

CHRONIC SPONTANEOUS URTICARIA

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Disclosure

- **No Conflict of Interest regarding the content covered in this presentation**

Objective

- Review classification of chronic urticaria
- Understand pathophysiology of chronic spontaneous urticaria
- Discuss diagnostic approach of chronic spontaneous urticaria
- Outline current treatment strategies

Definition

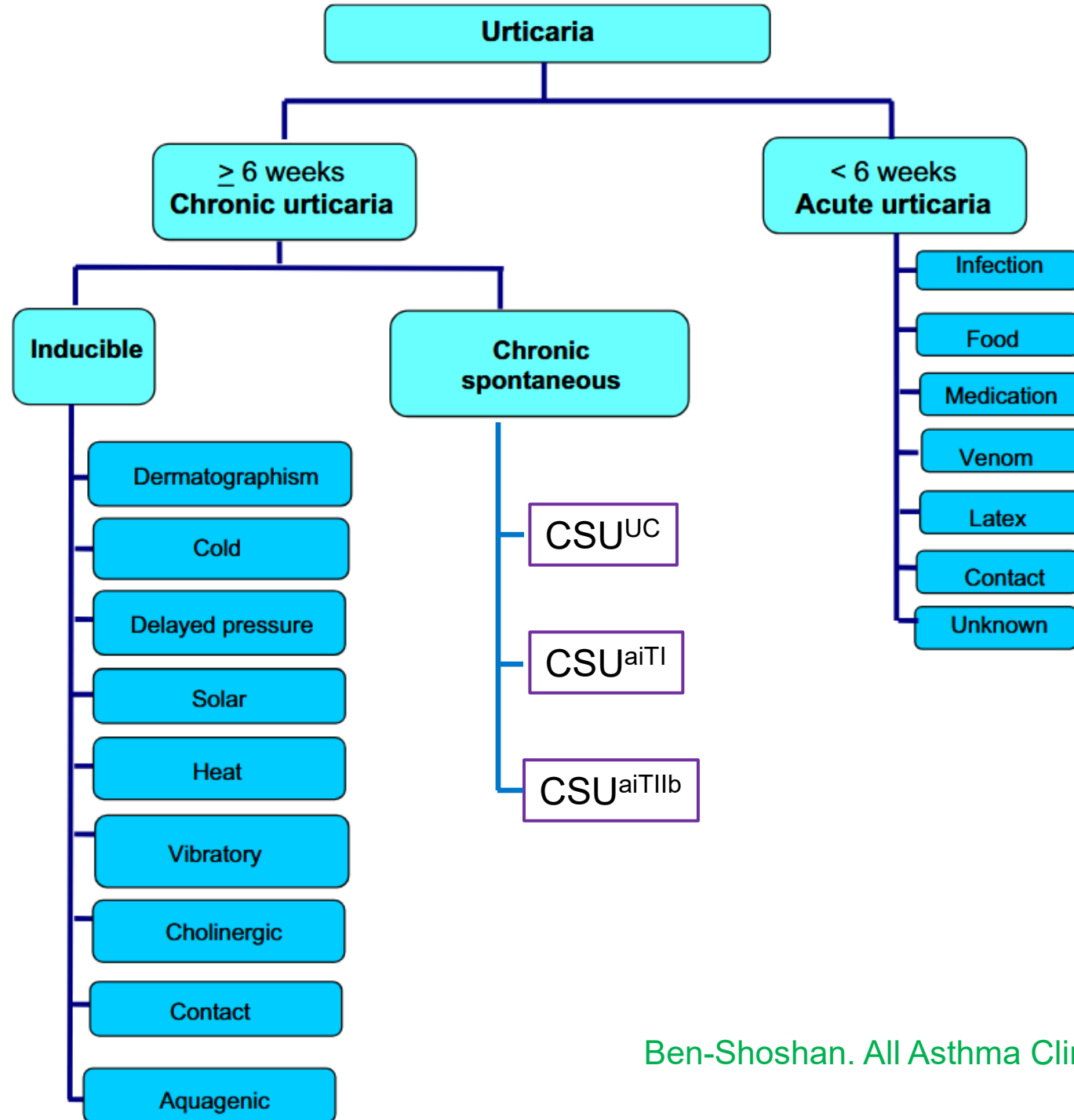
- Urticaria

- ❑ Sudden appearance of wheals and/or angioedema
- ❑ Central swelling surrounded by a reflex erythema
- ❑ Associated itching, or sometimes, burning sensation
- ❑ Skin returning to normal appearance within 1-24 h

- Angioedema

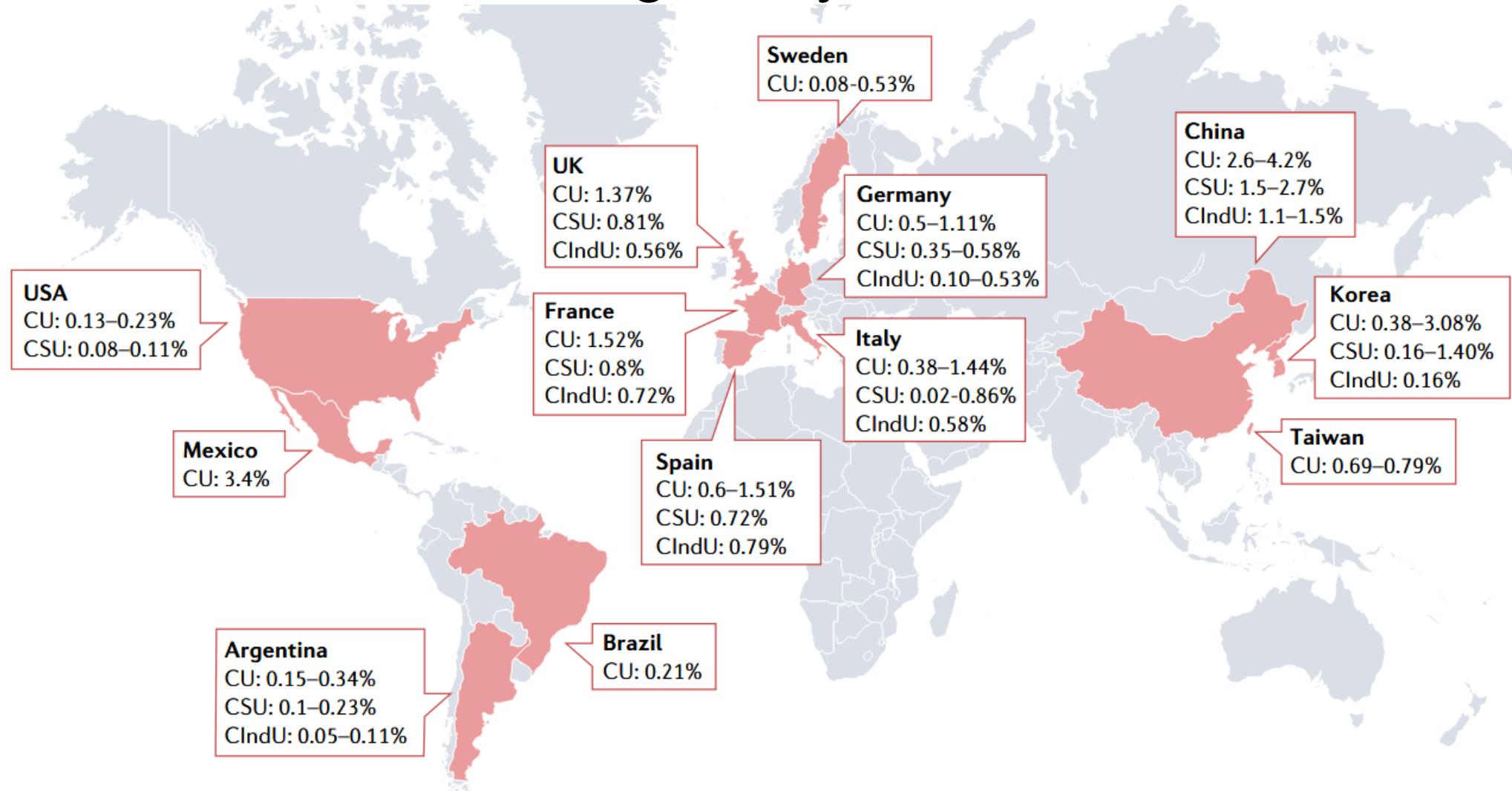
- ❑ Deeper subcutaneous swelling
- ❑ Less circumscribed than urticaria
- ❑ Sometimes pain rather than itching
- ❑ Leakage of plasma into subcutaneous/mucosal tissue

Classification



Epidemiology

- Prevalence: 86 million globally in 2017.



Parameter	Acute urticaria	Chronic spontaneous urticaria	Chronic inducible urticaria
Duration (weeks) ⁴	≤6	>6	>6
Point prevalence (%) ^a	≤14	0.02–2.7	0.05–1.5
Remission rates at 1 year (%) ^a	~60–90	10–80 ^b	0–49
Sex predominance ^{144a}	Female	Female	Female; male in CholU
Typical age of onset ^a	Any age, likely more frequent in children <5 years old	6–9 years old (children); 30–50 years old (adults)	4–12 years old (children); 20–35 years old (adults); CholU, 10–30 years old; DPU, ~40 years old
Aetiology ^{4a}	Idiopathic, infections, drugs, food, insect stings, inhalant allergens, physical factors	Idiopathic, autoimmune; rarely infections, cancer, hypothyroidism, hyperthyroidism, rheumatic diseases, type I hypersensitivity	Subtype-specific triggers including cold, heat, pressure, ultraviolet and visible light, vibration, water, sweating, contact allergens
Risk factors	High population density, allergic diseases in personal and parental history ^{2,15,32}	Autoimmune thyroid diseases ⁴²	Unknown; possibly environmental factors, for example temperature or climate ⁴⁸
Triggers ⁴	Differ	Non-definite, non-specific, for example stress, NSAIDs or foods	Definite, specific ^c
Proposed pathogenesis ^{4,9,10,53,106}	Unknown, allergic reactions, COX1 inhibition	Autoimmunity, cell infiltration, activation of coagulation and complement systems	Differs based on a subtype; immunological or non-immunological
Symptom frequency ⁴	Usually, daily or after exposure to causative factor, for example allergen	Daily or almost daily or an intermittent–recurrent course	When trigger is present
Frequent comorbidity ⁵	Infection	CIndU, autoimmune diseases, especially thyroiditis, mental health disorders	CSU, probably allergic diseases
Basic screening tests ⁴	None	Differential blood count and ESR and/or CRP; IgG anti-TPO and IgE in specialist care	Provocation testing

Disease Burden

- Humanistic burden

- Health-related quality of life (HRQoL):

- Mental health, sleep, daily activity

- 61.6% with HRQoL score 4-6 (0-6)

- Impact on daily living

- Social discomfort, itching/skin discomfort

- Stress/anxiety/irritation/insomnia

- Healthcare burden

- Frequent outpatient visit. Higher ED visit and hospitalization.

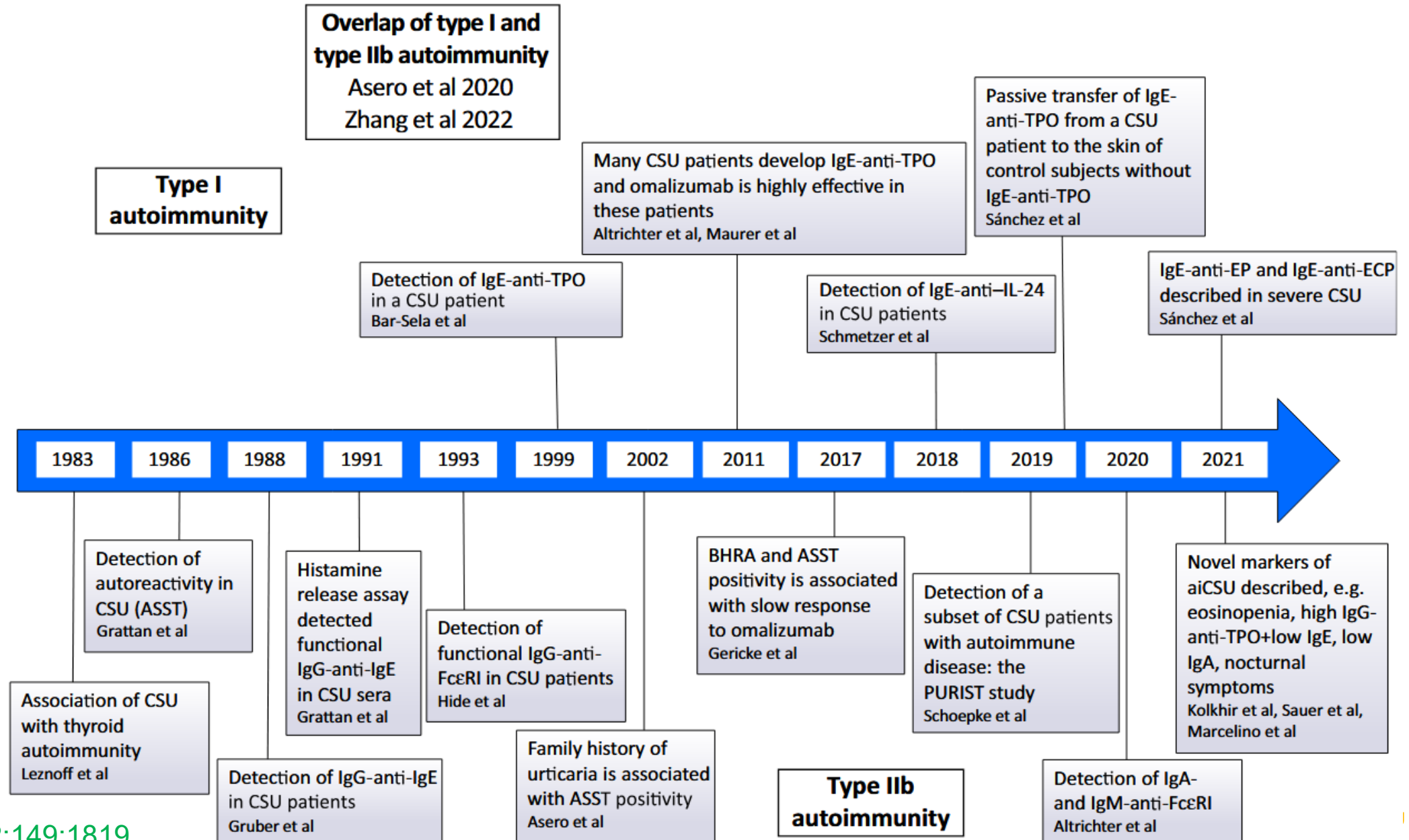
- 30% used ER over 10 months

- 7.3% hospitalized in 1 yr

- Financial burden

- In 2012, CSU annual cost \$997/pt (\$1,160 for diabetes, \$1,050 for hypertension)

Pathophysiology: Timeline



Pathophysiology: Mast Cells

- Chronic Autoimmune Urticaria

- Type I

IgE Abs for autoallergens

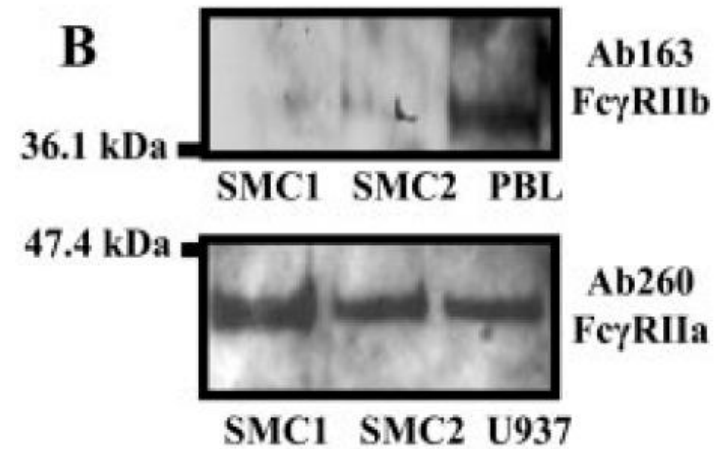
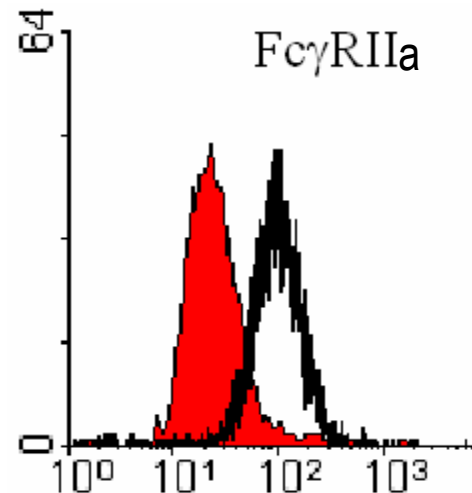
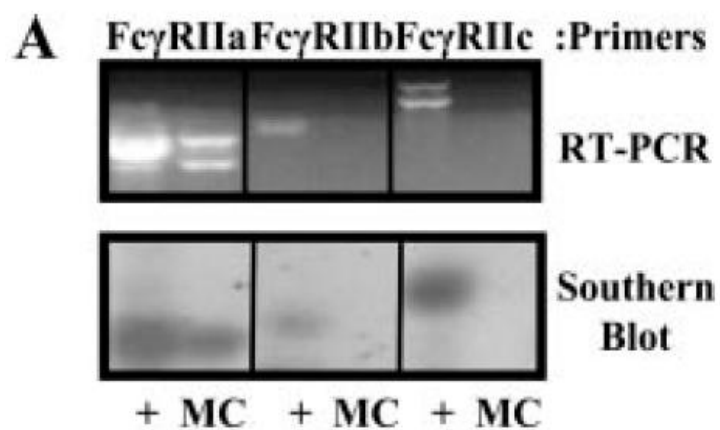
Antigen: IL-24, TPO, DNA

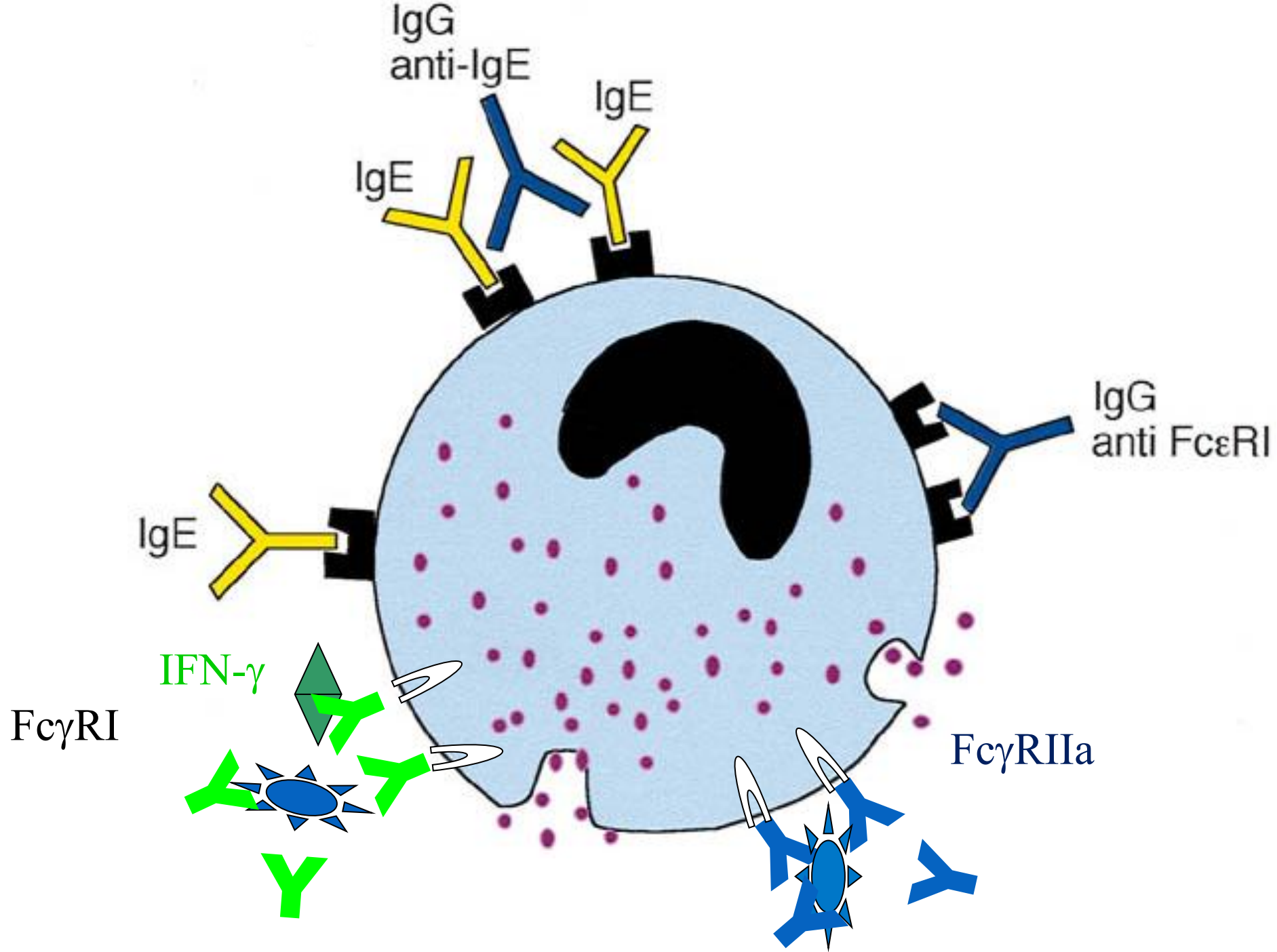
- Type IIb

IgG antoantibodies

Antigen: IgE receptor, IgE

IgG high and low affinity Receptors (FcγRI and FcγRIIa)

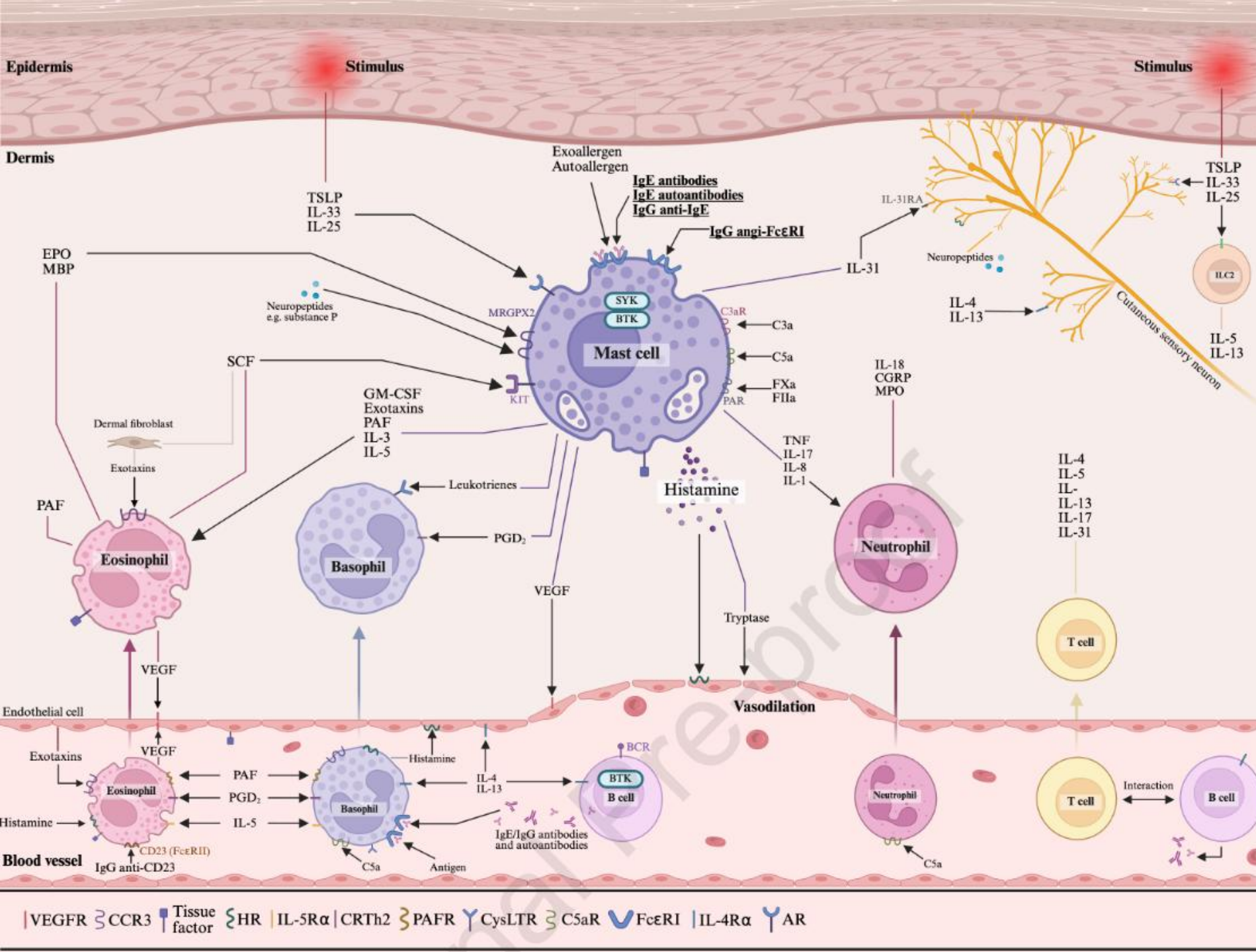




Pathophysiology: Mast Cells

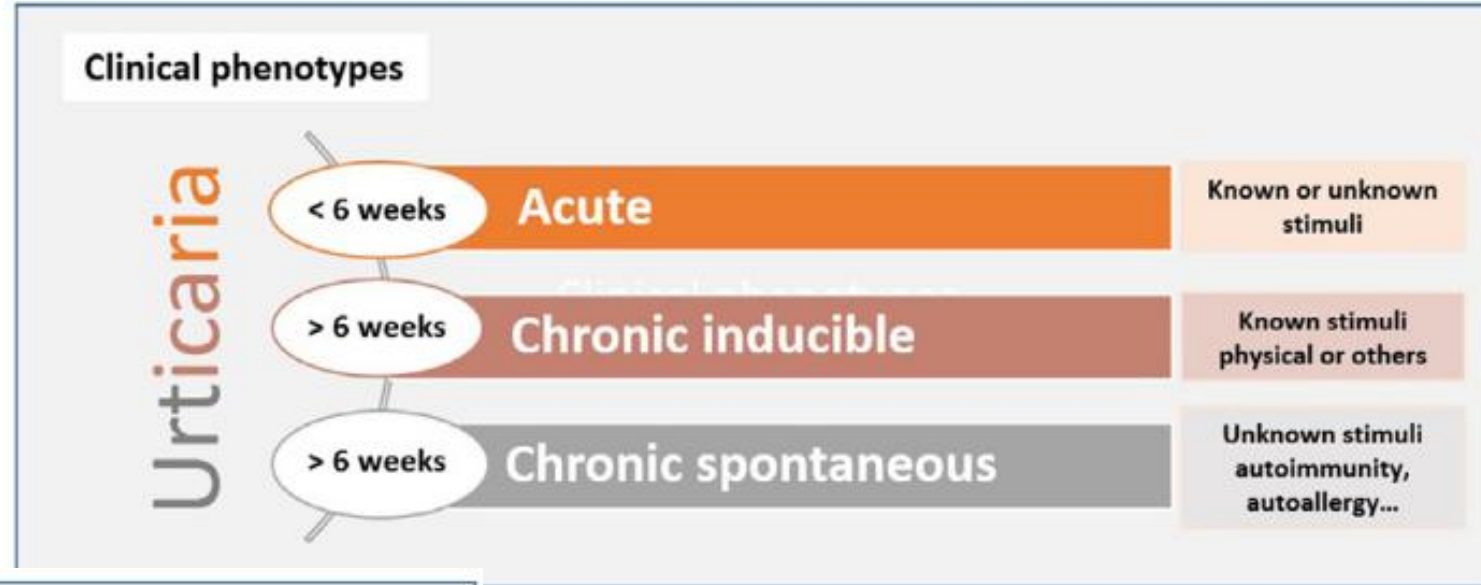
- Other activating receptors
 - ❑ Mas-related G-protein Coupled Receptor X2 (MRGPRX2)
Agonists: Substance P, MBP, EPO
 - ❑ C5aR, C3aR
 - ❑ PAR1, PAR2
Agonists: Thrombin, FXa
 - ❑ Kit

Urticaria Pathways



Warp. J Am Acad Derm. 2026
10.1016/j.jaad.2025.12.106

Phenotypes and Endotypes



Molecular endotypes

Urticaria

IgE – Ag – IgE crosslink	Allergy
C5a – C5aR / D-dimer – PAR	Plasma cascades
PGD2 – CRTh2 / IL-4 – IL4Rα	Inflammation
Subst P / MBP – MRGPRX2	Neurogenic / Eos
PAMPs / DAMPs – TLRs	Infection
IgG – FcεR1a / IgG – IgE – FcεR1a	Autoimmunity
FcεR1a – IgE – autoAg (TPO, IL-24...)	Autoallergy

Clinical Presentation

Suppl. Table 8 | Frequency of wheals, angioedema or both in selected patients with chronic spontaneous urticaria

First author (year) ^{Ref}	n	Wheals and angioedema, %	Only wheals, %	Only angioedema, %	Country
Champion (1969) ^{*102}	554	49.0	40.0	11.0	The UK
Juhlin (1981) ¹¹⁴	345	66.7	28.9	4.3	Sweden
Quaranta (1989) ¹¹⁵	86	53.5	36.0	10.5	USA
Sibbald (1991) ^{†97}	254	45.0	51.0	4.0	Canada
Volonakis (1992) ^{‡116}	226	15.0	78.4	6.6	Greece
Kozel (2001) ²⁵	78	53.9	33.3	12.8	The Netherlands
Kulthanan (2007) ^{†29}	450	34.0	65.0	1.0	Thailand
Zuberbier (2010) ^{‡70}	4,093	33.3	60.6	6.1	Germany
Magen (2013) ¹¹⁷	1,051	35.7	62.0	2.3	Israel
Dionigi (2016) ¹¹⁸	100	36.0	64.0	0.0	Brazil
Van den Elzen (2017) ¹¹⁹	178	51.1	24.2	24.7	The Netherlands
Weighted Average^{&}		36.9	57.2	5.9	

*Authors examined patients with all types of urticaria; †Authors do not distinguish between chronic spontaneous urticaria and chronic inducible urticaria;

‡Authors examined the total population; &Calculated based on the sample size.

n, number of patients/subjects; –, not reported;

Clinical Presentation

- Signs and symptoms occur at any time. But commonly during the evening and night. CSU^{au}
- Wheals occur anywhere, but favor arms and legs.
- Angioedema most commonly on the face.
- Wheals and/or angioedema occur daily or nearly daily in moderate to severe patients.
- Stress, food, drug (NSAIDs), infection can lead exacerbation.

Comorbidities

- Chronic inducible urticaria
- Autoimmune diseases
 - Autoimmune thyroid disease (Hashimoto)
 - Vitiligo
 - Rheumatoid arthritis
 - Autoimmune gastritis
- Infection
 - Helicobacter pylori
 - Dental infection
 - COVID-19
 - Not causal link
- Cancer (Immune dysregulation)

Diagnosis

- History
- Physical Exam
- Diagnostic Workup (Aims=7Cs)

History	Physical examination ^a	Basic tests ^b
Confirm	Rule out differential diagnoses	
Cause	Look for indicators of CSU ^{aiTI} , CSU ^{aiTIIb}	
Cofactors	Identify potential disease triggers, aggravators, and modifying factors	
Comorbidities	For example, check for CIndU, related autoimmune conditions, mental health	
Consequences	For example, evaluate sleep, mental health, sexual dysfunction, work, social performance	
Components	Assess potential biomarkers or predictors of treatment response	
Course	Monitor CSU activity, impact and control	

TABLE 8 | Recommended diagnostic tests in frequent urticaria subtypes.

Types	Subtypes	Routine diagnostic tests (recommended for every patient)	Extended diagnostic program ^a (based on history)—For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None ^b
	CSU	Differential blood count. ESR and/or CRP IgG anti-TPO and total IgE ^c	Avoidance of suspected triggers (e.g., drugs); Diagnostic tests for (in no preferred order): (i) infectious diseases (e.g., <i>Helicobacter pylori</i>); (ii) functional autoantibodies (e.g., Autologous Serum Skin Test (ASST) and Autologous Plasma Skin Test (APST), basophil activation test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, e.g., avoidance diet); (v) concomitant CIndU ^d ; (vi) severe systemic diseases (e.g., tryptase); (vii) other (e.g., lesional skin biopsy or lab test to exclude hereditary angioedema); (viii) C4 (screening) and C1INH (antigen and function) testing in patients with angioedema only phenotype

Differential Diagnosis

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin
- Mast cell activation syndrome (MCAS)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (e.g., HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), that is, Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), or Neonatal Onset Multisystem Inflammatory Disease (NOMID)
- Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia, or arthritis and lymphadenopathy)
- Gleich's syndrome (episodic angioedema with eosinophilia)
- Well's syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
- Bullous pemphigoid (prebullous stage)
- Adult-onset Still's disease (AOSD)
- Eosinophilic Dermatoses of Hematologic Malignancy (EDHM)
- Hypereosinophilic Syndromes (HES)

These differential diagnoses of urticaria are frequently misdiagnosed as urticaria because (1) they can present with wheals, angioedema, or both and/or (2) due to historical reasons. However, they are specific and distinct clinical entities

Disease Activity and Control

Disease activity

- Urticaria Activity Score (UAS)^{4,135}
- Angioedema Activity Score (AAS)¹³⁶
- Cholinergic Urticaria Activity Score (CholUAS)¹³⁸
- Cold Urticaria Activity Score (ColdUAS)¹³⁷

Disease control

- Urticaria Control Test (UCT)¹³⁹
- Angioedema Control Test (AECT)¹⁴⁰

Patient quality of life

- Chronic Urticaria-Quality of Life Questionnaire (CU-Q₂oL)²²³
- Angioedema-Quality of Life Questionnaire (AE-QoL)²²⁵
- Cholinergic Urticaria-Quality of Life Questionnaire (CholU-QoL)²²⁴

Urticaria Activity Score (UAS7, 0-42)

Urticaria Activity Score (UAS)		
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)

Angioedema Activity Score (AAS)

0-105

Score	Dimension	Answer options
—	Have you had a swelling episode in the last 24 h?	No, yes
0–3	At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	Midnight–8 a.m., 8 a.m.–4 p.m., 4 p.m.–midnight
0–3	How severe is/was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	No discomfort, slight discomfort, moderate discomfort, severe discomfort
0–3	Are/were you able to perform your daily activities during this swelling episode(s)?	No restriction, slight restriction, severe restriction, no activities possible
0–3	Do/did you feel your appearance is/was adversely affected by this swelling episode(s)?	No, slightly, moderately, severely
0–3	How would you rate the overall severity of this swelling episode?	Negligible, mild, moderate, severe

Patient name: _____ Date: (dd mmm yyyy): ____ ____ ____

Date of birth (dd mmm yyyy): ____ ____ ____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks*. *Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question*.

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?
☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all
2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?
☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all
3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?
☐ very often ☐ often ☐ sometimes ☐ seldom ☐ not at all
4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
☐ not at all ☐ a little ☐ somewhat ☐ well ☐ very well

Patient name: _____

Date: (dd mmm yyyy): ____ ____ ____

Date of birth (dd mmm yyyy): ____ ____ ____

Instructions: You have recurrent swelling referred to as angioedema. Angioedema is a temporary swelling of the skin or mucous membranes which can occur in any part of the body but most commonly involves the lips, eyes, tongue, hands and feet and which can last from hours to days. Some patients develop abdominal angioedema, which is often not visible but painful. Some forms of swelling can also be associated with hives also known as urticaria.

The following four questions assess your current state of health. For each question, please choose the answer from the five options that *best fits your situation*. Please answer *all questions* and please provide *only one answer to each question*.

1. In the last 4 weeks, how often have you had angioedema?

☐ very often ☐ often ☐ sometimes ☐ seldom ☐ not at all

2. In the last 4 weeks, how much has your quality of life been affected by angioedema?

☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all

3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?

☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all

4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?

☐ not at all ☐ a little ☐ somewhat ☐ well ☐ very well

Treatment of Chronic Urticaria

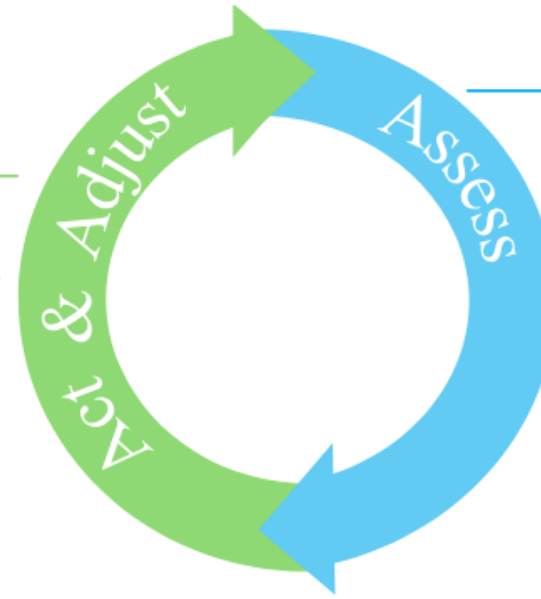
- Avoiding trigger
- Treat comorbidities

Medication	Recommended dose
Second-generation antihistamines	Up to 4x the recommended daily dose
Omalizumab	300 mg q4 weeks
Dupilumab	Loading dose of 600 mg followed by 300 mg q2weeks
Remibrutinib	25 mg PO BID
Cyclosporine	2-5 mg/kg/day (CSU ^{aiTIIb})

Principle of CSU Treatment

Act & Adjust

- Modify treatment and treat comorbidities
- Look at non-pharmacological interventions
 - esp. in CIndU
- Educate the patient
- Step up in inadequate control
- Change if side effects occur
- Step down if symptom free for 3-6 months



Assess

- Diagnostic procedures
- Comorbidities
- Severity – mainly use UCT, UAS, AAS
- Patient preferences
- Side effect of treatment

UCT Score

Control Level

Action

UCT < 12

Uncontrolled

- Step up* if:
- On 1-4 fold 2gAH > 7-28d
 - On OMA > 3m

UCT = 12 - 15

Well-controlled

Continue therapy and try to optimize

UCT = 16

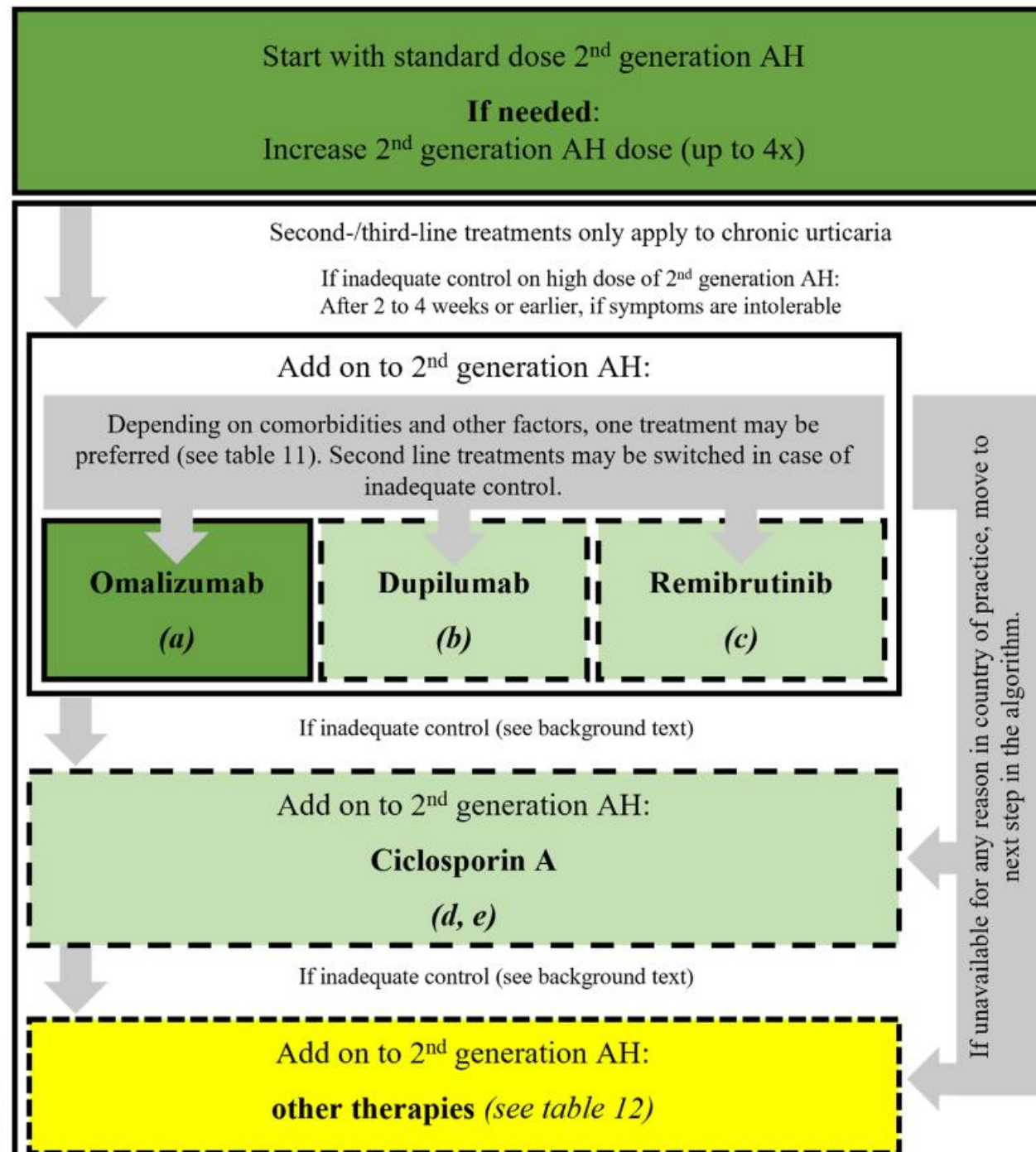
Completely Controlled

Step down*:
based on individual factors by reducing dose or extending intervals

Treatment Algorithm

Consider referral
to specialist

Should be performed under the
supervision of a specialist



Corticosteroids

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

We **recommend against** the long-term use of systemic glucocorticosteroids or depot preparations in CU.

↓↓

Strong consensus¹
Evidence- and consensus-based
(see Evidence Report, p. 103)

We **suggest** considering a short course of rescue systemic glucocorticosteroids in patients with an acute exacerbation of CU.

↑

¹> 95% agreement

Alternative Treatment Options

Although evidence from publications is low, clinical experience indicates that they may be useful in certain contexts. Interventions are listed in alphabetical order by frequency of use rather than efficacy

Intervention	Substance (class)	Possible indication
<i>Widely used</i>		
Tricyclic antidepressant with potent H1- and H2-antagonist activity	Doxepin ^a	CSU, Idiopathic cold-induced urticaria
Diet	Pseudoallergen-low diet ^b	CSU
H ₂ -antihistamine	Ranitidine ^c , famotidine, Lafutidine (available in Japan, South Korea, and India)	CSU
Immunosuppressive	Methotrexate Mycophenolate mofetil	CSU ± DPU ^d Autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU

Biomarkers for Treatment Response

Biomarkers for poor response to second-generation H1-AH

- High C-reactive protein levels
- High D-dimer levels

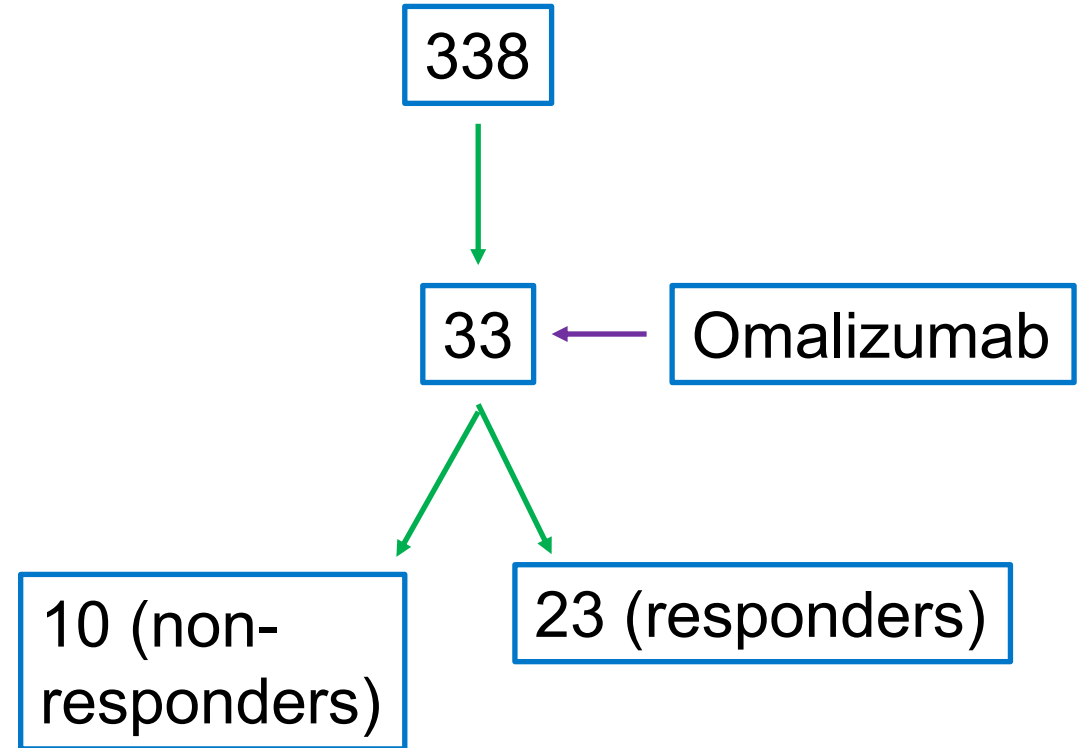
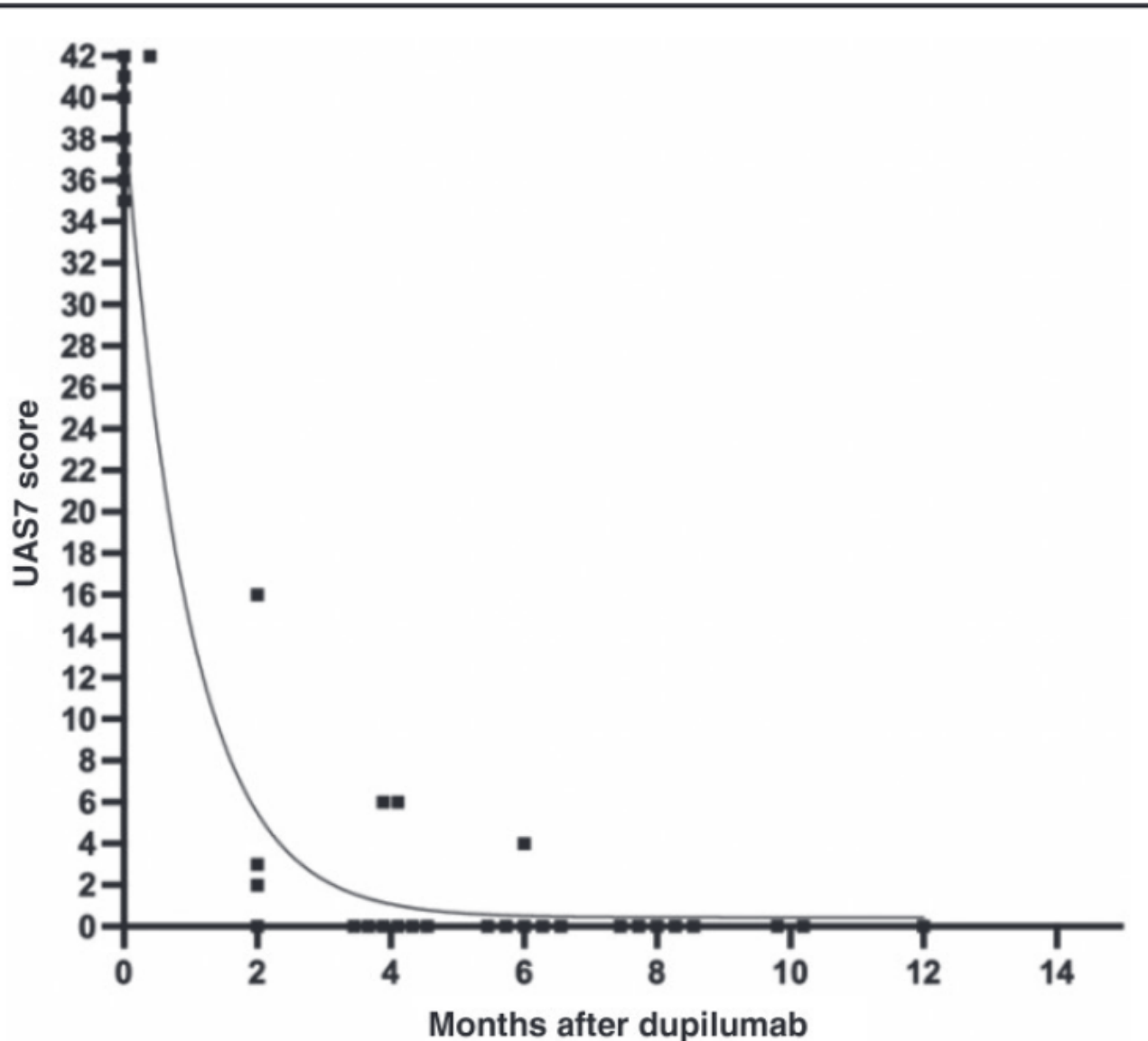
Biomarkers for poor and/or slow response to omalizumab

- Low baseline total IgE
- Positive ASST/BHRA
- Low baseline expression of FcεRI on basophils

Biomarkers for good response to cyclosporine

- Low baseline total IgE
- Positive BHRA

Omalizumab to Dupilumab?



Zhu. Clin Exp Derm. 2024;49:1227

Omalizumab to Dupilumab?

Patient	Age (years)	Sex	AD	asthma	Number of Oma Doses	Duration of Oma (months)	UCT Score Before Oma	UCT Score at baseline	UCT Score After 1 Month of Dup	UCT Score After 4 Months of Dup
1	17	F	-	-	6	7	5	6	9	3
2	72	M	+	-	18	16	4	4	8	8
3	19	F	-	-	18	25	11	9	9	3
4	16	F	+	-	20	20	4	10	12	12
5	38	F	+	-	25	30	2	7	12	4
6	79	M	-	-	3	3	7	8	9	8
7	40	M	-	-	85	82	5	9	8	7
8	55	M	-	-	4	5	1	4	12	16
9	39	F	-	-	22	36	2	4	6	5
10	30	F	-	+	29	29	9	4	9	12
11	50	F	-	-	13	13	8	8	6	11
12	32	F	-	+	16	24	1	5	1	8
Mean (±SD)	40.6 ± 19.5				21.6 ± 20.7	24.2 ± 20.1	4.9 ± 3.0	6.5 ± 2.2	8.4 ± 3.0	8.1 ± 3.9

Omalizumab Vs Dupilumab Vs Remibrutinib



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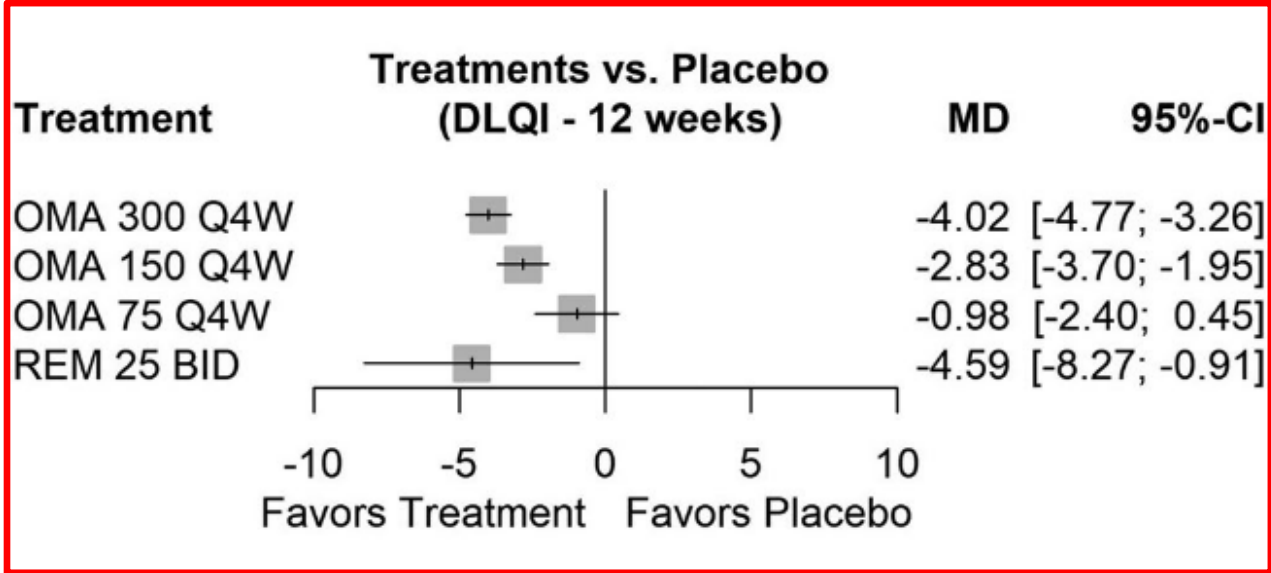
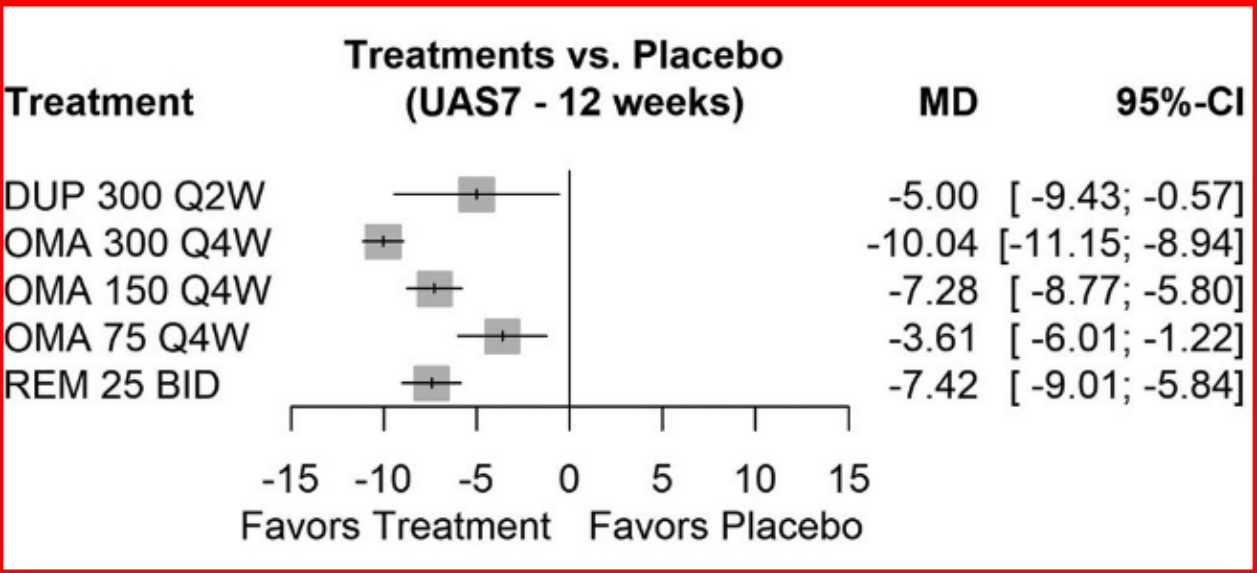
Comparative efficacy of omalizumab, dupilumab, and remibrutinib in chronic spontaneous urticaria: a network meta-analysis of randomized control trials

Grace Xiong, Daniel G. Rayner, Lauren Kim, Susheen Mahmood, Tiffany Yu & Mohannad Abu-Hilal

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Omalizumab Vs Dupilumab Vs Remibrutinib



Summary

- Urticaria Phenotypes: Acute Urticaria, Chronic Inducible Urticaria, and Chronic Spontaneous Urticaria.
- CSU Endotypes: Type I, Type IIb, Non-Type I/Type IIb
- Diagnosis progressed from minimal laboratory tests to pathway specific diagnostic tests to guide treatment.
- Management of chronic urticaria has evolved from anti-mediators and anti-inflammatory to biologics and mast cell activation inhibitors.

Thank You!