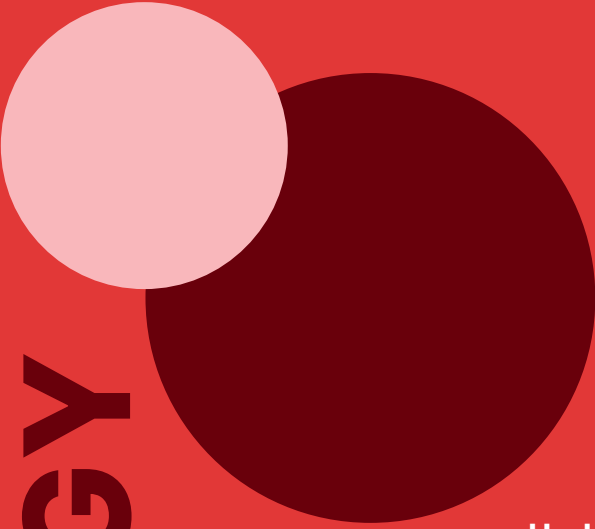




CANADIAN ALLERGY & IMMUNOLOGY TODAY

ISSN 2563-7711 (PRINT)
ISSN 2563-772X (ONLINE)

**VOLUME 5
ISSUE 2
FALL 2025**

Updates on the Treatment and Management of Urticaria in 2025

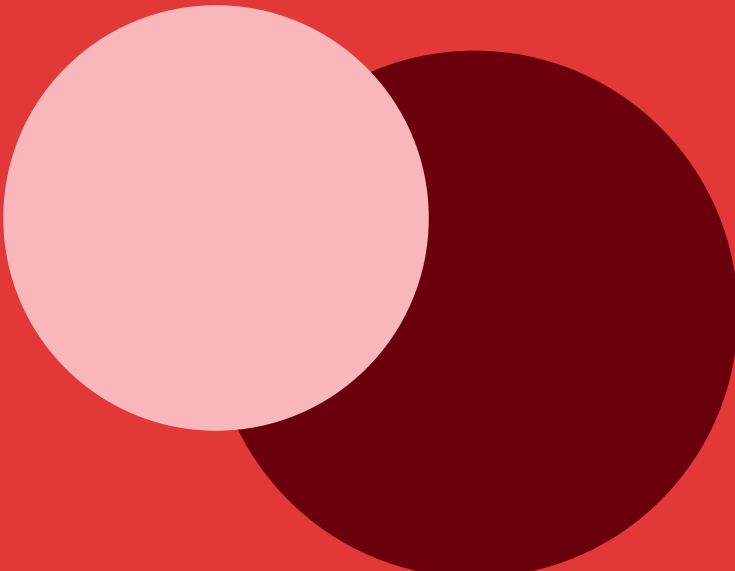
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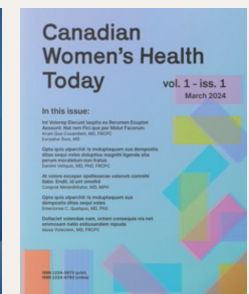
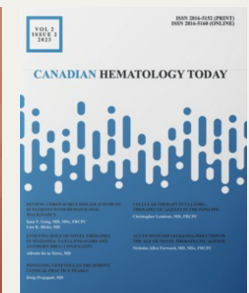
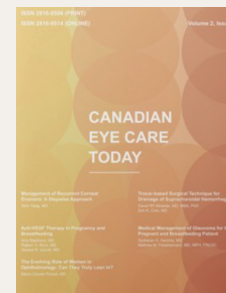
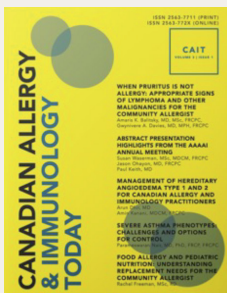
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Updates on the Treatment and Management of Urticaria in 2025

Karla Robles-Velasco, MD
Veronica Ferris Pasquini, MD
Patryck Pontes, MD
Hermenio Lima, MD

Chronic spontaneous urticaria (CSU) is increasingly recognized as a complex immune-mediated disorder, driven by interactions among T cells, mast cells, and inflammatory mediators. This paper summarizes the latest advances in urticaria treatment and management, incorporating new targeted therapies and evidence-based clinical guidelines.

Introduction

Chronic Urticaria (CU) is a long-lasting disease affecting up to 86 million people worldwide.^{1,2} It is increasingly recognized as a complex immune-mediated disorder, driven by dysregulated interactions between mast cells, their receptors, mediators, activating signals, and T cells.² This growing evidence has laid the framework for more effective, targeted treatments with the final aim of achieving sustained disease control, and reducing the associated morbidity and mortality.³ As of 2025, significant advancements have been made in the treatment and management of chronic spontaneous urticaria (CSU), with the

incorporation of new targeted therapies. While second-generation H1-antihistamines remain the first-line treatment, new biologic agents, including interleukin (IL)-4Ra monoclonal antibodies such as dupilumab, and emerging Bruton's tyrosine kinase (BTK) inhibitors, such as remibrutinib, have demonstrated efficacy in refractory cases.⁴⁻⁶ This review synthesizes findings from controlled clinical trials and real-world applications to present an evidence-based perspective on the evolving landscape of CSU management, focusing on advancements in targeted biologic therapies, immunomodulatory strategies, and precision medicine approaches.

Methods

A systematic literature search was conducted across major medical and scientific databases, including PubMed, Scopus, and Web of Science, using relevant keywords such as ("Chronic Urticaria"[Mesh]) AND ("Biological Therapy"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR "Janus Kinases"[Mesh] OR "Treatment Outcome"[Mesh]) for studies published between 2023 and January 2025. The selection criteria included randomized controlled trials and real-world cohort studies published in peer-reviewed journals. In [ClinicalTrials.gov](https://www.clinicaltrials.gov), we set the condition/disease as "Chronic Urticaria", other terms "Hives", all ages, all sex, and the study phase including early phase 1 through phase 4.

Results

A total of 406 studies were retrieved from medical scientific databases, alongside 185 clinical trials registered on clinicaltrials.gov. These included two in early phase 1, 27 in phase 1, 73 in phase 2, 62 in phase 3, and 21 in phase 4. The key findings are presented below, with further details provided in **Tables 1 and 2**.

Advances in Pathogenesis and Immunologic Understanding

The immunologic mechanisms involved in CU include:

1. **Mast cell activation and degranulation:** Occurs through the stimulation of their receptors (KIT [CD117], FcεRI, Mas-related G-protein-coupled receptor X2 [MRGPRX2], component 5a receptor [C5aR], protease-activated receptor [PAR]1, PAR2) or the inhibition of their negative receptors (sialic acid-binding immunoglobulin-like lectin-8 [SIGLEC-8], sialic acid-binding immunoglobulin-like lectin-6 [SIGLEC-6], CD200R, CD300a). This ultimately results in the release of potent mediators and chemokines such as IL-4, IL-5, IL-13, IL-17, IL-31, tryptase, prostaglandin D2 (PGD2), eotaxins, monocyte chemotactic protein-3 (MCP3), regulated upon activation, normal T-cell expressed and secreted (RANTES), platelet-activating factor (PAF), C3a, C5a, and tumour necrosis factor (TNF), or the activation of signalling pathways (for

example, BTK, Janus kinase inhibitor [JAK], and spleen tyrosine kinase [SYK]).⁷

2. **Cellular infiltrates:** Involves the activation of eosinophils, such as Major Basic Protein (MBP), basophils, and various T-cell subsets (Th2, Th1, Th17).^{8,9}
3. **Coagulation and complement activation:** The tissue factor produced by eosinophils triggers the coagulation cascade and complement system. This ultimately leads to the activation of coagulation factors X and II, which causes the degranulation of mast cells and basophils.¹⁰
4. **Autoantibodies:** In the context of autoimmune urticaria, immunoglobulin (Ig)E may bind to the α subunit of FcεRI. Additionally, IgG-anti-IgE, IgG-anti-IL-24, and IgE-anti-thyroid peroxidase (TPO) have also been discovered.¹¹
5. **Neurogenic inflammation:** Activation of histamine, IL-31, neuropeptides, and MRGPRX2 contributes to the inflammation of sensory nerves, as well as pruritus and urticaria symptoms.¹²

Updated Therapeutic Strategies for CSU

First-Line Treatment: Second-Generation H1-Antihistamines (sgAHs)

Current guidelines recommend starting treatment with standard-dose sgAHs, which are effective in approximately half of patients. If symptom control is inadequate, the dose may be increased up to fourfold if necessary, leading to symptom control in up to 63% of cases.^{13,14} No additional benefit was observed when combining different sgAHs.¹⁵

Biologic Therapies

Omalizumab: This anti-IgE monoclonal antibody (mAb) remains the preferred first-line add-on therapy for patients unresponsive to high-dose sgAHs. Studies have confirmed rapid symptom relief with dose adjustments improving response rates across various age groups, including children, adolescents, and older adults.^{16,17}

Dupilumab: This anti-IL-4Rα mAb has demonstrated significant reductions in urticaria activity (UAS7) in the LIBERTY-CSU CUPID trials, particularly among biologic-naïve CSU patients. Nonetheless, while patients who failed to respond

Mechanism	Molecule	Clinical Trial Identifier	Phase	Status	Route of Administration	Study Name	Notes
Anti-IgE mAb	Omalizumab	NCT01287117, NCT01292473, NCT01264939	4	Complete	Subcutaneous	GLACIAL, ASTERIA	
Anti-IgE mAb	LP-003	NCT062228560	2	Recruiting	Subcutaneous		
Anti-IgE mAb	JYB1904	NCT06509334	2	Recruiting	Subcutaneous		
Anti-IgE mAb	UB-221	NCT04404023, NCT04175704, NCT03632291	2	Not yet recruiting	IV infusion		
Anti-IL-4r mAb	Dupilumab	NCT04180488	3	Complete	Subcutaneous	LIBERTY-CSU CUPID	
Anti-KIT	Barzolvolimab	NCT06445023, NCT06455202	3	Recruiting	Subcutaneous	EMBARQ-CSU1, EMBARQ-CSU2	
Anti-KIT	Briquilimab	NCT06736262, NCT06162728, NCT06736262	2	Recruiting	Subcutaneous	BEACON study	
BTK inhibitor	HWH486	NCT06295302	2a	Recruiting	Oral		No results yet
BTK inhibitor	TAS5315	NCT05335499	2a	Complete	Oral		No results yet
BTK inhibitor	Remibrutinib	NCT05030311, NCT05032157	3	Complete	Oral	REMIX-1, REMIX-2	
BTK inhibitor	Rilzabrutinib	NCT05107115	2	Complete	Oral	RILECSU	
BTK inhibitor	HS-10561	NCT06864507	1 and 2	Not yet recruiting	Oral		
C5aR inhibitor	INF904	NCT06555328	2	Recruiting	Oral		No results yet
CRT2 antagonist	AZD1981	NCT02031679	2	Complete	Oral		Good results but no conclusions could be made due to the small sample size
IgE fusion protein	YH35324	NCT05960708	1	Complete	Subcutaneous		
IL-5 mAb	Mepolizumab	NCT03494881	1	Complete	Subcutaneous		

Mechanism	Molecule	Clinical Trial identifier	Phase	Status	Route of Administration	Study Name	Notes
JAK1 inhibitor	Porvocitinib	NCT05936567	2	Not yet recruiting	Oral		
JAK3/TEC inhibitor	Ritlecitinib (PF-06651600)	NCT06795373	2	Recruiting	Oral		
MRGPRX2 antagonist	EP262	NCT06050928, NCT06077773	2	Recruiting	Oral	CALM-CSU	No results yet
MRGPRX2 antagonist	EVO756	NCT06603220	2	Recruiting	Oral		
SYK inhibitor	GSK2646264	NCT02424799	1	Unknown	Topical		It was well tolerated but no conclusions could be made about changes in the urticaria activity score due to the low number of CSU patients recruited
TYK2/JAK1 inhibitor	TLL-018	NCT05373355, NCT06396026	3	Recruiting	Oral		

Table 1. Overview of Emerging Promising Therapeutic Agents for Chronic Spontaneous Urticaria that are Under Clinical Investigation; courtesy of Karla Robles-Velasco, MD, Veronica Ferris Pasquini, MD, Patryck Pontes, MD, and Hermenio Lima, MD.

Abbreviations: **BTK:** Bruton's tyrosine kinase; **CRTH2:** Chemoattractant receptor-homologous molecule expressed on Th2 cells; **C5aR:** Component 5a receptor; **mAb:** Monoclonal antibody; **MRGPRX2:** Mas-related G-protein-coupled receptor X2; **JAK1:** Janus kinase 1 inhibitor; **JAK3/TEC:** Janus kinase 3/Tyrosine kinase expressed in hepatocellular carcinoma; **TYK2:** Tyrosine kinase 2.

Mechanism	Molecule	Clinical Trial Identifier	Phase	Status	Notes
Anti CD80/CD86 - CD28	Abatacept	NCT00886795	1 & 2	Unknown	Pilot study with good results but no conclusions could be made due to the small sample size.
Anti-IgE mAb	Ligelizumab	NCT05024058, NCT04210843	3	Terminated	Phase III PEARL studies (CQGE031C2302 and CQGE031C2303) with ligelizumab met their primary endpoint of superiority vs. placebo at week 12 for CSU treatment, but not vs. omalizumab. The decision to discontinue was not based on safety concerns.
Anti-IgE mAb	UCB8600	NCT04444466	1	Terminated	Terminated due to internal company decision; not safety related.
Anti-IL5R alpha mAb	Benralizumab	NCT04612725	2b	Terminated	Study did not meet its primary endpoint.
Anti-KIT	THB001	NCT05510843	1	Terminated	The decision to discontinue the study was made after observing moderate drug induced liver injury in two participants enrolled in the first dose cohort.
Anti-Siglec-6 mAb	AK006	NCT06577116, NCT06072157	1	Terminated	AK006 did not demonstrate therapeutic activity in CSU.
Anti-Siglec-8 mAb	AK002 (Lirentelimab)	NCT05528861, NCT03436797	2	Terminated	Study did not meet its primary endpoints.
BTK inhibitor	Fenebrutinib	NCT03693625	2	Terminated	Recruitment was stopped after an interim analysis of the study data.
BTK inhibitor	Tirabrutinib	NCT04827589	2	Withdrawn	Development program was terminated.
C5aR	Avdoralimab	EudraCT No. 2020-002510-40	2	Terminated	Prematurely ended.
CD200R agonist	LY3454738	NCT04159701	2	Terminated	The study was terminated for lack of efficacy after an interim analysis was performed.
IL-1 β	Canakinumab	NCT01635127	2	Unknown	Lack of efficacy in treating adult patients with moderate to severe CSU.
IL-31 (via OSMR β)	KPL-716 (Vixarelimab)	NCT03858634	2	Complete	Results posted in clinicaltrials.gov showed no differences from placebo.
Tryptase inhibitor	MTPS9579A	NCT05129423	2	Withdrawn	Development of MTPS9579A was terminated for strategic/business reasons.
TSLP antagonist	Tezepelumab	NCT04833855	2b	Complete	Study did not achieve its primary endpoint.

Table 2. Investigational Therapies for Chronic Spontaneous Urticaria That Failed to Demonstrate Clinical Benefit or Were Discontinued; courtesy of Karla Robles-Velasco, MD, Verónica Ferris Pasquini, MD, Patryck Pontes, MD, and Herminio Lima, MD.

Abbreviations: **BTK:** Bruton's tyrosine kinase; **C5aR:** Component 5a receptor; **IgE:** Immunoglobulin E; **IL5R:** Interleukin 5 receptor; **mAb:** Monoclonal Antibody; **OSMR β :** oncostatin M receptor- β ; **SIGLEC-6:** Sialic acid-binding immunoglobulin-like lectin-6; **SIGLEC-8:** Sialic acid-binding immunoglobulin-like lectin-8.

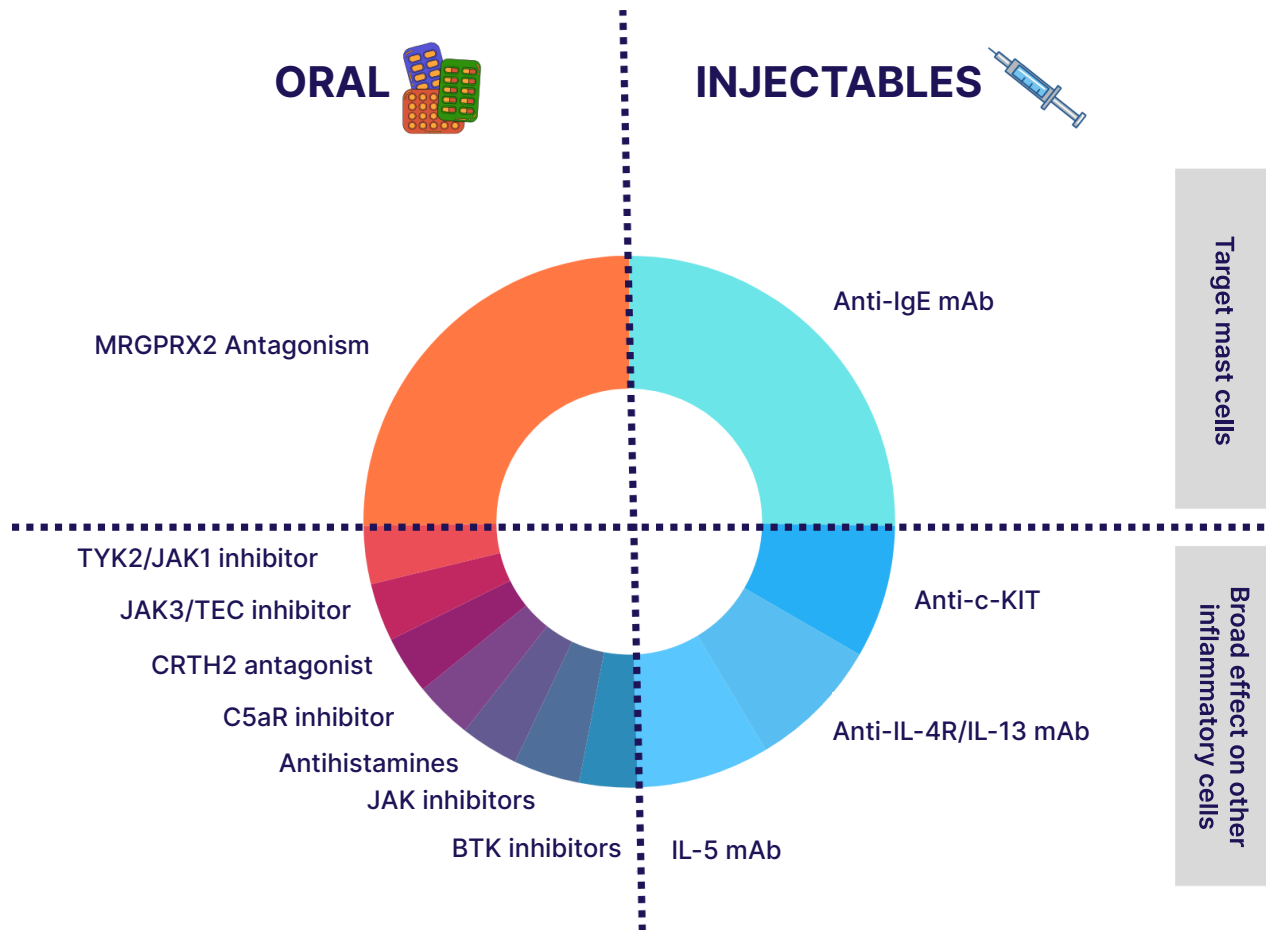


Figure 1. Overview of therapeutic strategies for Chronic Spontaneous Urticaria (CSU), categorized by route of administration, mechanism of action, and immunological target. The circular diagram segments include available and emerging treatments based on whether they are administered orally (left half) or via injection (right half). Therapeutic classes include MRGPRX2 antagonists, BTK and JAK inhibitors, anti-IgE therapies, anti-cytokine agents (targeting IL-4, IL-5, and IL-13), and mast cell-targeting antibodies such as anti-c-KIT. Vertical axis represents the target of action—from direct mast cell modulation (top) to broader anti-inflammatory effects (bottom); *courtesy of Karla Robles-Velasco, MD, Veronica Ferris Pasquini, MD, Patryck Pontes, MD, and Hermenio Lima, MD.*

Abbreviations: **BTK:** Bruton's tyrosine kinase; **CRTH2:** Chemoattractant Receptor-homologous molecule expressed on Th2 cells; **C5aR:** Component 5a receptor; **IL:** interleukin; **JAK1:** Janus kinase 1 inhibitor; **JAK3/TEC:** Janus kinase 3/Tyrosine kinase expressed in hepatocellular carcinoma; **mAb:** Monoclonal antibody; **MRGPRX2:** Mas-related G-protein-coupled receptor X2; **TYK2:** Tyrosine kinase 2.

to omalizumab exhibited positive results with dupilumab, the phase 3 study did not achieve its primary endpoint in this subset.⁶ Dupilumab is now approved for CSU treatment in Japan, the United Arab Emirates, Brazil, and the United States, and is currently undergoing evaluation in the European Union.¹⁸

Ligelizumab: This high-affinity monoclonal anti-IgE antibody was evaluated in the phase 3 PEARL 1 and PEARL 2 trials. While it showed

improvement of CSU symptoms compared to placebo, it did not show superiority over omalizumab. Consequently, its development for CSU was discontinued. Nonetheless, ligelizumab's higher affinity for IgE and favourable safety profile suggest potential utility for use in other IgE-mediated conditions.¹⁹

LP-003: This novel high-affinity, long-acting anti-IgE antibody has shown non-inferiority to

omalizumab in reducing the UAS7, based on an interim analysis of the phase 2 study.²⁰

JYB1904: Currently in phase 2, this anti-IgE mAb is actively recruiting patients for assessing its efficacy, safety and tolerability.²¹

UB-221: This is an IgG1 mAb that targets the Cε3 domain of IgE. Although its phase 1 trial (NCT03632291) was completed, no results have been posted on its efficacy or safety. A phase 2 trial is currently recruiting participants (NCT05298215).

Mepolizumab: This anti-IL5 mAb works by reducing eosinophil accumulation and activation. A phase 1 trial was completed but results have not yet been posted.²²

Tezepelumab: This is a high-affinity humanized IgG2 mAb against thymic stromal lymphopoietin (TSLP). The phase 2b INCEPTION study showed that the primary endpoint of UAS7 change at week 16 was not met compared to placebo. However, greater improvement was observed in anti-IgE-naïve patients, with a delayed, sustained reduction in CSU activity through week 32, particularly in those with lower baseline IgE levels and longer disease duration, suggesting a potential long-term TSLP blockade effect.²³

Vixarelimab (KPL-716, NCT03858634): This human mAb targets the oncostatin M receptor β and IL-31. Phase 2 trial results showed no differences in outcomes compared to placebo.²⁴

IgE Fusion Protein

YH35324: This long-acting IgETrap-Fc protein showed a favourable safety profile, dose-dependent exposure, and greater suppression of serum-free IgE levels compared to omalizumab. In a clinical study, higher rates of complete and well-controlled CSU were observed in the YH35324 6 mg/kg group, demonstrating its superior therapeutic potential over omalizumab.²⁵

MRGPRX2 Antagonists

EVO756: This MRGPRX2 antagonist targets mast cell-neuron interactions.²⁶ Phase 1 trial results demonstrated that EVO756 was a well-tolerated oral therapy that showed effective target engagement in CSU. A phase 2 trial (NCT06603220) is currently underway to further evaluate its safety and efficacy in Chronic Inducible Urticaria (CIndU).²⁷

EP262: This agent has completed a phase 1b trial for CIndU, though results are pending.²⁸ In addition, a phase 2 study (CALM-CSU)

(NCT06077773) is currently active and recruiting participants with CSU.²⁹

Anti-c-KIT Monoclonal Antibodies

Barzolvolimab: This anti-c-KIT mAb has shown promising results in phase 2 trials. In patients with antihistamine-refractory CSU, treatment with 150 mg every 4 weeks and 300 mg every 8 weeks demonstrated significant improvements in UAS7 scores at 12 weeks, showing clinically meaningful reductions versus placebo. Among CIndU patients, this therapy led to a 95% complete response rate and improved urticaria control. Barzolvolimab was well tolerated in both populations, with benefits including mast cell depletion in the skin, reduced tryptase levels, and enhanced quality of life.³⁰

Briquilimab: Initial findings from the phase 1b/2a study involving 47 participants indicate a low incidence of adverse events of mild severity related to c-KIT-expressing tissues. No changes in hair or skin pigmentation were observed, and mild taste changes were noted mainly after the first dose. A limited number of cases of low-grade neutropenia were reported but resolved without requiring treatment interruption. The pharmacokinetic results align with predictions, and full study data is expected in 2026.^{31,32}

Bruton's Tyrosine Kinase Inhibitors

Remibrutinib: The phase 3 REMIX-1 and REMIX-2 trials assessed oral remibrutinib (25 mg twice daily) in 925 patients. At week 12, remibrutinib significantly improved UAS7 scores compared to placebo and achieved higher rates of UAS7 ≤6 (~48% vs. ~22%) and complete response (~30% vs. ~8%). These benefits were sustained through week 24 (P <0.001). Adverse events were similar between groups, though petechiae occurred more frequently in the remibrutinib group (3.8% vs. 0.3%). These findings confirm remibrutinib's strong efficacy and favourable safety profile (NCT05030311, NCT05032157),⁵ positioning it as a promising alternative for patients who are unresponsive to omalizumab and dupilumab.

TAS5315: This BTK inhibitor, which also exhibits IL2-inducible T-cell kinase (ITK) inhibitory activity,³³ was evaluated in a clinical trial of 126 patients with CSU. At week 12, TAS5315 (doses ranging from 0.25–4 mg) showed greater reductions in HSS7 scores (-5.10 to -9.55) compared to placebo (-4.34). The highest rate of no-hives (HSS7=0) was observed in the 4 mg

group (47.1%), with 50% of these responders maintaining a no-hives status through week 20. Petechiae were the most common adverse event, though they were mild. TAS5315 demonstrated prolonged CSU improvement beyond treatment discontinuation, making it a potential option for patients unresponsive to H1-antihistamines.^{33,34}

HWH486: In a phase 1 study of 96 participants, 44 adverse events were reported, 31.2% of which were treatment-emergent adverse events in the HWH486 group and 25% in the placebo group. Most adverse events were mild, (grade 1) except for one case of grade 2 anemia. No major adverse events, withdrawals, or deaths occurred. Overall, the incidence of adverse events was similar between HWH486 and placebo groups ($P = 0.77$, $P = 1.00$), except for a significant difference observed across the 50, 100, 200, 400, and 800 mg groups ($P = 0.03$). The findings support a favourable safety profile for HWH486.³⁵

Rilzabrutinib: The phase 2 RILECSU trial³⁶ showed that rilzabrutinib significantly reduced UAS7 and itch severity score over 7 days (ISS7) scores in CSU patients uncontrolled with H1-antihistamines, with improvements observed as early as week 1 and sustained through week 12 ($P < 0.02$). A 52-week follow-up study confirmed ISS7 reductions across subgroups. Additionally, rilzabrutinib was shown to reduce IgG anti-FcεRI autoantibodies, suggesting reduced mast cell and basophil activation. The treatment was well tolerated, with headache, nausea, and diarrhea as the most commonly reported side effects, supporting it as a promising CSU treatment.^{37,38}

Spleen Tyrosine Kinase Inhibitor

GSK2646264: This phase 1/1b study evaluated GSK2646264 cream in healthy volunteers and patients with Cold Urticaria (ColdU) or CSU. The cream was well tolerated. In ColdU patients, it reduced the critical temperature threshold in four out of nine patients. However, due to the small sample size, no conclusions could be drawn regarding its efficacy for CSU.³⁹

Janus Kinase Inhibitors

Povorcitinib (JAK 1 inhibitor): This agent is currently being evaluated in a phase 2 study, which is active but not yet recruiting.⁴⁰

Ritlecitinib (JAK3/Tyrosine-kinase (TEC) inhibitor): Also known as PF-06651600, is a recently discovered JAK3 inhibitor with selectivity for JAK3 over the other three JAK isoforms. PF-06651600 also irreversibly inhibits the TEC

kinase family (BTK, bone marrow tyrosine kinase on chromosome X [BMX], ITK, resting lymphocyte kinase [RLK], TEC). It is currently in a phase 2 study, and actively recruiting participants.

TLL-018 (Tyrosine kinase 2 inhibitors (TYK2)/Janus kinase 1 inhibitor): This dual TYK2/JAK1 inhibitor has shown strong efficacy in patients with moderate-to-severe CSU who are unresponsive to antihistamines. In a 41-patient trial, significant improvements in UAS7 and ISS7 scores were observed by week 4 and were sustained through week 12 ($P < 0.01$). At week 12, up to 64.3% of patients achieved a UAS7 score of zero. Reported adverse events were mild to moderate across all groups.⁴¹ A phase 3 trial is currently ongoing.⁴²

Component 5a Receptor (C5aR) Inhibitor

INF904: In phase 1 studies, INF904 showed good tolerability and safety across doses ranging from 3 mg to 240 mg. It achieved a $\geq 90\%$ blockade of C5a-induced neutrophil activation over 14 days, highlighting its potential to disrupt inflammatory processes. A phase 2 study is currently recruiting participants.⁴³

Third-Line Therapy: Cyclosporine A and Off-Label Agents

Cyclosporine A: Recommended only after failure of omalizumab, dupilumab, or remibrutinib. Cyclosporine A provides potent immunosuppressive action, but long-term safety remains a concern.

Off-label Therapies for Refractory CSU

In clinical practice, following failure of omalizumab at 300 mg subcutaneously every 4 weeks, a stepwise, individualized approach is recommended. This may include increasing omalizumab to 450 mg or 600 mg every 4 weeks, or shortening the dosing interval to every 2 weeks, as supported by real-world and expert consensus data. For patients who remain uncontrolled despite optimized omalizumab therapy, consideration should be given to transitioning to alternative biologic or small-molecule agents, such as dupilumab or remibrutinib, where available, or to well-established off-label immunomodulatory therapies.

For patients with difficult-to-treat CSU, dapsone, hydroxychloroquine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and rituximab are being

explored. Additionally, emerging biologics such as fenebrutinib,⁴⁴ reslizumab,⁴⁵ and mepolizumab,²² have shown promising results but require further study.

Discussion and Conclusions

Recent advances in CSU treatment indicate a shift toward precision medicine and targeted immunologic treatments. While high-dose second-generation H1-antihistamines remain the cornerstone of first-line treatment, the introduction of novel biologics (dupilumab) and BTK inhibitors (remibrutinib) has expanded therapeutic options, particularly for patients with refractory disease. These advances are supported by a better understanding of CSU pathogenesis, which includes mast cell signalling, autoimmune mechanisms, and neurogenic inflammation. Although these therapies show promise, many of the novel drugs presented remain in early stages of clinical development. Further study is needed to determine their long-term safety, cost-effectiveness, and optimal patient selection criteria. The implementation of these new medicines into clinical practice must be supported by strong, evidence-based guidelines that consider both clinical efficacy and patient-centred outcomes.

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Financial Disclosures

K.R-V.: None declared.

V.F.P.: None declared.

P.P.: None declared.

H.L.: None declared.

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Venom Immunotherapy in 2025: Practical Insights for Community Allergists

Arun Dhir, MD

Introduction

Hymenoptera venom allergy (HVA), caused by stings from bees, wasps, hornets, and yellow jackets, is one of the most common identifiable causes of anaphylaxis in adults.¹ While local reactions are common, systemic responses can be fatal. Venom immunotherapy (VIT) offers long-term protection and is often curative.²⁻⁴ Introduced in the 1920s, VIT remains the only disease-modifying treatment for HVA.⁵

Hymenoptera Venom Allergy Background

HVA affects up to 3% of adults and 0.8% of children.⁵ Hymenoptera stings can trigger a range of reactions. Large local reactions, while uncomfortable, are not predictive of future systemic reactions and generally do not warrant VIT. Systemic reactions extend beyond the sting site, and may include urticaria, angioedema, respiratory distress, gastrointestinal symptoms, or

hypotension, and require a thorough evaluation.²⁻⁴ The Ring and Messmer classification (**Table 1**), widely used in both research and clinical guidelines, categorizes systemic reactions from Grade I (cutaneous only) to Grade IV (life-threatening).^{2,3} Even generalized urticaria following a sting may justify assessment for VIT, especially in high-risk individuals, as will be discussed.

Diagnosis of Hymenoptera Venom Allergy

Accurate diagnosis of HVA requires integrating a comprehensive clinical history with venom allergy testing.

Clinical history: A detailed history is essential. Clinicians should document the suspected insect, nature and severity of the sting reaction, timing of symptom onset and resolution, and any treatment administered. Contextual factors, such as the setting (e.g., outdoors, near flowers or food)

Grade	Skin ¹	Abdomen	Respiratory tract	Cardiovascular system
I	Pruritus, Flush, Urticaria, Angioedema	–	–	–
II	Pruritus, Flush, Urticaria, Angioedema	Nausea, Cramps	Rhinorrhea, Hoarseness, Dyspnea	Tachycardia ($\uparrow \geq 20$ bpm), Hypotension ($\downarrow \geq 20$ mmHg), Arrhythmia
III	Pruritus, Flush, Urticaria, Angioedema	Vomiting, Defecation	Laryngeal edema, Bronchospasm, Cyanosis	Shock, Loss of consciousness
IV	Pruritus, Flush, Urticaria, Angioedema	Vomiting, Defecation	Respiratory arrest	Cardiac arrest

Table 1. Severity scale for the classification of anaphylactic reactions (according to Ring and Messmer); *adapted from Ruëff et al.*²

¹Generalized skin symptoms apart from the sting area

Classification is based on the most severe symptom encountered (none of the symptoms are obligatory).

and distinguishing features (e.g., presence of a retained stinger) should be noted. Additionally, relevant co-factors, such as exercise, alcohol consumption, or medication use, should be recorded. While history alone rarely identifies the culprit insect, it remains valuable in guiding diagnostic testing and management.

Skin prick tests (SPT) and intradermal tests (IDT): These tests should be reserved for individuals with a history suggestive of systemic reactions, as asymptomatic sensitization is common. Traditionally, testing begins with a 100 µg/mL SPT, followed by incremental IDT up to 1.0 µg/mL. However, several studies support a safe and efficient single-step IDT using the 1.0 µg/mL concentration.^{2-4,6} A graded approach may still be warranted for patients with severe sting reactions. Testing performed too soon after a sting can fall within a refractory period, and may yield false negatives in up to 50% of patients; therefore, retesting after 4 to 6 weeks is recommended.²⁻⁴

In-vitro testing: Guidelines permit either skin testing or in vitro testing as a first step, depending on practicality. Specific IgE (sIgE) to whole venom extracts is commonly used, though component-resolved diagnostics (CRD) are increasingly accessible in community settings. CRD helps distinguish true double-venom allergy from cross-reactivity, especially when the culprit insect is uncertain or test results are ambiguous. For example, a relatively common situation is a patient who appears to be sensitized to both honeybee

and yellow jacket venoms on standard sIgE tests. CRD assesses sensitization to specific venom components, improving diagnostic precision and guiding appropriate venom selection (**Figure 1**). sIgE to rApi m 1 is highly specific for honeybee allergy and helps exclude false positives related to cross-reactive carbohydrate determinants. Among vespids, major species-specific allergens include Ves v 1 and Ves v 5; for Polistes species, Pol d 1 and Pol d 5 are commonly used. Identifying the exact venoms to which a patient is truly sensitized informs immunotherapy selection and may influence cost, as VIT is not universally publicly funded. When clinical history and CRD do not clarify sensitization, immunotherapy with both venoms may be warranted, particularly in high-risk patients.^{1,4} CRD may also help predict VIT outcomes and guide dosing; for instance, predominant Api m 10 sensitization has been identified as a risk factor for honeybee VIT failure, and higher maintenance doses may be considered in these cases.⁷

Basal serum tryptase: Measuring baseline serum tryptase is particularly important in patients with severe reactions (Grade III or IV), hypotension without urticaria, or systemic reactions despite negative venom-specific IgE.⁴ Elevated levels may indicate an underlying mast cell disorder, such as mastocytosis or hereditary alpha-tryptasemia (HαT), both associated with increased reaction severity and implications for VIT management.¹⁻³ HαT is a relatively common genetic trait caused by increased TPSAB1 copy numbers and is linked

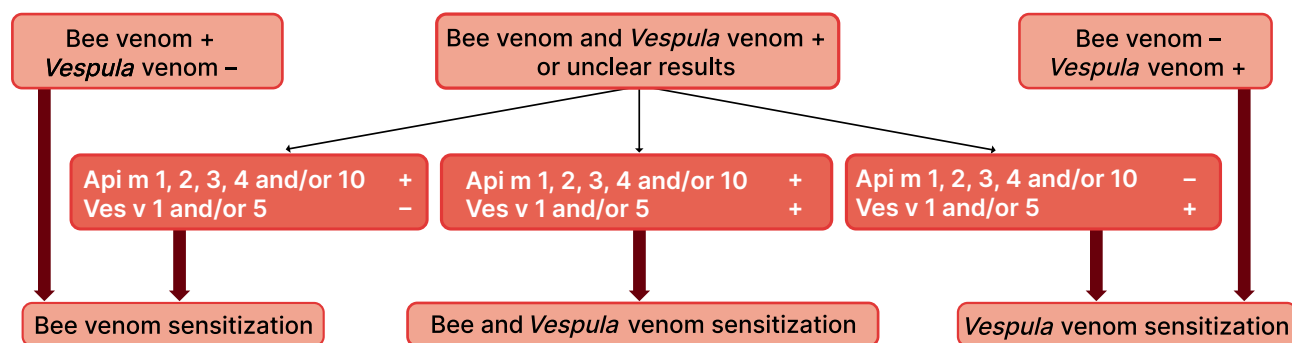


Figure 1. Stepwise diagnosis using whole venoms (bee venom and *Vespula* venom) along with allergen components from bee venom (Api m) and *Vespula* venom (Ves v); adapted from Ruëff et al.²

to more severe venom-induced anaphylaxis. Evaluation for HxT and clonal mast cell disease should be considered when baseline serum tryptase exceeds 8 ng/mL.¹ These patients may require extended treatment duration or higher maintenance doses.

Basophil activation test (BAT): A specialized assay that measures basophil activation after venom stimulation. Currently, its use is largely limited to research rather than routine clinical practice.

Indications for Venom Immunotherapy

The decision to start VIT requires a documented systemic sting reaction and confirmed venom sensitization. Patients with only local reactions generally do not require testing or VIT.²⁻⁴

- **Severe systemic reactions (Grades II–IV):** VIT is strongly recommended for moderate-to-severe reactions with confirmed venom sensitization.²⁻⁴
- **Isolated cutaneous reactions (Grade I):** VIT may be offered when additional risk factors are present, such as a high likelihood of future stings, significant quality-of-life impact, presence of a mast-cell disorder or elevated tryptase, or relevant cardiovascular disease or treatment with beta-blockers or ACE inhibitors.²⁻⁴

- **Children:** VIT is safe and effective; even mild systemic reactions may warrant treatment to prevent escalation and reduce anxiety.^{3,8}
- **Large local reactions:** VIT is usually unnecessary but can be considered for very frequent, disabling reactions, such as in beekeepers.²⁻⁴

Contraindications and Precautions

Below are the main contraindications and precautions for initiating or continuing VIT, drawn from current guidelines:

- **Absolute contraindications:** Severe, uncontrolled asthma; unstable cardiovascular disease; immune-complex or severe autoimmune disease; and active malignancy undergoing cytotoxic chemotherapy.²⁻⁴
- **Pregnancy:** Initiating VIT during pregnancy is generally not recommended. However, a well-tolerated maintenance regimen started prior to conception may be continued after an individualized risk-benefit discussion.^{2,4}

- **β -blockers and ACE inhibitors:** These medications may exacerbate anaphylaxis and reduce epinephrine effectiveness, but they are not absolute contraindications to VIT.¹⁻⁴ Patients should be informed of these potential interactions, and coordination with their cardiovascular specialist is advised to consider alternative agents when feasible.² In patients with heart failure, however, ACE inhibitors are generally continued given their proven survival benefit.² Optimizing underlying cardiac disease typically outweighs theoretical VIT risks, since cardiovascular comorbidities significantly increase HVA mortality.^{1,2} When discontinuation of β -blockers or ACE inhibitors is not possible, VIT should be administered with extended post-injection observation and readiness for anaphylaxis management.⁴

Venom Immunotherapy Protocols and Administration

VIT is administered with gradually increasing doses to induce desensitization and long-term protection.

Venom selection: Choose venoms matching confirmed allergic sensitization. As mentioned, CRD are especially useful when dual sensitization or an uncertain culprit insect is suspected. For vespid allergy, a single *Vespula* extract usually suffices because of strong cross-reactivity, whereas *Polistes* allergy requires a specific *Polistes* extract.^{2,3}

Dosing: The standard maintenance dose is 100 μ g for both bee and wasp venoms. High-risk bee-allergic patients (e.g., those with mastocytosis, severe previous reactions, or elevated tryptase) may benefit from 200–400 μ g. Mixed-vespid products use 300 μ g.²⁻⁴ In children, 50 μ g can be adequate, though 100 μ g is often preferred.⁴

Updosing Protocols

Different protocols aim to balance speed and safety:

Conventional protocol: Involves weekly or bi-weekly injections over 4 to 6 months.^{3,4} This is generally considered the safest approach

Rush protocols: Achieve the maintenance dose rapidly, typically within days to weeks, through multiple daily injections. These protocols offer quicker protection but carry a higher risk

of systemic reactions during updosing. They can significantly enhance patient convenience and provide faster protection, a critical advantage for highly anxious patients or those with high occupational exposure risk.³⁻⁵ A novel 3-session outpatient rush venom immunotherapy protocol described by McCarthy et al. has demonstrated promising results for safety and efficacy.⁹

Ultra-rush protocols: The most rapid protocols, reaching maintenance within hours or a single day, typically in a hospital setting due to the highest risk of systemic reactions. Such protocols should be considered for high-risk patients needing exceptionally rapid protection (e.g., beekeepers).^{3,4}

Maintenance dosing: Once the target dose is achieved, injections are usually administered every 4 weeks; many guidelines allow extension to 6 weeks from year 2 or 3.²⁻⁴

Premedication: A non-sedating H1 antihistamine before each injection can reduce local and mild systemic reactions but does not reliably prevent severe events.^{2,4}

Duration of Venom Immunotherapy

VIT is generally continued for 3 to 5 years, but discontinuation must be individualized according to each patient's risk factors and preferences.

- **Severity of initial reaction:** Patients who experienced severe systemic reactions involving cardiovascular compromise (Grade IV anaphylaxis) face a higher risk of relapse and often benefit from extended or lifelong therapy.²⁻⁴
- **Mastocytosis or elevated baseline serum tryptase:** Those with mast cell disorders or persistently elevated baseline tryptase have increased risks of systemic reactions, treatment failure, and recurrence. All major guidelines recommend lifelong VIT for this population regardless of sting severity.²⁻⁴
- **Systemic reactions during VIT:** A systemic reaction to a field sting while on maintenance indicates insufficient protection. In such cases, clinicians may increase the maintenance dose, shorten injection intervals, or prolong the overall duration of therapy.²⁻⁴
- **Pediatric patients:** Children typically achieve excellent long-term outcomes. Multiple studies support discontinuing VIT after 3 years in most pediatric cases.²⁻⁴

- **Patient-specific factors:** Individuals with high occupational or environmental exposure, significant anxiety about future stings, or uncertain sting history may reasonably continue VIT beyond 5 years. These contextual factors should guide shared decision-making.²⁻⁴

Currently, no validated biomarker reliably predicts long-term protection; thus, repeat skin tests or specific IgE measurements before discontinuing therapy are not recommended.^{3,4,10}

Safety and Management of Adverse Reactions

Venom immunotherapy (VIT) is generally well tolerated, with most adverse reactions being mild and localized.

Local reactions: Swelling, erythema, and pruritus at the injection site are common and typically self-limiting. Non-sedating H1-antihistamines are frequently used for symptom relief and may be taken prophylactically to improve tolerability, as mentioned. Leukotriene receptor antagonists such as montelukast have also been used as adjuncts, although supporting evidence is limited. Topical corticosteroids may also be used.²

Systemic reactions: These can occur during both the build-up and maintenance phases. Risk factors include rapid updosing protocols, higher venom doses, concurrent infections, physical exertion, and underlying mast cell disorders. Such reactions should be managed according to standard anaphylaxis protocols. After a systemic reaction to VIT, therapy can be continued with consideration for premedication with an H1-antihistamine and modification of the up dosing schedule.²⁻⁴

Omalizumab: For patients with recurrent systemic reactions despite dose modifications, or those with severe mastocytosis, off-label use of omalizumab has shown benefit.^{2,3,5} However, no standardized protocol currently exists regarding its timing or dosing.

Efficacy of VIT and Its Assessment

VIT is highly effective in preventing systemic allergic reactions to future stings. A systematic review and meta-analysis reported systemic reactions on re-sting in only 2.7% of VIT-treated compared with 39.8% of untreated controls.⁸ In addition to reducing clinical reactivity, VIT significantly improves quality of life by decreasing anxiety and fear of future stings.⁴ Protection typically begins within the first few months of therapy and is sustained throughout the maintenance interval.²⁻⁴ Although laboratory markers such as specific IgE levels or basophil activation tests may change during treatment, they are not routinely used for clinical decision-making. The absence of systemic reactions to field stings remains the most reliable indicator of successful VIT.

Conclusions

Recent advances have made VIT more precise and adaptable. Component-resolved diagnostics guide precise venom selection, and accelerated up dosing protocols safely shorten the induction phase. Individualized risk stratification with baseline tryptase and hereditary alpha-tryptasemia screening enables tailored management. Adjunctive omalizumab and flexible maintenance schedules further reduce barriers and sustain protection. Together, these innovations empower allergists to deliver a truly patient-centred, individualized approach to VIT.

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Financial Disclosures

A.D.: Honoraria: BioCryst, Novartis; **Advisory boards:** ALK, Celltrion

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About the Author



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Dr. Mukherjee is an Assistant Professor in the Division of Respirirolgy, Department of Medicine, and a translational scientist affiliated with the Research Institute of St. Joe's, Hamilton. She has demonstrated expertise in investigating inflammatory mechanisms of chronic respiratory diseases, in particular autoimmunity, response to treatment and development/validation of clinical biomarkers. Her research has identified the presence of localized autoimmune responses in the airways of patients with complex airways disease and determined their pathogenic role in driving disease severity. Of recent, she has identified autoimmune responses in acute-severe COVID and linked autoimmunity with post-acute COVID-19 sequelae (or Long COVID). In the field of respiratory medicine, she published ~65 manuscripts, and in the past 5 years these have accumulated >2500 citations (*Google Scholar h-index 24, i10-index 40*). Dr. Mukherjee's research program focuses on "Lung autoimmunity and biomarkers". She is a past recipient of the Emerging Researcher Award in Allergic Asthma awarded conjointly by the Canadian Institutes of Health Research (CIHR) and the Canadian Asthma, Allergy and Immunology Foundation (CAAF). Her lab is funded by federal and non-federal sources including CIHR-ICRH and industry. Dr Mukherjee was recently named the AstraZeneca Chair in Respiratory Diseases (2023–2028).

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Pearls from the European Academy of Allergy and Clinical Immunology (EAACI) Congress, 2025

Manali Mukherjee, PhD

Introduction

The European Academy of Allergy and Clinical Immunology (EAACI) Congress 2025, held in Glasgow, Scotland, United Kingdom from June 13 to 16, centred on the overarching theme of "Breaking boundaries in Allergy, Asthma, and Clinical Immunology: Integrating Planetary Health for a Sustainable Future." Indeed, this year's theme emphasized the intersection of environmental health and allergic diseases. The vibrant congress featured several presentations on immunological diseases in both adult and pediatric populations, along with breakthroughs in clinical and translational domains. Key topics included asthma,

allergy, chronic spontaneous urticaria, and current global challenges such as pollution and climate change. This report highlights several key studies, organized under three main themes: pediatric studies, biologics in combined airways disease, and biomarkers.

Pediatric Studies

Pediatric allergic diseases, including asthma, atopic dermatitis (AD), food allergies, and allergic rhinitis, are driven by dysregulated immune responses, often characterized by type 2 inflammation. Key immunologic features

include elevated immunoglobulin E (IgE) levels, eosinophilia, and cytokines such as interleukin (IL)-4, IL-5, and IL-13. Disease onset and progression are influenced by early-life exposures, genetic predisposition, and epithelial barrier dysfunction. Understanding immune endotypes in children is crucial for developing targeted therapies, including biologics. Recent advances highlight the role of epithelial-derived cytokines such as thymic stromal lymphopoietin and IL-33, offering new therapeutic avenues, particularly in pediatric asthma.¹ Precision medicine approaches are increasingly important in managing pediatric allergic diseases effectively and safely.

1. Abstract: Treatment of severe atopic dermatitis in pediatric patients with dupilumab and effects of therapy on nasal and skin microbiota: preliminary experimental evidence

This study was presented by Dr. Crisitiana Indolfi (Naples, Italy).

Atopic dermatitis (AD) is a common chronic inflammatory skin condition affecting up to 20% of children worldwide. Typically emerging in early childhood, it can significantly impair quality of life due to persistent itching, sleep disturbances, and emotional distress. Pediatric AD is frequently associated with immune dysregulation and skin barrier dysfunction, which predispose children to infections and allergic comorbidities. A recent study shows that in pediatric patients, *Staphylococcus aureus* colonization induces pruritus, barrier dysfunction, and inflammation, making AD management particularly challenging.² Severe cases may be resistant to conventional therapies, prompting the need for targeted biologics. As understanding of AD pathophysiology advances, treatments such as dupilumab are gaining prominence for their ability to modulate immune pathways and restore skin health in children.

This retrospective study evaluated the impact of **dupilumab** on clinical outcomes and microbial composition in children aged 6–16 years with moderate-to-severe **AD**. Thirty participants were divided into three groups: severe AD treated with dupilumab, moderate AD without biologics, and healthy controls. Nasal and skin swabs were analyzed via matrix-assisted laser

desorption/ionization (MALDI)-time of flight (TOF) spectrometry for microbiota.

Results:

Over a 12 month period, dupilumab treatment led to significantly improved disease severity Eczema Area and Severity Index (EASI), itch intensity Numerical Rating Scale (NRS), and quality of life Children's Dermatology Life Quality Index (C-DLQI).

- **EASI:** Median score decreased from 24.5 to 1.2 at 12 months ($P < 0.001$)
- **NRS:** Reduced from 10 to 3 ($P < 0.01$)
- **C-DLQI:** Declined from 13.5 to 3.5 ($P < 0.1$)

Untreated AD patients showed higher colonization compared to both dupilumab-treated patients and healthy controls. There was a significant reduction in *Staphylococcus aureus* colonization in skin and nasal cavities among dupilumab-treated patients ($P < 0.001$), suggesting a restoration of microbial balance.

Key Takeaways:

Dupilumab is a safe and effective treatment for moderate-to-severe pediatric AD, offering substantial clinical improvement and restoring microbial balance. This groundbreaking pediatric study follows what has been identified in the adult population demonstrating that dupilumab modifies both nasal and skin microbiota in children, reducing infection risk and highlighting the therapeutic potential of biologics in managing complex AD cases.

2. Abstract: Primary and safety outcomes of a phase 3, open-label, single-arm, 12-week study of treatment with PI3K δ inhibitor leniolisib in paediatric patients aged 4–11 years with activated PI3K δ syndrome (APDS)

This study was presented as an oral abstract by Dr. M. Semeraro.

Leniolisib is an FDA-approved PI3K δ inhibitor used to treat activated phosphoinositide 3-kinase delta syndrome (APDS)³ in patients aged ≥ 12 years who weigh ≥ 45 kg. However, data on the safety and efficacy of leniolisib in pediatric patients (< 12 years) remains limited. This

abstract, presented at EAACI by Drs. V.K. Rao and G. Uzel, reported findings from a phase 3, open-label, single-arm study that evaluated the safety and efficacy of leniolisib, in pediatric patients aged 4–11 years diagnosed with APDS—a rare genetic immunodeficiency marked by lymphoproliferation and immune dysregulation. Conducted across multiple international sites, the trial enrolled 21 children who received weight-adjusted doses of leniolisib twice daily for 12 weeks. The study met its co-primary endpoints: a reduction in lymph node size and a significant increase in naïve B cells, indicating improved immune regulation. Secondary outcomes included favourable changes in spleen volume and immunoglobulin levels. Importantly, leniolisib was well tolerated, with only mild to moderate adverse events reported, none of which led to treatment discontinuation.

Results:

After 12 weeks of leniolisib treatment across all dose levels:

- Mean change from baseline (CFB) in log₁₀-transformed index lymph node sum of product of diameters (SPD) was –0.1956 (n=19).
- Mean CFB in naïve B cell percentage (CD19+, CD27–, CD10– out of total B cells) was 33.3%.
- Mean changes from baseline in immunoglobulin levels (n=14): IgM, 2.7 to 1.6 g/L; IgG, 10.1 to 11.1 g/L; and IgA, 0.88 to 0.83 g/L.
- Leniolisib was generally well tolerated: 20 patients had treatment-emergent adverse events, which were either Grade 1 (n=20, 95.2%) or Grade 2 (n=8, 38.1%); none were serious. No adverse events and no discontinuations of study treatment occurred.

Key Takeaways:

This pediatric trial builds on earlier adult and adolescent studies, including a placebo-controlled phase 3 trial published in *Blood*, which demonstrated similar efficacy and safety outcomes in older patients.³ The consistent results across age groups supports leniolisib's potential as a targeted, disease-modifying APDS treatment. With more than 25% of APDS patients under 12, this study addresses a crucial unmet need in pediatric immunology. A trial in children aged 1–6 years is underway, and regulatory submissions for broader pediatric approval are expected.

Biomarkers

Biomarkers are increasingly recognized as essential tools in asthma management, enabling personalized approaches to diagnosis, monitoring, and treatment. They help identify key inflammatory pathways—particularly type 2 inflammation—guiding the use of targeted biologics. As asthma is now understood to be a heterogeneous disease, biomarkers such as blood eosinophils and fractional exhaled nitric oxide (FeNO) are gaining prominence in patient stratification and predicting therapeutic response. While these markers have improved outcomes, especially in moderate-to-severe asthma, their benefits remain modest, underscoring the need for more precise biomarkers that reflect the actual lung pathology. This urgency was evident at EAACI 2025, where the importance of biomarker-driven patient selection was a recurring theme, and several promising new biomarkers were presented in key studies.

3. Abstract: Baseline type 2 biomarkers and mucus plug response in patients with uncontrolled moderate-to-severe asthma treated with dupilumab in the VESTIGE study

This study was presented by Dr. Arnoud Bourdin (Montpellier).

Mucus plugging is a cardinal feature of fatal asthma.⁴ Elevated mucus scores, indicated by luminal plugging on computed tomography (CT) scans in patients with moderate-to-severe asthma, are associated with chronic airway inflammation driven by type 2 cytokines—particularly IL-13, which contributes to excessive mucus production and airway obstruction. Given its role in disease severity and symptom burden, mucus is currently under extensive investigation as a treatable trait in asthma.⁵ Dupilumab, a monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signalling, was evaluated in the phase 4 VESTIGE study (NCT04400318) for its impact on mucus burden. The primary results were published in *Lancet Respiratory Medicine*, (March 25;13(3):208–220; PMID: 39947221). This post hoc analysis assessed changes in mucus plug score and volume in patients stratified by baseline levels of type 2 inflammatory biomarkers, including FeNO and blood eosinophil counts. In this randomized, double-blind trial, 109 adults

with uncontrolled asthma and elevated type 2 inflammation received either dupilumab or placebo biweekly for 24 weeks. Changes in mucus plug score and volume from baseline to Week 24 were analyzed in patient subgroups categorized by initial FeNO levels (<50 or ≥50 ppb) and eosinophil counts (<400, ≥400, or ≥500 cells/μL). Mucus plug scores were determined from pre-bronchodilator multidetector CT scans, which measured the number of bronchopulmonary segments that were completely blocked (on a scale from 0 to 18). Mucus volume was quantified using voxel-based imaging analysis of all visible mucus plugs.

Results:

- At Week 24, dupilumab significantly reduced mucus plug scores compared to placebo across all biomarker subgroups.
- The effect was consistent regardless of FeNO levels (<50 or ≥50 ppb) and across stratification based on blood eosinophil counts (especially in patients with counts ≥400 and ≥500 cells/μL).
- Patients with lower eosinophil counts (<400) also showed numerical improvements.
- Mucus plug volume, measured using voxel quantification from CT scans, decreased significantly at Week 24 in the dupilumab group compared to placebo.
- The least squares mean difference in mucus volume was approximately -0.107 mL for dupilumab versus placebo ($p < 0.001$), indicating a robust treatment effect.

Key Takeaways:

Dupilumab significantly reduced mucus plug scores and volumes compared to placebo across all biomarker subgroups, regardless of FeNO levels or eosinophil counts. These findings suggest that dupilumab effectively reduces mucus burden in asthma patients with type 2 inflammation, reinforcing its potential role in targeting mucus as a modifiable trait in asthma management.

4. Abstract: Basal serum tryptase: sex-and age-specific reference intervals in the pediatric and adult population

This study was presented by Y. Chantran (Paris, France).

Mast cells are increasingly recognized as central players in the pathophysiology of allergic diseases and asthma. These immune cells release a variety of mediators, including histamine, tryptase, and cytokines, which drive inflammation, bronchoconstriction, and tissue remodelling. Their activation contributes to both immediate hypersensitivity reactions and chronic airway inflammation. In asthma, mast cells are often located in close proximity to airway smooth muscle, influencing disease severity and response to therapy. Emerging research expands the role of mast cells beyond traditional allergy paradigms, highlighting their importance in asthma endotyping and identifying novel therapeutic targets. Their relevance continues to grow in precision medicine and biomarker development.

Tryptase is often used as a biomarker of mast cell activity. Indeed, baseline serum tryptase (bST) serves as a key biomarker in clonal mast cell disorders and is a minor diagnostic criterion for systemic mastocytosis. Elevated bST levels are also associated with increased risk and severity of hypersensitivity reactions and are linked to Hereditary alpha-Tryptasemia (HαT). Traditional reference values for bST have been challenged, prompting the need for age- and sex-specific reference intervals (RIs) to improve diagnostic accuracy and clinical decision-making in mast cell-related disorders and allergy. The aim of the study was to define and validate age- and sex-specific RIs for bST from infancy through old age, and to develop an accessible, user-friendly online tool in order to assist physicians and pathologists in interpreting bST values of their patients.

Method:

A training cohort consisting of 21,216 bST values from a nation-wide ambulatory community-based clinical database in France was used to compare five indirect methods for establishing bST RIs. The most accurate method was then applied to determine age- and sex-specific bST RIs. These were validated in a separate cohort of 572 HαT-positive adolescents from a population-based birth study. Mucus plug scores and volumes were assessed using CT-based voxel quantification.

Key Results:

- Across all age and sex groups, the median and 95th percentile bST values were 4.6 µg/L and 8.4 µg/L, respectively.
- bST levels declined from infancy through puberty, then gradually increased with age.
- Females consistently exhibited lower bST levels than males, particularly during adolescence and early adulthood.
- In the validation cohort, 4.9% (28/572) of participants exceeded the 95th percentile for their age and sex.
- A free, user-friendly online tool was developed to help physicians and pathologists interpret patient bST values using age- and sex-specific percentiles.

Key Takeaways:

This study establishes validated, age- and sex-specific reference intervals for bST from infancy through old age and introduces a practical online tool to support clinical interpretation. These findings enhance the precision of bST-based diagnostics for mast cell-related disorders and allergic conditions. An unmet need remains for evaluating tryptase levels in blood and sputum of patients with asthma and allergy, indicating the importance of developing detection methods and validated reference intervals. This study forms a stepping stone toward addressing this unmet need.

Update on Biologics in the Combined Airways: Adult Studies

In addition, several sessions discussed asthma and rhinosinusitis as components of a unified airway disease, with a focus on phenotypes and inflammatory molecular endotypes. This concept of a combined airways disease/unified disease is rooted in the understanding that the respiratory tract functions as a unified system, where inflammation in one region often affects the other. This combined airway disease is increasingly recognized as a distinct clinical phenotype, particularly in patients with type 2 inflammation, where shared immunological pathways (e.g., IL-4, IL-5, and IL-13) drive disease in both the nose and lungs. A holistic approach, rather than managing these conditions as separate

entities, can improve symptom control, reduce exacerbations, and enhance quality of life. An interesting plenary talk by Dr. Brian Lipworth (University of Dundee, Scotland) addressed “Head-To-Head Comparison of Biologic Efficacy in Asthma: What Have We Learned”, now published in *Allergy* (PMID: 40156481).⁶

5. Abstract: Efficacy of two years of treatment with anti-IL-5/R therapy for reduction in use of oral glucocorticoids in patients with eosinophilic granulomatosis with polyangiitis

This study was presented by Dr. Florence Roufosse (Paris, France).

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare inflammatory disease characterized by eosinophilia, vasculitis, and asthma. Sinus disease and severe asthma are two of the six diagnostic criteria and frequently occur together in affected patients. Standard treatment involves oral glucocorticoids (OGCs) and immunosuppressants, which carry significant toxicity and relapse risk. Targeted anti-IL-5/receptor therapies—**mepolizumab** and **benralizumab**—address eosinophilic inflammation and have shown efficacy in inducing remission. The MANDARA trial⁷ compared these therapies over 52 weeks, followed by a 1-year open-label extension (OLE) in which all patients received benralizumab. Full results are now published (2025) (PMID: 40781045).⁸

This phase 3 randomized, double-blind trial followed by a one-year OLE evaluated the long-term efficacy and safety of anti-IL-5/receptor therapies in adults with relapsing or refractory EGPA. A total of 128 participants were enrolled, with 66 continuing benralizumab treatment and 62 switching from mepolizumab to benralizumab. Key endpoints included the proportion of patients achieving remission—defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and an OGC dose ≤4 mg/day—alongside relapse rates, blood eosinophil counts, patterns of OGC use and withdrawal, and safety outcomes including adverse events.

Results:

- The remission rates were comparable at Week 104: 62.1% (benralizumab/benralizumab) vs. 67.7% (mepolizumab/benralizumab). Approximately 50% of patients who achieved early remission maintained it through 2 years.
- During the first year of OLE, 77.3% (benralizumab/benralizumab) and 67.7% (mepolizumab/benralizumab) experienced no relapses.
- Most relapses were airway-related.
- Complete withdrawal of OGC was achieved by ~44% of patients in both groups by Week 104, with median cumulative OGC doses reduced by ~61–62% in year 2 compared to year 1.
- Blood eosinophil counts remained low (median ~20 cells/ μ L) in both groups, and switching to benralizumab led to further eosinophil depletion.

Key Takeaways:

Benralizumab provides durable remission, significant reduction in glucocorticoid use, and sustained eosinophil depletion over 2 years in EGPA patients. Switching from mepolizumab to benralizumab seemed to maintain the clinical benefits and low biomarker levels in a significant proportion of patients. However, supporting benralizumab as a foundational therapy in EGPA management remains inconclusive.

6. Abstract: Tezepelumab reduces OCS use and improves sino-nasal symptoms in OCS-dependent patients with severe asthma and comorbid chronic rhinosinusitis (overall and with nasal polyps): results from the phase 3b WAYFINDER study

This study was presented by David Jackson (United Kingdom).

Tezepelumab is a monoclonal antibody that blocks thymic stromal lymphopoietin, a key epithelial cytokine involved in initiating airway inflammation. Unlike other biologics, it acts upstream in immune pathways, offering potential efficacy across multiple asthma phenotypes. Approved for severe asthma, it also shows

promise in broader airway disease management. Chronic rhinosinusitis (CRS), with or without nasal polyps (NP), frequently coexists with severe asthma. The WAYFINDER study (NCT05274815) evaluated the impact of tezepelumab on OCS reduction and sino-nasal symptoms in OCS-dependent asthma patients, including those with CRS.

The original study was a 52-week, open-label, single-arm trial. Adults with severe asthma on maintenance OCS received tezepelumab 210 mg every 4 weeks. The co-primary endpoints included achieving a reduction in OCS dose to ≤ 5 mg/day or complete discontinuation, without loss of asthma control. Sino-nasal symptoms were assessed using the Sino-Nasal Outcome Test-22 (SNOT-22) score.

Key Results:

- Reduction of OCS to ≤ 5 mg/day was achieved in 87.8% of patients with CRS overall and 91.7% of those with chronic rhinosinusitis with nasal polyps (CRSwNP).
- Complete discontinuation of OCS occurred in approximately 46% (CRS overall) and 50.0% (CRSwNP).
- Mean SNOT-22 scores improved by 15.7 points (CRS) and 18.9 points (CRSwNP) with approximately half of patients in both groups classified as SNOT-22 responders.

Key Takeaway:

Tezepelumab effectively reduces OCS dependence and improves sino-nasal symptoms in patients with severe asthma and CRS, supporting its role in managing combined airway disease.

Summary

Several sessions at this year's European respiratory congress at Glasgow, UK highlighted promising new therapies and biomarker-based treatment guidance strategies for both adult and pediatric populations, with a focus on treating multiple modalities of immunological diseases. The meeting also highlighted studies on mental health and public monitoring of diseases. The next annual meeting, marking the 70th anniversary, will take place in Istanbul, Turkey, from June 12–15, 2026.

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Financial Disclosures

M.M: None declared.

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