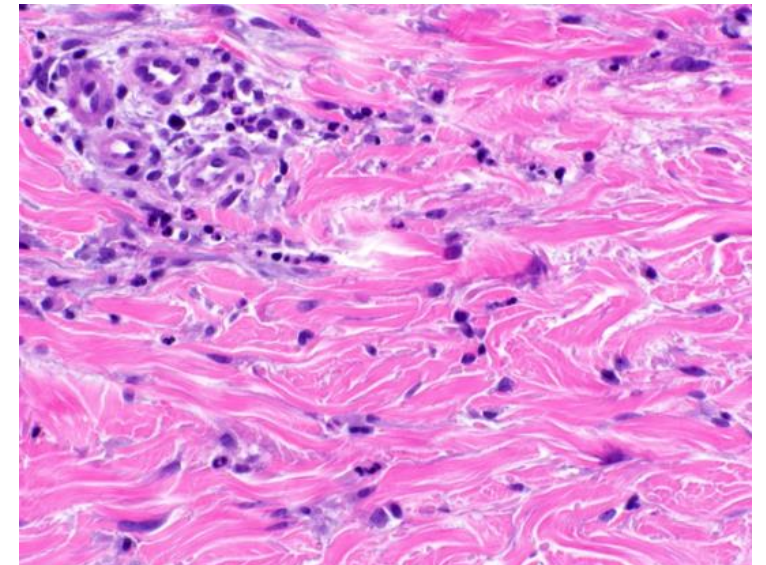
C

D

**Urticaria:** transient and disappear

# Neutrophilic urticarial dermatosis

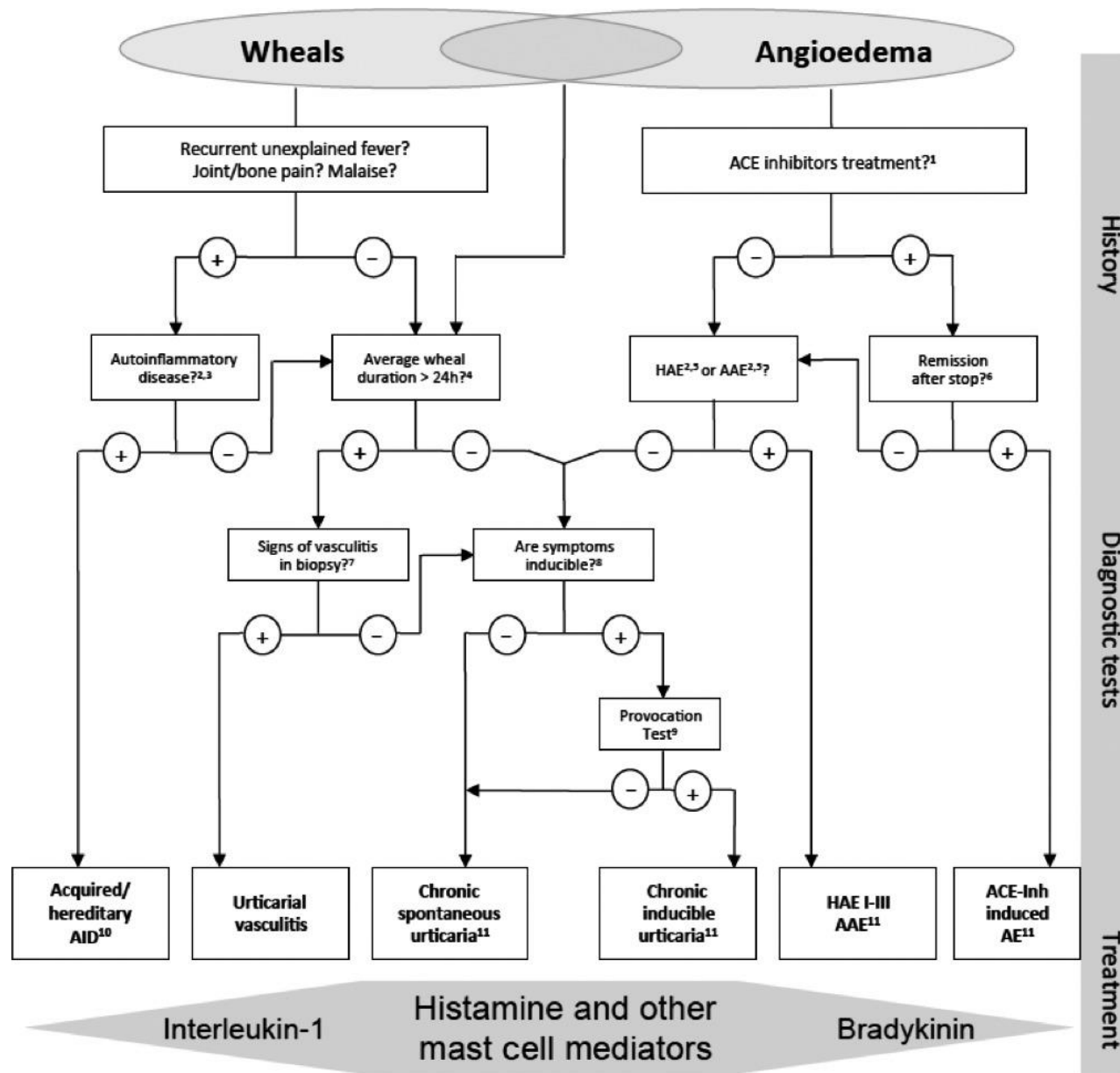
- Neutrophil chemotaxis to skin, a/w systemic diseases IBD, RA, CAPS, Sjogren, AOSD, SLE, CML, VEXAS syndrome



Hou Z, Hinds BR, Cohen PR. Crohn disease-associated neutrophilic urticarial dermatosis: report and literature review of neutrophilic urticarial dermatosis. *Dermatol Online J.* 2017 Nov 15;23(11):13030

# Angioedema (photo removed)

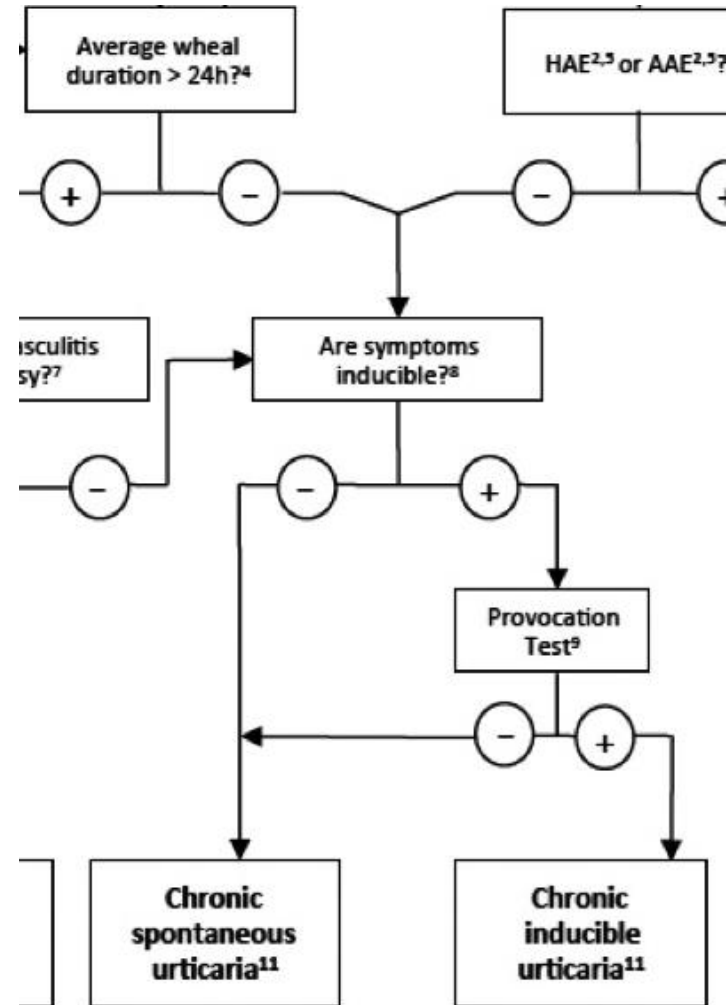
- Sudden, deep swelling of dermis or mucous membranes
- Painful > itch
- Resolution over hours, can take 72 hours
- *Seen in 40-50% of patients with CSU*



Zuberbier et al; The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-1414.



# Chronic urticaria: inducible vs spontaneous

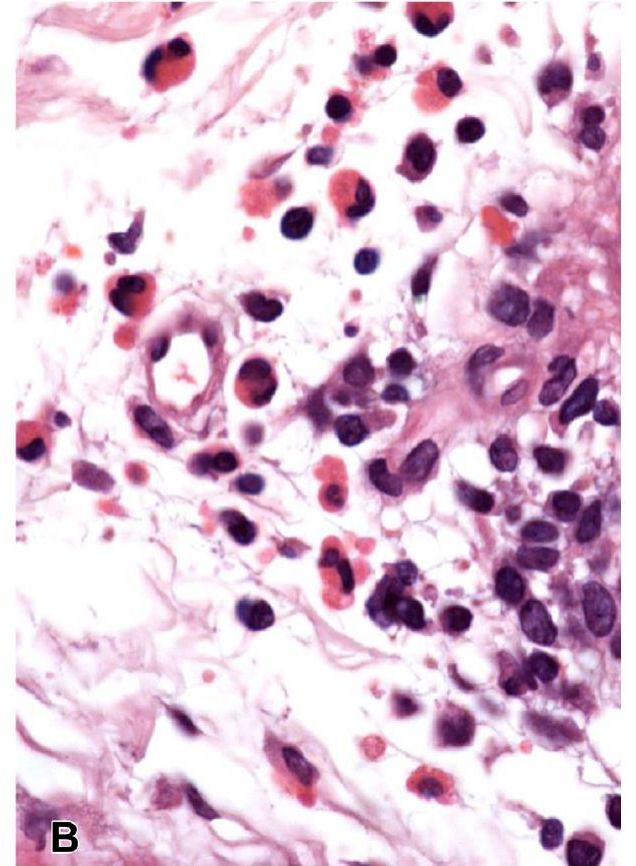
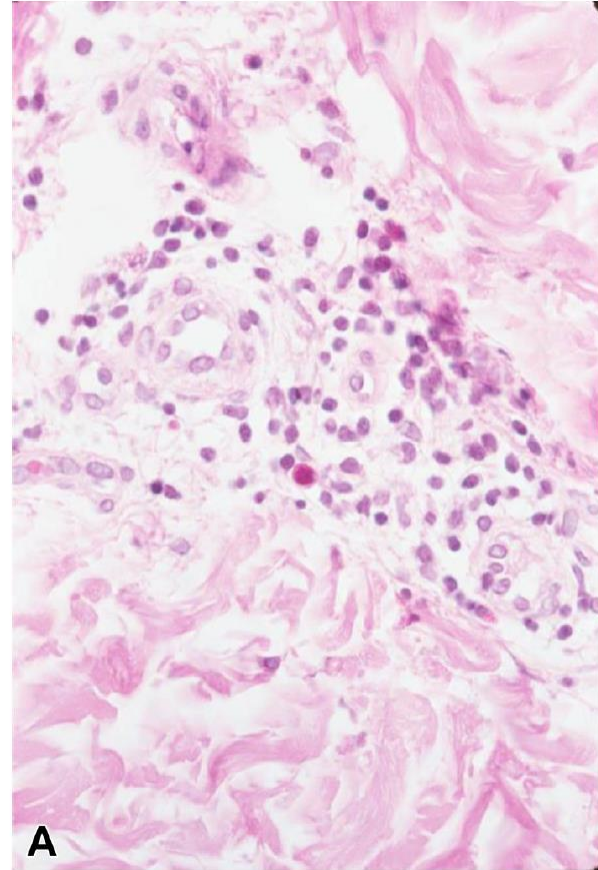


# Take-home 1:

History is critical for confirming diagnosis, but skin biopsy can help when in doubt.

Chronic Spontaneous Urticaria is intermittent urticaria that continues for greater than 6 weeks and lacks an identifiable physical trigger

# Focus: Chronic Spontaneous Urticaria



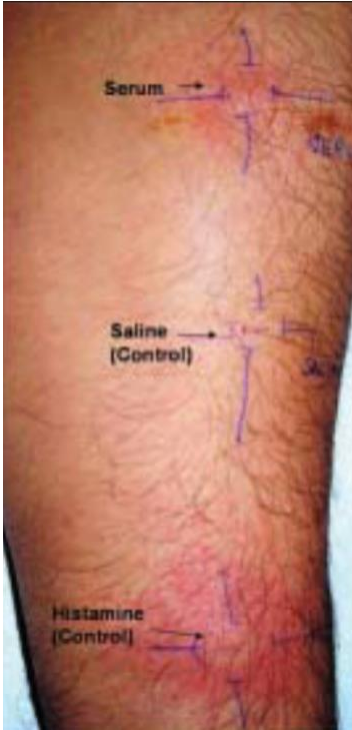
Giménez-Arnau AM, DeMontojoye L, Asero R, Cugno M, Kulthanan K, Yanase Y, Hide M, Kaplan AP. The Pathogenesis of Chronic Spontaneous Urticaria: The Role of Infiltrating Cells. *J Allergy Clin Immunol Pract.* 2021 Jun;9(6):2195-2208.

# Pathogenesis: where to start?

## Problem:

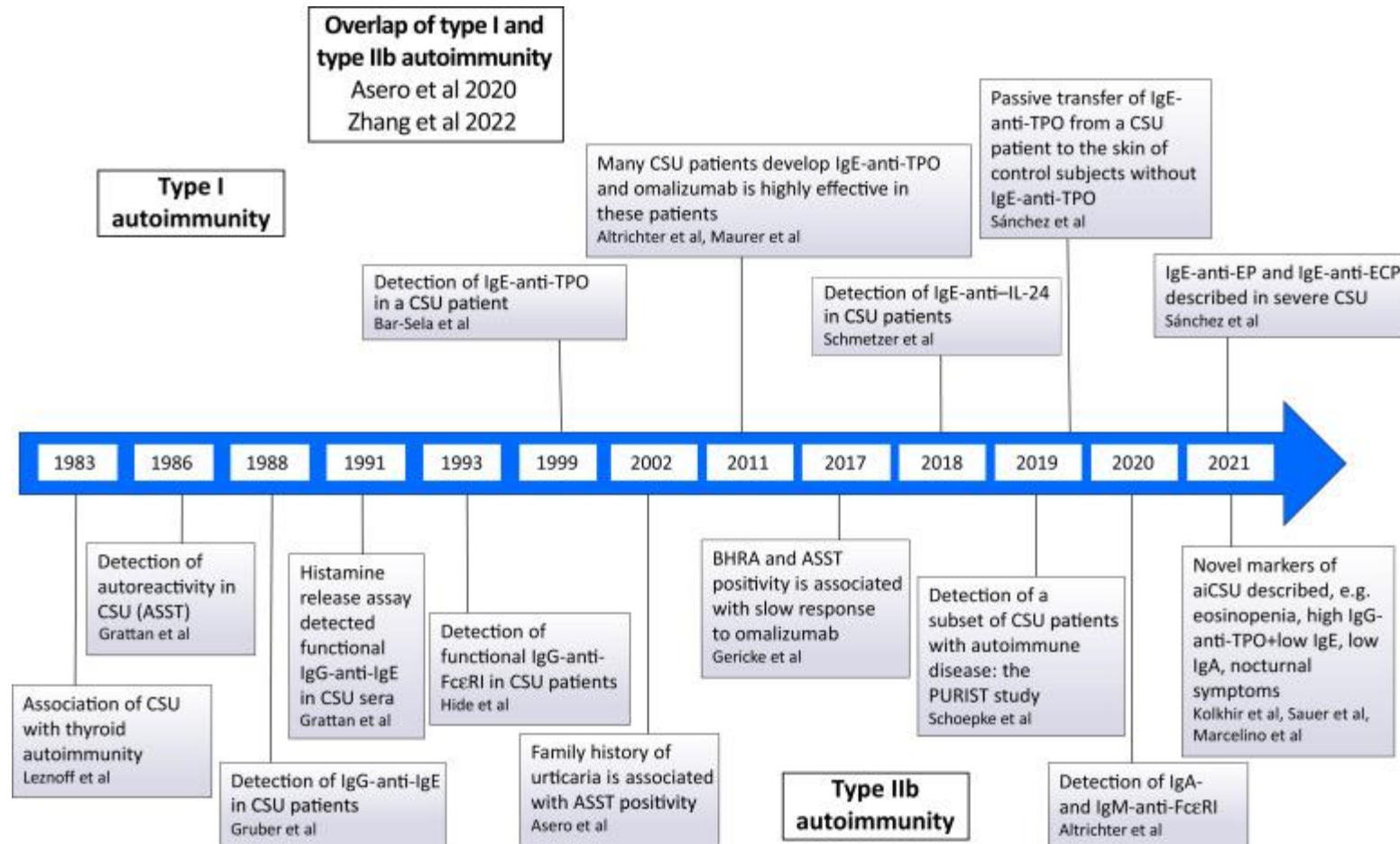
1. CSU is a reaction pattern in the skin
2. CSU is a collection of different mediators

# 1986: Autologous serum skin test (ASST)



- Intradermal Injection of patient's serum
- 35-58% of patients with CSU are ASST positive
- Histamine is injected as control → 15 minutes
- Serum has mediators that activate cells in the skin

# Autoimmune antibodies identified



Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, Xiang YK, Maurer M. Autoimmune chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022 Jun;149(6):1819-1831. doi: 10.1016/j.jaci.2022.04.010. PMID: 35667749.

# Discovered auto-antibodies

## IgE-mediated: type I autoimmune

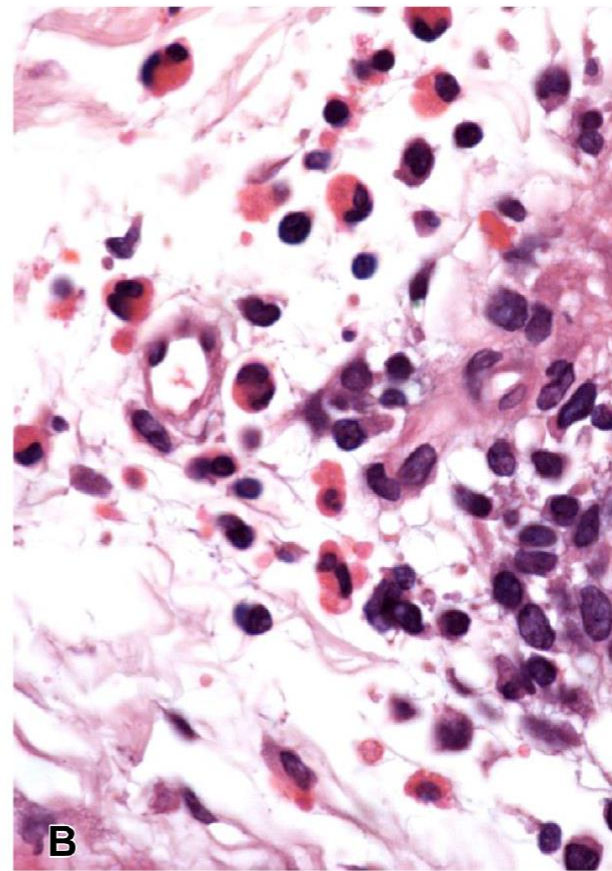
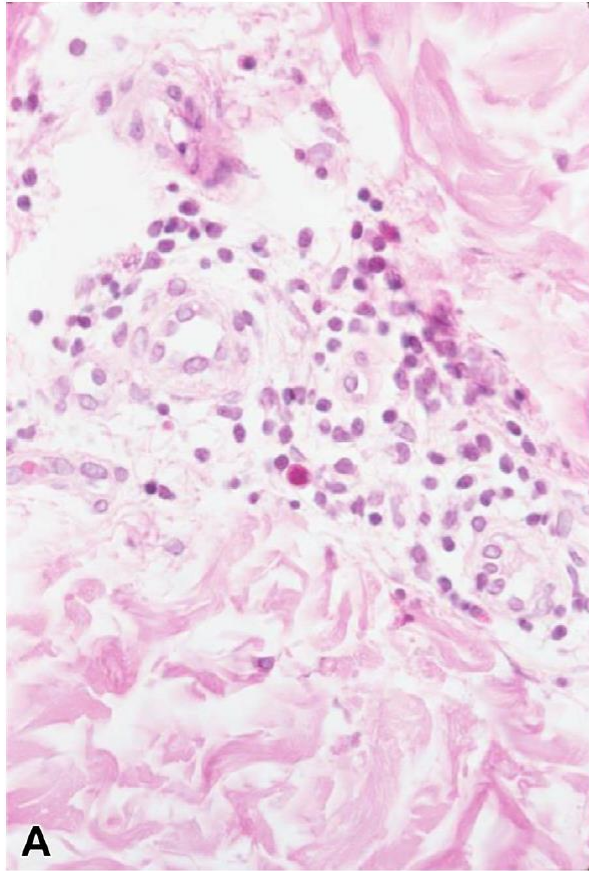
- IgE-Anti-IL-24 (71% of CSU patients c/t 20% HC)
- IgE-Anti-TPO (34% of CSU patients c/t 8.1% Controls)

## IgG-mediated: type IIb autoimmune:

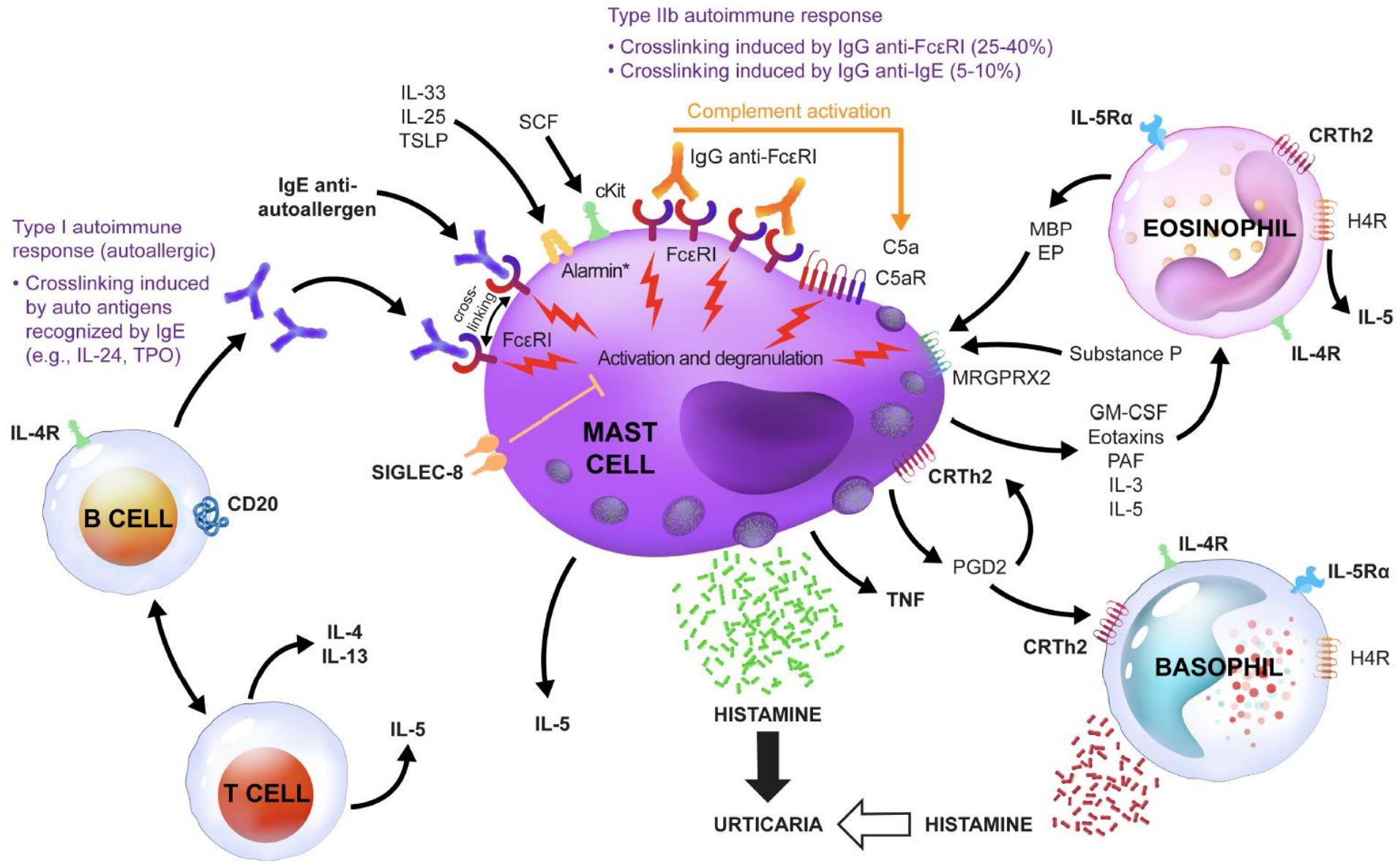
- IgG-anti-FcεRI
- IgG-anti-IgE



# Other cell types play a role:







Kaplan A, Lebwohl M, Giménez-Arnau AM, Hide M, Armstrong AW, Maurer M. Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. *Allergy*. 2023 Feb;78(2):389-401. doi: 10.1111/all.15603. Epub 2022 Dec 7.

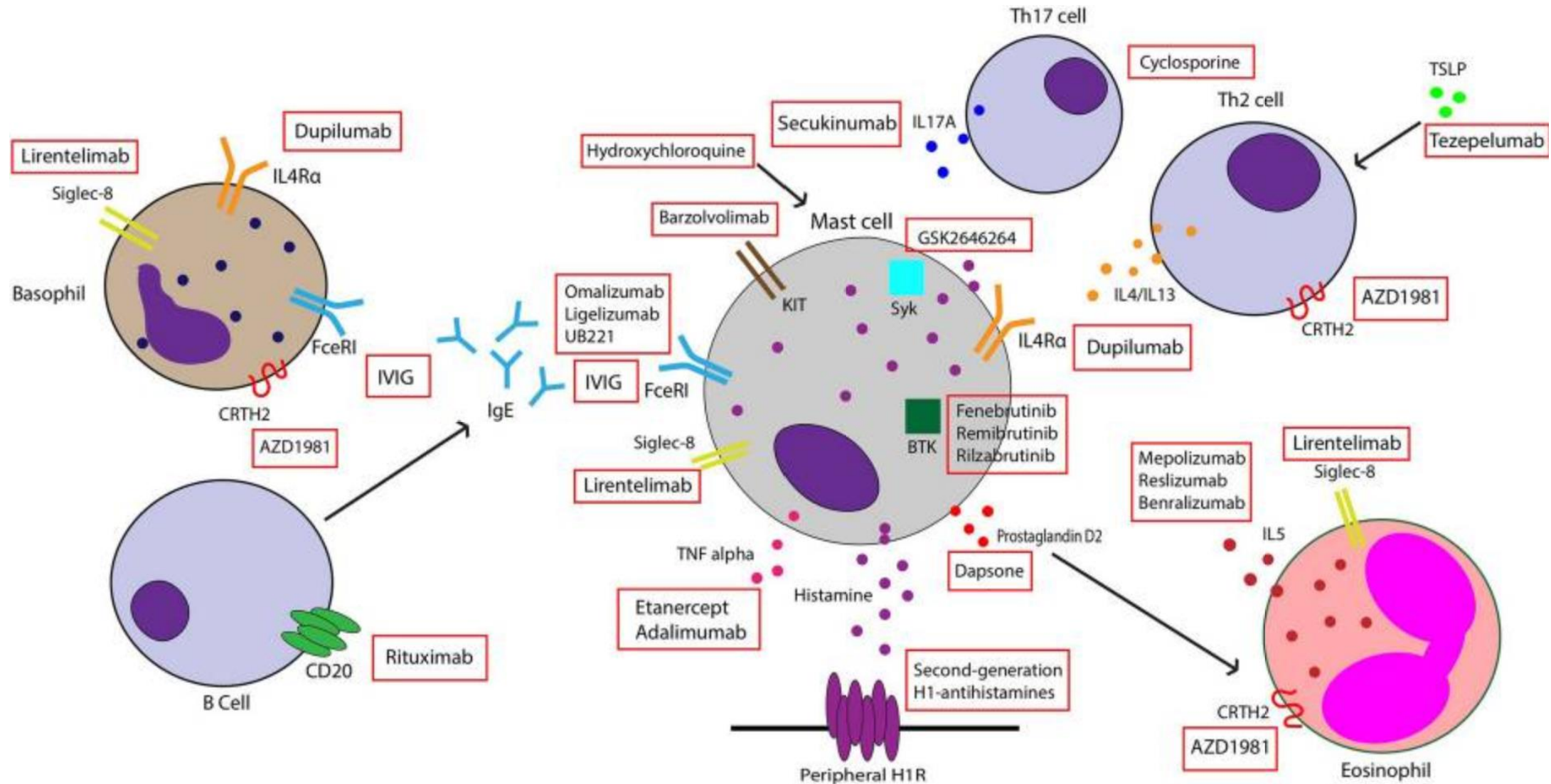
## Take-home 2:

Auto-antibodies are thought to trigger CSU, but downstream involvement in other cell types is valid

# Where is the field moving?

New therapies target different pathways and cell types

# Treatment approaches -> clinical trials



# Endotypes exist but are likely incomplete

- Newer technologies including BCR sequencing, transcriptomics of tissue and blood are needed
- Clinical trials rarely include disease endotypes or biomarker analysis

## Take-home 3:

Multiple clinical trials underway, many new medications will soon be available.

Personalized medicine needed



*Update on ongoing Dupixent® (dupilumab) chronic spontaneous urticaria Phase 3 program*

- \* In a Phase 3 trial in patients refractory to omalizumab, Dupixent did not reach statistical significance in an interim analysis despite numeric improvements observed across key endpoints; trial will be stopped due to futility

[News > Medscape Medical News](#)

# **FDA Calls for More Data on Dupilumab for Chronic Spontaneous Urticaria, Manufacturers Announce**

Marcia Frellick  
October 23, 2023



# Comparison: immunobullous diseases

Disease	Target antigen	Routine multi-step approach <sup>1</sup>
<b>Pemphigus vulgaris</b>	Desmoglein 3	<i>Desmoglein 3 ELISA</i> [22]
<b>Pemphigus foliaceus</b>	Desmoglein 1	<i>Desmoglein 1 ELISA</i> [22]
<b>Paraneoplastic pemphigus</b>	Desmoglein 3	<i>Desmoglein 3 ELISA</i> [22]
	Envoplakin	<i>Envoplakin ELISA</i> [21]
	Periplakin/ Desmoplakin I/II	Immunoblot with extract of cultured HaCaT cells [21] Indirect IF microscopy on rat and monkey bladder
<b>Bullous pemphigoid</b>	BP180	<i>BP180 NC16A ELISA</i> [20]
	BP230	<i>BP230 ELISA</i> [51]
	Soluble ectodomain of BP180 (LAD-1)	BP180 4575 (c-terminal fragment) Immunoblot [33,63] LAD-1 Immunoblot [33,63]
<b>Pemphigoid gestationis</b>	BP180	<i>BP180 NC16A ELISA</i> [20] Complement binding test
	Soluble ectodomain of BP180 (LAD-1)	Immunoblot with conditioned medium of cultured HaCaT cells (IgA reactivity) ) [33,63]
<b>Linear IgA dermatosis</b>	BP230	<i>BP230 ELISA</i> [51]
	Soluble ectodomain of BP180 (LAD-1)	Immunoblot with conditioned medium of cultured HaCaT cells (IgA reactivity) [33]
<b>Lichen planus pemphigoides</b>	BP180	<i>BP180 NC16A ELISA</i> [51]
	BP230	<i>BP230 ELISA</i> [51]
<b>Mucous membrane pemphigoid</b>	Soluble ectodomain of BP180 (LAD-1)	Immunoblot with conditioned medium of cultured HaCaT cells (IgG and IgA reactivity) [33]
	BP180	<i>BP180 NC16A ELISA</i> [20]
	BP230	<i>BP230 ELISA</i> [51]

van Beek N, Rentzsch K, Probst C, Komorowski L, Kasperkiewicz M, Fechner K, Bloecker IM, Zillikens D, Stöcker W, Schmidt E. Serological diagnosis of autoimmune bullous skin diseases: prospective comparison of the BIOCHIP mosaic-based indirect immunofluorescence technique with the conventional multi-step single test strategy. *Orphanet J Rare Dis.* 2012 Aug 9;7:49. doi: 10.1186/1750-1172-7-49. PMID: 22876746; PMCID: PMC3533694.

# What can we do in academia?

- Collect high quality data for biomarker analysis and clear endotyping  
---> Document UAS7, itch severity score, medication start dates + dosing
- Data can be used to predict treatment response
- **Leverage our research centers: endotyping, assay development**

# UAS7 score: useful in clinical practice

**Table III The 7-Day Urticaria Activity Score for assessing disease activity in CSU**

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

- 0-6 score per day x 7 days = 42 maximum

# Available testing:

## Recommended testing:

- Anti-TPO (IgG), [not IgE ☹️ ]
- Total IgE, CRP, CBC w/ diff, ?TFTs

## Additional testing:

- IgE Antibody (Anti-IgE IgG) - **Quest**
- Urticaria-induced Basophil Activation – **ARUP**

## Secondary considerations (history driven):

- Consider H. pylori, ANA, stool O&P

IgE Antibody (Anti-IgE IgG)

Test Code

18877  

CPT Code(s)\*

83520

**ARUP**  
LABORATORIES

Testing

Services

[ARUP Home](#) > [Lab Test Directory](#) > Urticaria-Induced Basophil Activation

2005416

Urticaria-Induced Basophil Activation

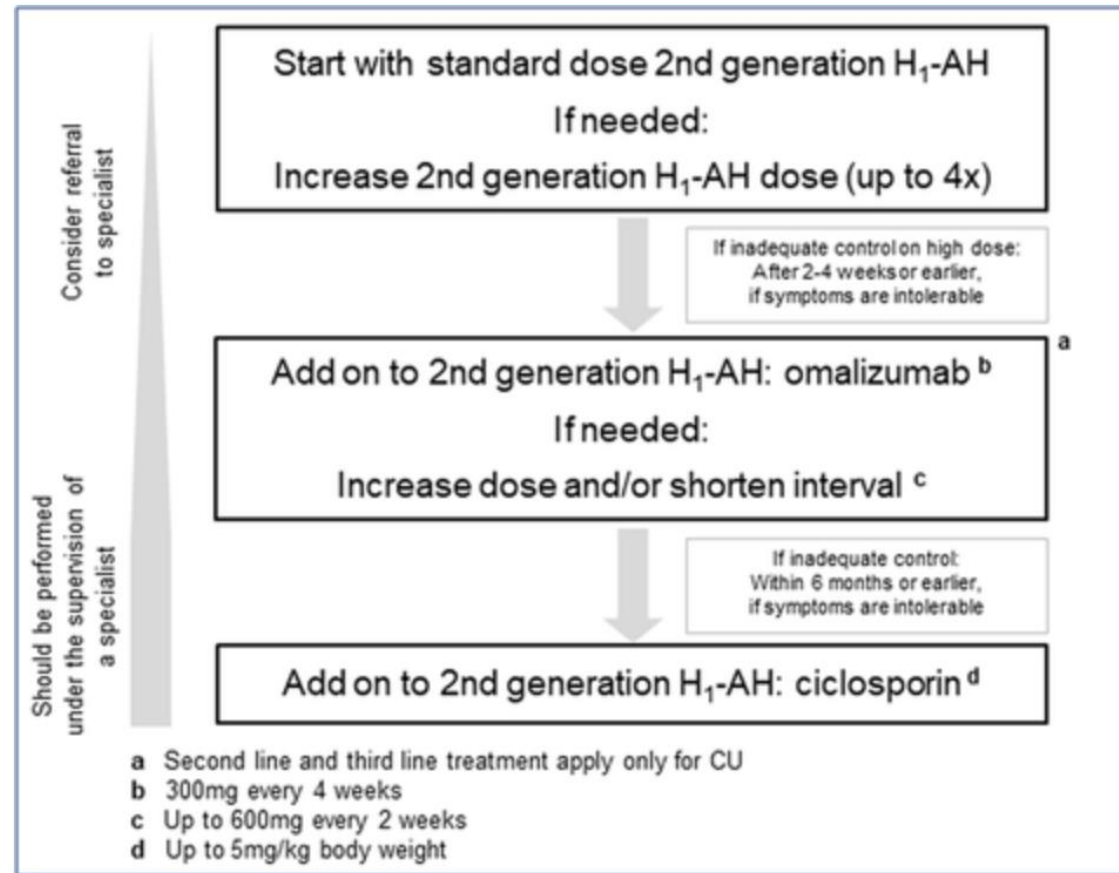
# Take home summary

1. Obtain careful history. Get skin biopsy if needed
2. Auto-antibodies, mast cells and basophils are central to urticarial initiation, but eosinophils, B cells and T cells are mediators
3. New clinical trials will transform treatment algorithms
4. High quality clinical and scientific data are needed to guide the future

Thank you

Extra slides:

# Current guidelines for treatment



Zuberbier et al; The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-1414.



# Clinical trial data points:

## Omalizumab:

- Meta-analysis of 294 patients: UAS7 decrease of **25.6** (range 0-42)

## Dupilumab:

- CUPID-study A: UAS7 decrease was -20.5 for Dupi, -10.5 placebo. (B): discontinued early.

## Remibrutinib:

- Primary outcomes achieved REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157)