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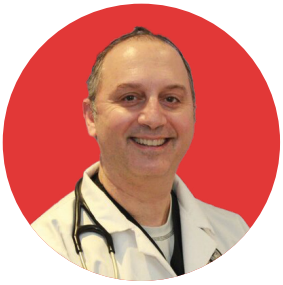

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**References:**

**1.** Data on File. BioCryst Pharmaceuticals.
**2.** ORLADEYO® Product Monograph. BioCryst Pharmaceuticals. June 2, 2022.


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# Emerging Biologics in the Management of Atopic Dermatitis

**Melinda Gooderham, MSc, MD, FRCPC**

## Introduction

Atopic dermatitis (AD) is a chronic, relapsing and remitting inflammatory skin disease marked by intense pruritus that significantly impacts the daily activities and quality of life of those affected.[1] Topical therapies such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have been the mainstay of treatment and may offer symptomatic relief. However, their efficacy is often suboptimal, they carry the potential for adverse effects, application adherence can be challenging, and they are not suitable for more widespread disease. Conventional systemic agents such as methotrexate and cyclosporine are used off-label for AD. However, these medications are associated with off-target toxicities and are generally unsuitable for long-term use due to safety concerns. Advances in understanding the immunopathogenesis of AD (**Figure 1**)[1-3] have led to the development of multiple new therapies. These include biological agents that target these pathways by neutralizing specific cytokines or their receptors. This paper will review the therapies that have been recently approved or are currently in various stages of development.

## Targeting IL-13

Dupilumab and tralokinumab are well-established monoclonal antibodies that target Type 2 inflammatory cytokines. Dupilumab targets the interleukin (IL)-4Ra subunit, thereby inhibiting IL-4 and IL-13 signalling, whereas tralokinumab specifically targets the IL-13 cytokine. Both treatments have shown efficacy in improving the signs and symptoms of AD and have a favourable safety profile. Dupilumab is also approved for treating other Type 2 inflammatory conditions including asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. More recently, the United States Food and Drug Administration (FDA) has also approved it for chronic spontaneous urticaria.[4]

Lebrikizumab is a high-affinity monoclonal antibody that neutralizes IL-13, and has recently been approved for treating moderate-to-severe AD in adolescents and adults in multiple regions. In phase 3 clinical trials[5,6] (ADvocate1, ADvocate2, and ADhere), lebrikizumab demonstrated improvements in AD signs, symptoms, and quality of life. It was well tolerated as monotherapy (ADvocate 1 and 2)[5] or in combination with

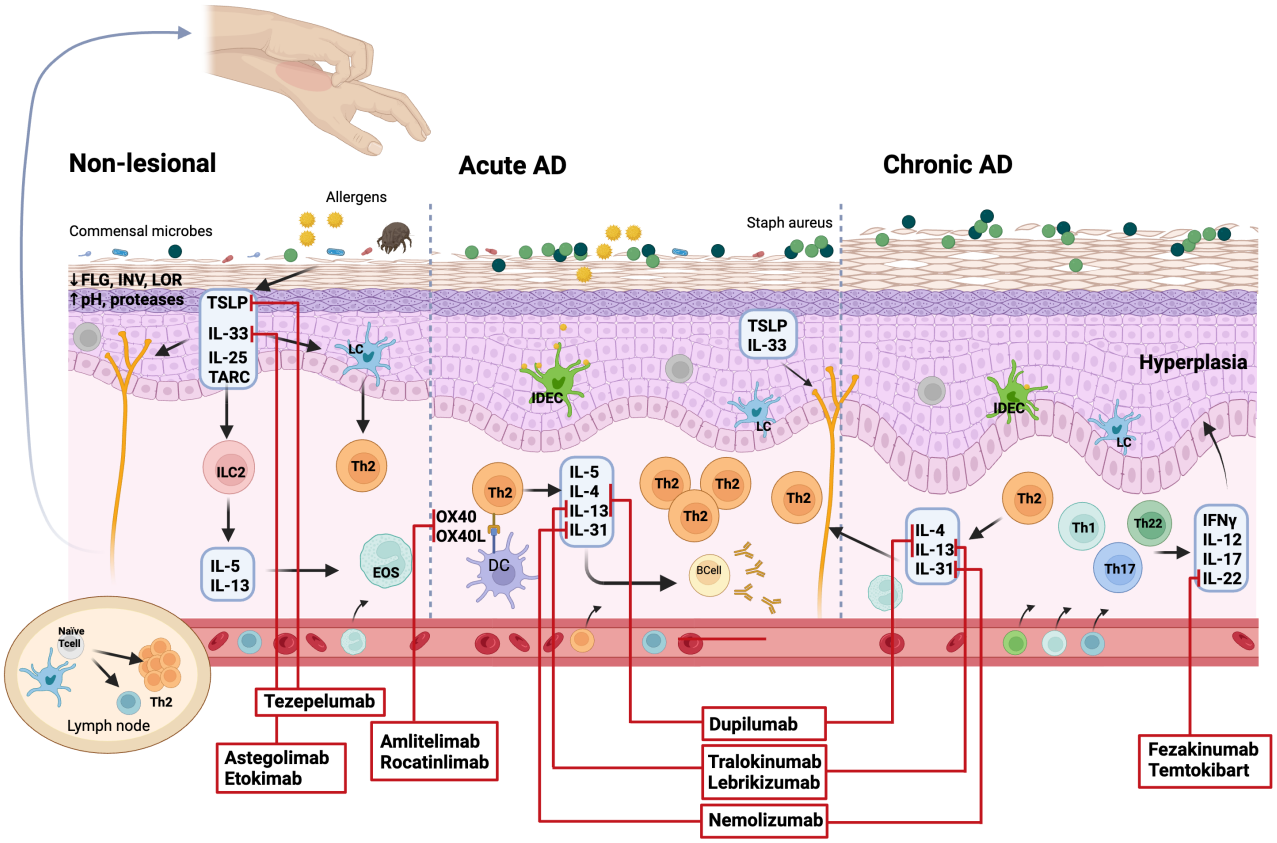


**Figure 1.** Immunopathogenesis of atopic dermatitis and biologic targets[1,3,4]; *created with www.biorender.com.*

Disruption of the epidermal barrier in AD triggers keratinocytes to release alarmins (e.g. TARC, IL-25, IL-33, TSLP), activating dendritic cells, ILC2s, and TH2 cells, which drive Type 2 immune responses, IgE production, and pruritus through interaction with sensory neurons. This immune cascade is further amplified by skin-homing T cells, eosinophils, and resident memory T cells, contributing to chronic inflammation, cutaneous remodelling, and neuroinflammation in later stages of disease (chronic AD).

**Abbreviations: AD:** atopic dermatitis, **EOS:** eosinophil, **FLG:** filaggrin; **IDEC:** inflammatory epidermal dendritic cells, **INV:** involucrin, **IgE:** immunoglobulin E, **IL:** interleukin, **ILC2:** group 2 innate lymphoid cells, **LOR**: loricrin, **TARC:** Thymus and activation-regulated chemokine, **Th:** T helper, **TSLP:** thymic stromal lymphopoietin.

TCS (ADhere).[6] In the ADvocate1 and 2 trials, lebrikizumab significantly improved skin clearance by week 16. A total of 43.1% of patients in ADvocate1 and 33.2% in ADvocate2 achieved an Investigator's Global Assessment (IGA) score of 0 or 1 with a ≥2-point improvement from baseline, compared to 12.7% and 10.8% in the respective placebo groups (P<0.001). Additionally, 59.3% (ADvocate1) and 51.9% (ADvocate2) of lebrikizumab-treated patients achieved a 75% or greater improvement in the Eczema Area and Severity Index (EASI-75) compared to 16.4% and 18.1%, respectively, in the placebo arms (P < .001). Further, the ADhere trial revealed that 41.2% of patients achieved the IGA endpoint versus 22.1% in the placebo + TCS group (P=0.01). Additionally, 69.5% of patients reached EASI-75 compared to 42.2% in the placebo+ TCS group (P=0.002).[6] Across all three trials, lebrikizumab was generally well tolerated. The most common adverse events included conjunctivitis, injection site reactions, and nasopharyngitis, most of which were mild to moderate in severity. Discontinuation rates were low and comparable to placebo.[5,6]

## Targeting IL-31

Pruritus, the hallmark symptom of AD, develops due to the increased production of pruritogenic cytokines, such as thymic stromal lymphopoietin (TSLP), IL-4, IL-13, and IL-31. These cytokines are released by various cell types and activate histamine-independent itch pathways. The IL-31 signalling pathway is a suitable target in AD because IL-31 not only directly communicates with neurons responsible for transducing itch signals, but it also stimulates nerve elongation and neurite branching in the skin.[1,3]

Nemolizumab, an IL-31 receptor antagonist approved by the FDA to treat moderate-to-severe AD with associated pruritus, was studied in the pivotal trials ARCADIA 1 and ARCADIA 2.[7] These 48-week, double-blinded, placebo-controlled phase 3 studies evaluated nemolizumab, which was administered as a 60 mg subcutaneous loading dose at baseline, followed by 30 mg every 4 weeks. This treatment was given alongside background topical therapies (TCS, TCI) in adolescents and adults with moderate-to-severe AD.

For the primary endpoints, nemolizumab significantly improved IGA success and EASI-75 responses at week 16 compared to placebo. In the ARCADIA 1 trial, IGA success was achieved by 36% in the nemolizumab group versus 25% in the placebo group. Further, EASI-75 was achieved by 44% of those in the nemolizumab group versus 29% receiving placebo. Similar results were observed in the ARCADIA 2 trial.[7] For the key secondary endpoints, nemolizumab showed significant improvements in pruritus relief (≥4-point reduction in the Peak Pruritus Numerical Rating Scale [PP-NRS] score) as early as week 1, with these benefits sustained through week 16. Additionally, by week 16, nemolizumab also reduced sleep disturbances (≥4-point reduction in Sleep Disturbance Numerical Rating Scale [SD-NRS] score). Furthermore, nemolizumab led to higher proportions of participants achieving itch-free or nearly itch-free states (PP-NRS <2) and showed combined improvements in skin clearance and pruritus relief compared to placebo.[7] The safety profile was favourable, with rates of adverse events similar to those of the placebo group. Most reported adverse events were of mild-to-moderate severity, with the most common being worsening AD and asthma-related events.[7]

## Targeting the OX40-OX40L Axis

OX40 is a costimulatory molecule that plays a key role in AD by promoting T-cell activation, differentiation, and survival through its interaction with OX40L (**Figure 1**). This pathway amplifies inflammation by driving the proliferation of Th2 cells and other T helper cell subsets (Th1, Th17, Th22) in AD. As a result, it impairs skin barrier function, sustains chronic inflammation, and contributes to AD progression and recurrence.[8] The OX40-OX40L pathway is being investigated as a target for managing AD through the use of monoclonal antibodies. Amlitelimab targets the OX40L, while rocatinlimab targets the OX40 receptor.[8]

A phase 2b randomized controlled 52-week trial evaluated amlitelimab in adults with moderate-to-severe AD. The trial compared four dosing regimens of amlitelimab (250 mg plus a 500 mg loading dose, 250 mg, 125 mg, or 62.5 mg) administered every 4 weeks versus a placebo. The primary endpoint showed least squares mean percentage changes ranging from -51.6% to -61.5% for the four amlitelimab groups versus -29.4% for placebo (P<0.001) at week 16. Sustained clinical responses and reductions in inflammatory biomarkers were noted during 24 weeks of treatment and up to 32 weeks after drug withdrawal. This demonstrates that targeting this pathway has the potential for durable responses even after therapy has ended. No safety concerns were noted, with low rates of serious adverse events and similar rates of treatment-emergent adverse events compared to placebo.[9] Phase 3 trials are currently underway.

Rocatinlimab, which targets the OX40 receptor, has also been investigated in a phase 2 trial, with a robust phase 3 program currently ongoing.[10] In a double-blinded, placebo-controlled phase 2b trial, the efficacy and safety of rocatinlimab were evaluated in adults with moderate-to-severe AD. Patients received varying doses of rocatinlimab (150 mg or 600 mg every 4 weeks, or 300 mg or 600 mg every 2 weeks) or a placebo for 18 weeks. This initial treatment period was followed by an 18-week active-treatment extension and a 20-week off-treatment follow-up. The primary endpoint was met as all rocatinlimab dosing regimens significantly reduced EASI scores at week 16 compared to placebo. The most notable improvement was observed in the 300 mg every 2 weeks group (−61.1% versus −15.0% for placebo, P<0.0001). This study also showed

that rocatinlimab significantly improved patient-reported outcomes, including pruritus, sleep disturbance, and health-related quality of life, with benefits maintained for at least 20 weeks post-treatment.[12]

## Targeting IL-22

IL-22 plays a key role in epidermal dysfunction and chronic inflammation by promoting epidermal hyperplasia and inhibiting skin barrier function. Consequently, it contributes to the chronic, lichenified lesions observed in AD. In a previous, double-blinded, phase 2a trial, the efficacy and safety of fezakinumab, an IL-22 monoclonal antibody, were evaluated in adults with moderate-to-severe AD.[13] The primary endpoint, which was the change in the SCORing Atopic Dermatitis (SCORAD) score at week 12, was not met, as the difference between the fezakinumab and placebo groups was not statistically significant (mean decline: 13.8 versus 8.0; P=0.134). However, significant improvements were observed in the severe AD subset (SCORAD ≥50) at week 12 (mean decline: 21.6 versus 9.6; P=0.029).[13] Although further studies were not pursued, this trial identified IL-22 as a potential target.

Temtokibart is a novel monoclonal antibody that specifically targets the IL-22 receptor subunit alpha-1 (IL-22RA1) of the heterodimeric IL-22 receptor, blocking signalling of IL-22, IL-20, and IL-24 signalling through the IL-20 receptor, Type 2. In a phase 2a study (NCT04922021) temtokibart was evaluated for its efficacy and safety. By week 16, temtokibart demonstrated significant improvements compared to placebo, with EASI-75 achieved by 51.7% of patients versus 24.1% in the placebo group, EASI-90 by 34.5% versus 10.3%, and EASI-100 by 20.7% versus 0%.[14] Further phase 3 studies are planned.

## Other Targeted Pathways

Another approach of pathway-directed therapy has explored targeting the epithelial alarmin cytokines, including TSLP and IL-33. TSLP acts on Th2 cells to produce Th2 cytokines, such as IL-4, IL-5, IL-13, and IL-31, and directly stimulates sensory nerves to induce itch.[15] A randomized phase 2a clinical trial assessed the efficacy and safety of tezepelumab, a monoclonal antibody targeting TSLP that was previously approved for asthma, in adults with moderate-to-severe AD treated with TCS.[16] While tezepelumab showed numerical improvements over placebo in clinical endpoints such as EASI-50 (64.7% versus 48.2% at week 12, P=0.091) and pruritus reduction, these differences were not statistically significant.[16] Another alarmin cytokine that has been investigated is IL-33. A phase 2 randomized controlled trial investigated astegolimab, an anti-IL 33 receptor monoclonal antibody, in patients with moderate-to-severe AD.[17] The study did not show a statistically significant improvement in the primary endpoint, the percent change in EASI score from baseline to week 16 compared to placebo (-51.47% versus -58.24%, P=0.56).[17] In an unpublished phase 2 trial, with results posted on **ClinicalTrials.gov** (NCT03533751), etokimab, a monoclonal antibody targeting the IL-33 cytokine, was evaluated across four dosing groups. However, the trial did not demonstrate a significant difference from placebo in either primary or secondary outcomes.[18] The lack of success in targeting these single upstream cytokines or their pathways highlights the complexity of AD immunopathogenesis and the diverse inflammatory signalling involved in this chronic condition. However, problems with the study design of these proof-of-concept trials cannot be ruled out. Currently, a high-affinity, high-potency anti-TSLP monoclonal antibody, bosakitug, is being investigated in a phase 2 trial as monotherapy and in combination with dupilumab. The results are eagerly awaited to help determine the value of targeting an upstream alarmin.[19]

## Challenges and Future Directions

AD is a complex heterogeneous inflammatory condition. Many patients do not respond adequately to, or have safety or tolerability issues with, current therapies. Therefore, there is an unmet need to explore new targets in the immunopathogenesis of AD to address this therapeutic gap. Multiple agents are currently in various phases of development, including IL-4/-13, IL-22, IL-31, TSLP, and OX40-OX40L inhibitors. Some of these, such as lebrikizumab and nemolizumab, have already received approval in some regions. Other agents are close to completing their phase 3 programs, including amlitelimab and rocatinlimab, and will likely be the next candidates for approval. Furthermore,

antibodies targeting the same cytokines but engineered with YTE technology—Fc modifications that enhance neonatal Fc receptor (FcRn) binding to prolong their half-life—are also in development to support less frequent dosing. APG777 and IMG007 are examples of such antibodies, with a YTE modification targeting IL-13 and OX40, respectively. Both are currently undergoing phase 2 studies in AD.[20]

Ongoing challenges in developing and approving targeted antibodies include long-term safety concerns with chronic immunomodulation, regulatory and reimbursement hurdles, and the need for predictive tools such as biomarkers to determine which therapy would be best for each patient. Despite these challenges, the development of biologic therapies to date has transformed the therapeutic landscape of AD management. This advancement has been driven by our better understanding of the immunopathogenesis of AD. With continuous innovation, the future of AD management offers renewed hope for disease control and an improved quality of life for patients worldwide.

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## Financial Disclosures

**M.G.: Investigator, speaker and/or adviser:** AbbVie, Acelyrin, Alumis, Amgen, Akros, Arcutis, Aristea, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Inmagene, JAMP Pharma, Janssen, LEO Pharma, L'Oreal, MedImmune, Meiji, Moonlake, Nektar, Nimbus, Novartis, Organon, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union, Ventyx and Vyne.

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# Updates in Epinephrine Guidelines

**Susan Waserman, MSc, MDCM, FRCPC**
**Heather Cruickshank, BA**

## Introduction

Epinephrine is the first line treatment for anaphylaxis, which is a serious allergic reaction that can rapidly progress and may cause death.[1] As a nonselective adrenergic agonist, epinephrine rapidly works to increase vasoconstriction and peripheral vascular resistance, increase cardiac output, reverse bronchoconstriction and mucosal edema, and inhibit the release of mediators of inflammation from mast cells and basophils.[2] The anaphylaxis guidelines developed by the Joint Task Force on Practice Parameters (JTFPP) in 2020,[2] the World Allergy Organization (WAO) in 2020,[3] and the European Academy of Allergy and Clinical Immunology (EAACI) in 2021[4] advise clinicians to prescribe self-injectable epinephrine to individuals at risk of anaphylaxis and educate them on when and how to administer it. In 2023, the JTFPP updated its anaphylaxis practice parameter to address seven key topic areas, including multiple questions and recommendations related to epinephrine prescription and use.[5] The practice parameter authors graded each recommendation as conditional or strong, based in part on the certainty of the supporting evidence. We provide an overview of key recommendations and discuss their applications in the Canadian context.

It is important to note that in Canada, EpiPen® autoinjectors are currently the sole epinephrine delivery devices available with premeasured doses of epinephrine for the emergency treatment of allergic reactions. These autoinjectors should be administered intramuscularly into the anterolateral thigh. Additional epinephrine devices may become available in the future, including the first epinephrine nasal spray (neffy®).[6] There is a wider variety of epinephrine devices available in the United States, including multiple brands of epinephrine autoinjectors (Adrenaclick®, Auvi-Q®, EpiPen®/EpiPen® Jr., and generic versions). Additionally, there is one brand of epinephrine prefilled syringe (Symjepi™) and one brand of nasal spray (neffy®). Although the anaphylaxis practice parameter update was published before the U.S. Food and Drug Administration had approved neffy®, we believe its recommendations for epinephrine prescription and use may be appropriately extended to include epinephrine nasal spray where it is available.

## When Should Clinicians Prescribe Epinephrine?

The anaphylaxis practice parameter update recommends that clinicians routinely prescribe epinephrine to patients who are at higher risk of anaphylaxis.[5] When deciding whether to prescribe epinephrine to patients at lower risk, the guideline suggests that clinicians should engage patients in shared decision making (SDM), taking into consideration their individual risk factors, values, and preferences. This recommendation is graded as conditional, based on evidence with very low certainty. Researchers have not yet validated any risk-stratification algorithms to guide epinephrine prescription. The practice parameter authors advise clinicians to consider the patient's specific diagnosis, history of allergic reactions, likelihood of allergen exposure, and potential comorbidities and cofactors that might affect the severity of an allergic reaction when assessing the patient's risk level. They also advise clinicians to discuss not only the potential benefits but also the potential financial and psychosocial burdens of epinephrine prescription. **Table 1** provides a non-exhaustive list of factors that may either reduce or increase a patient's likelihood of requiring treatment with epinephrine, which may help guide SDM on whether to prescribe it.

## How Many Doses of Epinephrine Should Clinicians Prescribe?

The practice parameter update suggests that clinicians should consider a patient's risk factors for severe anaphylaxis, their values and preferences, and context-specific considerations when deciding whether to prescribe a single dose of epinephrine versus multiple doses.[5] It advises routinely prescribing more than one dose of

| Allergic Condition | Lower Likelihood | Higher Likelihood |
|---|---|---|
| **IgE-mediated Food allergy** | | • History of prior systemic allergic reaction after exposure |
| **Pollen food Allergy syndrome** | • No history of anaphylaxis to causative food | • History of anaphylaxis to causative food |
| **Venom or insect bite/sting allergy** | • History of only large local or cutaneous systemic reaction(s)<br>• History of anaphylaxis, but on maintenance VIT or discontinued VIT after more than 5 years of treatment with no high-risk factors | • History of anaphylaxis, not treated with a complete course of VIT<br>• Current VIT, with history of prior systemic reaction(s) to VIT<br>• Honeybee allergy<br>• Elevated basal tryptase level<br>• Frequent exposure |
| **Latex allergy** | • Low likelihood of exposure | • Occupational exposure |
| **Drug allergy** | • Low likelihood of exposure | • Occupational exposure (e.g., compounding, mixing, or preparation of medications) |
| **Exercise-induced anaphylaxis** | | • All cases |
| **Physical urticarias** | | • Cold induced |
| **Aeroallergen immunotherapy** | • No history of prior systemic reaction(s) to AIT and no relevant comorbidities (e.g., asthma) | • History of prior systemic reaction(s) to AIT and/or relevant comorbidities (e.g., asthma) |

**Table 1.** Likelihood of Requiring Treatment With Prescribed Epinephrine; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

**Abbreviations: AIT:** aeroallergen immunotherapy, **EAI:** epinephrine autoinjector; **VIT:** venom immunotherapy

epinephrine to patients who have a history of prior biphasic reactions or who have previously required multiple doses of epinephrine to treat an episode of anaphylaxis. For patients without such history, the burdens of prescribing multiple doses may in some cases outweigh the anticipated benefits. This recommendation is graded as conditional, based on evidence with very low certainty. A 2021 systematic review and meta-analysis found that fewer than 10% of reported cases of anaphylaxis were treated with multiple doses of epinephrine.[7] Most cases of anaphylaxis resolve with a single dose. However, it is impossible to predict with certainty whether a patient will require multiple doses to treat anaphylaxis. The practice parameter authors identified multiple risk factors and cofactors for severe and fatal anaphylaxis that may help guide SDM (**Table 2**). They note that the presence of one or more risk factors does not necessarily indicate an absolute need for multiple doses of epinephrine, nor does the absence of any risk factor preclude the possibility that a patient will experience anaphylaxis requiring multiple doses to treat. Additionally, context-specific considerations, such as the proximity of local emergency services, are also important to discuss while engaging in SDM.

| Drug-induced Anaphylaxis | Food-induced Anaphylaxis | Venom Bite- or Sting-induced Anaphylaxis | Non-trigger–related Cofactors/Risk Factors |
|---|---|---|---|
| • Age >60 years<br>• Cardiovascular diseases<br>• Respiratory diseases<br>• Antihypertensive drugs | • Adolescence<br>• Uncontrolled asthma<br>• Alcohol consumption<br>• Peanut- or tree nut-induced reaction<br>• Exercise | • Older age<br>• Male sex<br>• Hereditary α-tryptasemia<br>• Mast cell disorders<br>• Cardiovascular diseases<br>• NSAIDs<br>• Antihypertensive drugs | • Mast cell disorders<br>• Infections<br>• Perimenstrual period<br>• NSAIDs<br>• Alcohol consumption<br>• Psychological burden<br>• Exercise<br>• Unknown cause |

**Table 2.** Risk Factors and Cofactors Potentially Associated With Severe or Fatal Anaphylaxis; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

**Abbreviation: NSAIDs:** nonsteroidal anti-inflammatory drugs

## Which Epinephrine Device Should Clinicians Prescribe?

The practice parameter update advises clinicians to consider dosage, needle length, affordability, access, and patient treatment preferences when deciding which epinephrine device to prescribe.[5] This recommendation is graded as conditional, based on evidence with very low certainty. Most of the listed considerations are more relevant in the United States, where multiple devices are available. In Canada, the primary consideration is dosage. The standard dosing of intramuscular epinephrine in healthcare settings is 0.01 mg/kg of bodyweight, up to a maximum dose of 0.5 mg per administration; however, epinephrine autoinjectors for emergency treatment of allergic reactions in the community are only available with certain premeasured doses.[8] EpiPen® autoinjectors are currently available in 0.15 mg and 0.3 mg doses. According to the manufacturer, the 0.15 mg dose is appropriate for children weighing 15–30 kg, and the 0.3 mg dose is appropriate for children and adults weighing ≥30 kg. However, the practice parameter supports switching to the 0.3 mg dose at 25 kg to limit underdosing. It also advises clinicians that the 0.15 mg dose is appropriate to prescribe to infants and toddlers weighing <15 kg. These recommendations are consistent with previous position statements issued by the Canadian Society of Allergy and Clinical Immunology (CSACI).[9,10]

The introduction of neffy® or other epinephrine devices to the Canadian market would expand treatment options. We expect that neffy® would provide an appealing option for many patients. A recent survey of physicians revealed that 86% agreed that patients would prefer needle-free epinephrine administration.[11] According to the manufacturer, neffy® can be thawed after accidental freezing without impacting product quality,[12] and a recent analysis found it to be more shelf-stable at high temperatures (40–50°C), compared with EpiPen®.[13]

## When Should Patients Administer Epinephrine?

The practice parameter update suggests that clinicians should counsel patients to promptly administer epinephrine at the first sign of suspected anaphylaxis,[5] which is consistent with previously published guidelines.[2-4] Definitions and clinical criteria for anaphylaxis have been published by multiple organizations, including the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN)[14] and WAO.[3] The Global Allergy and Asthma Excellence Network (GA²LEN) recently issued a consensus report aimed at resolving the differences between the NIAID/FAAN and WAO criteria.[1] According to this report: "[Anaphylaxis] may involve the skin/mucosa (e.g., urticaria, flushing, angioedema), respiratory system (e.g., upper airway obstruction, bronchospasm, cough), cardiovascular system (e.g., syncope, hypotension, shock), and/or gastrointestinal system (e.g., severe abdominal pain, repetitive vomiting, diarrhea). Life-threatening anaphylaxis is characterized by airway, breathing, and/or

cardiovascular compromise and may occur without skin/mucosa involvement".[1]

The practice parameter update generally recommends against pre-emptive epinephrine use when no signs or symptoms of an allergic reaction have yet developed after a suspected or known exposure to a causative allergen.[5] This recommendation is graded as conditional, based on evidence with very low certainty. The authors found no evidence that pre-emptive epinephrine use prevents anaphylaxis in asymptomatic patients. However, there are scenarios in which administering epinephrine may be warranted before a reaction meets the clinical criteria for anaphylaxis. For example, a more proactive approach to epinephrine administration may be appropriate for patients with underling mastocytosis or a history of rapidly progressive near-fatal anaphylaxis.

## When Should Clinicians Counsel Patients to Activate Emergency Medical Services?

The practice parameter update suggests that immediate activation of emergency medical services (EMS) may not be necessary if a patient experiences a prompt, complete or near complete, and durable response to treatment with epinephrine.[5] It may be appropriate for patients and caregivers to consider managing anaphylaxis at home in such cases. Clinicians should counsel patients and caregivers to always activate EMS if the anaphylaxis is severe, if it does not promptly and completely or nearly completely resolve, or if it returns or worsens after the first dose of epinephrine. This recommendation is graded as conditional, based on evidence with very low certainty. CSACI issued similar guidance in 2023,[15] advising that home management of anaphylaxis after epinephrine use may be appropriate in certain circumstances. Both the practice parameter and the CSACI statement emphasize the importance of SDM to determine whether home management is suitable to consider. **Table 3** presents several considerations for and against home management, which the practice parameter authors have adapted from Casale et al. 2022.[16]

## What Other Counselling Should Clinicians Provide Regarding Epinephrine?

Clinicians should educate and counsel patients and caregivers on:

- The essentials of epinephrine carriage, storage, and use
- How to properly administer their epinephrine device
- The most common adverse effects of epinephrine
- How to manage rare serious adverse events
- Strategies to overcome barriers to adherence

These recommendations are consistent with current standard practice and are worth reiterating, given the gaps that researchers have identified in patients' epinephrine-related education, knowledge, skills, carriage, and use.[17,18] There are no absolute contraindications to administering epinephrine for anaphylaxis. The adverse effects are typically mild and transient, with tremors, palpitations, and anxiety being most commonly reported.[19] Cardiac adverse events, such as arrhythmias or myocardial infarction, may occur in rare cases but are primarily associated with intravenous administration of epinephrine in hospital settings.[20]

## What About Stock Epinephrine?

Prescription and self-carriage of epinephrine help to ensure that treatment is available for patients at risk of anaphylaxis. However, epinephrine carriage rates remain suboptimal, and anaphylaxis can sometimes occur in individuals with no prior history of allergic reaction. To improve treatment access, the practice parameter update suggests that childcare centres and schools should stock undesignated epinephrine.[5] It also encourages other community venues to stock undesignated epinephrine, if feasible. For example, such venues may include theme parks, sports arenas, restaurants, or other settings. These recommendations are graded as conditional, based on evidence with very low certainty. Identified barriers to stocking and administering undesignated epinephrine include the cost of epinephrine devices, gaps in administrative support, training requirements, and concerns about legal liability.[21,22] Collaboration among stakeholders is necessary to address feasibility concerns and strengthen institutional capacity for stock epinephrine programs.

| Considerations for Home Management | Considerations Against Home Management |
|---|---|
| • Patients/caregivers engaged in the shared decision-making process | • Patients/caregivers not comfortable with managing anaphylaxis without activating EMS/ED |
| • Immediate access to at least two EAIs | • No availability of EAIs or only one EAI |
| • Immediate access to person(s) who can provide help if needed | • Being alone, without immediate access to person(s) who can provide help if needed |
| • Clear understanding of the symptoms warranting the immediate use of EAI, availability of the anaphylaxis treatment plan | • Being unaware of the allergic symptoms that warrant the use of an EAI |
| • Familiarity with the EAI device administration technique | • Lack of technical proficiency with administration of an EAI<br>• Hesitance about intramuscular injection (needle phobia) |
| • Clear understanding of the benefits of early epinephrine treatment in anaphylaxis | • Concerns about the potential epinephrine adverse effects |
| • Good adherence to previous treatment recommendations, for example, using an EAI for anaphylaxis in the past or using controller medications for chronic conditions | • Poor adherence to previous treatment recommendations, for example, not administering EAI for anaphylaxis in the past or not using controller medications for chronic conditions |
| | • History of severe/near-fatal anaphylaxis treated with more than two doses of epinephrine, hospitalization, intubation |

**Table 3.** Considerations for and Against Home Management of Anaphylaxis; *reprinted from Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176, with permission from Elsevier.*

**Abbreviations: EAI:** epinephrine autoinjector, **ED:** emergency department, **EMS:** emergency medical services

## Conclusions

The JTFPP's 2023 anaphylaxis practice parameter update affirms the benefits of prescribing epinephrine devices with premeasured doses of epinephrine to patients at higher risk of anaphylaxis. While patients at lower risk may also benefit from epinephrine prescription, the financial or psychosocial burdens might outweigh the anticipated benefits in some cases. The practice parameter update emphasizes the importance of engaging patients in SDM and considering their individual risk factors, values, preferences, and context-specific considerations when deciding whether to prescribe epinephrine, how many doses to prescribe, and how to counsel them on managing anaphylaxis after epinephrine is administered.

Clinicians should counsel patients to immediately activate EMS after administering epinephrine if anaphylaxis is severe, if it does not promptly and completely or nearly completely resolve, or if symptoms return or worsen after the first dose. Home management of anaphylaxis without EMS activation may be appropriate if the patient experiences a prompt, complete or nearly complete, and durable response to treatment with the first dose of epinephrine, has additional epinephrine available, and determines with their clinician that it is a suitable option for them. The certainty of the evidence underlying the practice parameter recommendations is generally very low, indicating that more research is needed to confirm the best strategies for epinephrine prescription and use.

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## Financial Disclosures

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# Use of the REMA Score to Distinguish Individuals with Systemic Mastocytosis From Those with Hereditary Alpha-tryptasemia

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***Background:*** Systemic mastocytosis (SM) and hereditary alpha-tryptasemia (HαT) may present with overlapping clinical manifestations of mast cell activation, making them difficult to distinguish on clinical grounds. Diagnosing SM requires a bone marrow or tissue biopsy whereas HαT can be diagnosed with a buccal swab for genetic testing. Another potential method to differentiate SM from HαT is through a validated scoring system. For example, the Spanish Network on Mastocytosis, Red Española de Mastocitosis (REMA) score has been validated as a predictor of mast cell clonality in SM by using basal serum tryptase levels, clinical symptoms, and sex. This study aims to determine whether REMA scores can differentiate sufficiently between individuals with SM and HαT, thereby confidently ruling in or out the need for more invasive investigations such as bone marrow or tissue biopsy.

***Methods:*** A retrospective chart review was conducted on 39 patients with SM and 24 patients with HαT to calculate their individual REMA scores. A two-sample Wilcoxon test was conducted to assess the difference in median REMA scores between patients with SM and those with HαT. Within the SM cohort, subgroup analysis was performed to compare REMA scores based on the *KIT* D816V mutation and SM subtype. The area under the curve was calculated to evaluate the discriminatory property of the REMA score.

***Results:*** The Median REMA score within the SM cohort was 2 (0.50, 4.00) compared to -1 (-1.50 0.00) within the HαT cohort ($p < 0.001$). REMA scores in patients with SM did not differ based on the *KIT* mutation status. A REMA score cut-off of 0.5 was able to distinguish SM and HαT with a specificity of 83.3% (67%,96%).

***Conclusion:*** This novel comparison of REMA scores in patients with SM and HαT highlights a potential role for the calculated REMA score in informing decisions about the need for invasive testing for patients presenting with symptoms of mast cell activation. However, larger comparative studies are needed before incorporating REMA scoring into routine care.

## Introduction

Tryptases are trypsin-like proteases derived from mast cells and are expressed by allergic effector cells, tissue mast cells, and basophils.[1-3] The genes *TPSB2* and *TPSAB1* encode alpha and beta-tryptases, respectively. The frequency of alleles containing alpha-tryptase isoforms encoded at *TPSAB1* varies significantly based on an individual's race and ethnicity.[1] Basal serum tryptase levels, with an upper limit of normal at 11.4 ng/mL, reflect the total alpha and beta tryptase in the absence of acute mast cell activation.[1,4] Elevated basal serum tryptase levels, found in approximately 4–6% of the Western population,[5] can be caused by rare hematologic disorders such as systemic mastocytosis (SM) and myelodysplastic syndrome, reactive conditions such as allergic disorders and chronic urticaria, and other conditions such as kidney failure and hereditary alpha-tryptasemia.[6]

Amongst the conditions associated with elevated basal serum tryptase levels, SM, and hereditary alpha-tryptasemia (HαT) often exhibit overlapping clinical manifestations of mast cell activation, and are often difficult to distinguish on clinical grounds.[4,7] Diagnosing SM requires a bone marrow or tissue biopsy.[8] In contrast, HαT, an autosomal dominant trait defined by germline replications of the *TPSAB1* gene encoding alpha tryptase, can be diagnosed non-invasively with a buccal swab for genetic testing.[7] The prevalence of these conditions varies significantly, with SM estimated to affect 1 in 10,000–20,000 individuals while HαT is estimated to occur in 5% of the general population.[4,7]

The Spanish Network on Mastocytosis (Red Española de Mastocitosis) has developed a highly sensitive and simple clinical score known as the Red Española de Mastocitosis (REMA) score. This score has been validated as a predictor of mast cell clonality and SM by using a combination of basal serum tryptase levels, clinical symptoms, and sex.[9] A REMA score of 2 or higher is associated with a high probability of mast cell clonality and SM, whereas a score below 2 is associated with a low probability of mast cell clonality and SM.[9] To our knowledge, no published studies have compared REMA scores between individuals with SM and HαT. We hypothesize that individuals with HαT would have lower REMA scores compared to those with SM, and that using REMA scoring to differentiate these conditions would lead to more informed and targeted investigations for patients presenting with symptoms of mast cell activation.

## Methods

All patients were assessed at a tertiary care teaching hospital and identified by retrospective chart review as approved by the St. Michael's Hospital Research Ethics board. Patients of all ages were included if they had been formally diagnosed with either SM (according to WHO diagnostic criteria) or HαT via buccal swab genetic testing.[10] Patients were excluded if there were no investigations confirming either their diagnosis or if they had not undergone basal tryptase testing.

The REMA score was calculated for all patients.[9] For those with multiple basal serum tryptase measurements, the highest basal serum tryptase level was used. Patients with SM were further stratified according to the presence of the *KIT* D816V mutation and the WHO subtype of systemic mastocytosis.[11]

A two-sample Wilcoxon test was conducted to assess the statistical significance of differences in median REMA scores between patients with SM and those with HαT. Additionally, subgroup analysis within the SM cohort was conducted to assess the statistical significance of differences in median REMA scores between patients with and without the *KIT* D816V mutation, as well as among patients with different WHO subtypes of SM.

The optimal cut-off values of the REMA score for distinguishing between SM and HαT were calculated using receiver operator characteristic (ROC) curves. Chi-squared and Fisher Exact tests were performed to determine which REMA score variables were most strongly associated with predicting a diagnosis of SM or HαT. P-values ≤0.05 were considered statistically significant. All statistical analyses were performed with R 3.6.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria) and R studio 1.2.5033 statistical software (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA).[12,13]

## Results

The study included 39 patients with SM and 24 patients with HαT. **Tables 1 and 2** provide details on each patient's sex, age, tryptase levels, REMA score, and where applicable, SM subtype, and c-KIT mutation status. The median REMA score within the SM cohort was 2 (0.50, 4.00)

| Age | Sex | Serum Tryptase (*mcg/L*) | REMA Score |
|---|---|---|---|
| **56** | Female | 12.8 | -1 |
| **52** | Female | 16 | -3 |
| **52** | Male | 20.2 | -1 |
| **39** | Female | 13.6 | 0 |
| **13** | Male | 13.9 | 1 |
| **69** | Female | 12.4 | -4 |
| **1** | Female | 13.4 | -4 |
| **31** | Female | 21.9 | -3 |
| **59** | Female | 19.2 | 0 |
| **33** | Female | 11.3 | -1 |
| **48** | Female | 14 | -1 |
| **34** | Female | 13 | -1 |
| **7** | Female | 11.4 | -4 |
| **46** | Female | 28 | 2 |
| **25** | Female | 11.9 | -1 |
| **40** | Female | 11.4 | -1 |
| **36** | Female | 11.9 | -1 |
| **67** | Female | 15 | 0 |
| **25** | Female | 14.5 | -1 |
| **51** | Male | 12.1 | 1 |
| **39** | Female | 12.2 | -1 |
| **31** | Female | 12.2 | -4 |
| **52** | Male | 16 | 2 |
| **33** | Female | 11.4 | -1 |

**Table 1.** Patient demographics, serum tryptase, and Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score of patients with hereditary alpha-tryptasemia; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

| Age | Sex | Serum Tryptase (*mcg/L*) | REMA Score | SM Subtype | c-KIT Mutation Status |
|---|---|---|---|---|---|
| **42** | Female | 60.1 | 5 | Indolent | C-kit mutation + D816V |
| **42** | Female | 50.1 | 2 | Indolent | C-kit mutation + D816V |
| **44** | Female | 23.5 | 0 | Indolent | C-kit mutation + D816V |
| **33** | Male | 42.2 | 4 | Indolent | C-kit mutation + D816V |
| **23** | Female | 65.1 | 2 | Indolent | C-kit mutation + D816V |
| **47** | Female | 11.4 | 1 | Indolent | C-kit mutation + D816V |
| **76** | Male | 166 | 4 | Smoldering | C-kit mutation + D816V |
| **37** | Male | 424 | 1 | Mast cell leukemia | C-kit mutation + D816V |
| **39** | Female | 10.8 | -1 | Indolent | C-kit mutation + D816V |
| **53** | Female | 32 | 2 | Indolent | C-kit mutation - |
| **65** | Female | 81.1 | 5 | Indolent | C-kit mutation + D816V |
| **42** | Female | 63.1 | 2 | With associated hematologic neoplasm | C-kit mutation - |
| **37** | Male | 11.3 | 5 | Indolent | C-kit mutation - |
| **39** | Female | 55.2 | 2 | Indolent | C-kit mutation + D816V |
| **72** | Female | 44.5 | 2 | Indolent | C-kit mutation + D816V |
| **42** | Female | 50.1 | 2 | Indolent | C-kit mutation + D816V |
| **50** | Male | 16.8 | 2 | Indolent | C-kit mutation + D816V |
| **67** | Male | 39 | 4 | Indolent | C-kit mutation + D816V |
| **56** | Female | 21.3 | -3 | Indolent | C-kit mutation - |
| **34** | Male | 20 | 2 | Indolent | C-kit mutation + D816V |
| **35** | Female | 16.6 | 0 | Indolent | C-kit mutation - |
| **38** | Female | 29.4 | -1 | Indolent | C-kit mutation - |

| | | | | | |
|---|---|---|---|---|---|
| **27** | Female | 26 | 2 | Indolent | C-kit mutation + D816V |
| **38** | Female | 193 | 2 | Indolent | C-kit mutation + D816V |
| **68** | Male | 180 | 4 | Smoldering | C-kit mutation + D816V |
| **52** | Female | 59.3 | 2 | Indolent | C-kit mutation + D816V |
| **57** | Female | 38.8 | 5 | Indolent | C-kit mutation + D816V |
| **34** | Male | 25.4 | 4 | Indolent | C-kit mutation + D816V |
| **29** | Female | 35.3 | -1 | Indolent | C-kit mutation + D816V |
| **66** | Male | 21.3 | 2 | Indolent | C-kit mutation + D816V |
| **65** | Male | 36.5 | 4 | Indolent | C-kit mutation + D816V |
| **44** | Female | 20.5 | 0 | Indolent | C-kit mutation + D816V |
| **27** | Female | 9.5 | -1 | Indolent | C-kit mutation - |
| **51** | Female | 22.4 | 0 | Indolent | C-kit mutation + D816V |
| **43** | Male | 60.8 | 4 | Indolent | C-kit mutation - |
| **58** | Male | 33.3 | 4 | Indolent | C-kit mutation - |
| **47** | Female | 199 | 5 | Aggressive | C-kit mutation + D816V |
| **38** | Male | 59.2 | 4 | Indolent | C-kit mutation + D816V |
| **52** | Female | 13.9 | -1 | Indolent | C-kit mutation + D816V |

**Table 2.** Patient demographics, serum tryptase, Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score, systemic mastocytosis (SM) subtype, and c-KIT mutation status of patients with SM; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP*.

compared to -1 (-1.50, 0.00) in the HαT cohort (p<0.001). Within the SM cohort, 28 patients had the *KIT* D816V mutation whereas the remaining 11 patients did not. The REMA scores for patients with the *KIT* D816V mutation (2, interquartile range [IQR] 1-4) did not differ significantly from those without the mutation (2, IQR -0.5-4; p=0.56). The variation in REMA scores between the different SM subtypes could not be accurately assessed, as the majority of patients in the SM cohort were classified as having indolent SM. **Table 3** provides the distribution of SM subtypes.

**Table 4** presents the sensitivities, specificities, positive predictive values, and negative predictive values for various REMA score thresholds in differentiating SM from HαT. The area under the curve was 0.869 (0.786, 0.953). **Figure 1** shows the ROC curve with 85% confidence intervals. Overall, a REMA score cut-off of 0.5 distinguished between SM and HαT with a sensitivity of 74.4% and a specificity of 83.3%.

Chi-squared and Fisher Exact tests revealed that serum tryptase was the variable in the REMA score most strongly associated with a diagnosis of SM or HαT (p<0.001).

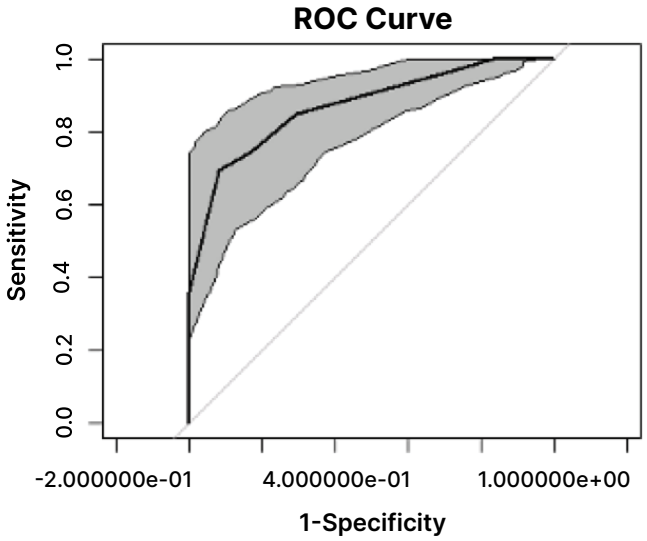


**Figure 1.** Receiver operator characteristic curve with 85% confidence intervals; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

**Abbreviations: ROC:** receiver operator characteristic

## Discussion

The diagnostic work up and appropriate classification of patients with symptoms of mast cell activation can be challenging given the heterogeneity of patient presentations. Distinguishing between SM and HαT can be particularly difficult without invasive tests such as bone marrow or tissue biopsies. Our study used a retrospective chart review to investigate the role of the previously validated REMA score in guiding the decisions about whether to proceed with invasive investigations, such as bone marrow or tissue biopsies. The findings suggest that REMA scoring could be a valuable tool to guide decision making in the diagnostic work up of patients with symptoms of mast cell activation, as patients with SM and HαT had significantly different REMA scores. Our results suggest that a REMA score of 0 or lower (below the 0.5 cut-off identified above) may be used by clinicians to support the decision to start with genetic testing for HαT as opposed to invasive testing with bone marrow or tissue biopsies in the diagnostic work up for SM. This has important implications for reducing potentially unnecessary health care expenditures and avoiding potentially unnecessary and uncomfortable testing for patients. This is especially important given that HαT is approximately 500 times more prevalent than SM.[4,7]

Our study has limitations that may affect its generalizability. Our patient population was extracted from one tertiary care teaching hospital in Toronto, Ontario, Canada and may not adequately reflect the heterogeneous global population of patients with SM and HαT. The indolent subtype of SM was disproportionately represented within the SM cohort. Finally, our study did not examine REMA scoring in patients with both SM and HαT, an overlap increasingly recognized within the literature, with an estimated 12-17% of SM patients found to have concurrent HαT in two studies.[14,15] Ultimately, these limitations highlight further areas for additional investigation. Future studies should apply REMA scoring to larger cohorts of patients with SM and HαT, especially those with different WHO subtypes of SM, and those diagnosed with both SM and HαT.

| World Health Association Subtype | # (% of Total Systemic Mastocytosis Cohort) |
|---|---|
| **n** | 39 |
| **Indolent** | 34 (87.2%) |
| **Smoldering** | 2 (5.1%) |
| **Aggressive** | 1 (2.5%) |
| **Mast Cell Leukemia** | 1 (2.5%) |
| **With Associated Hematologic Neoplasm** | 1 (2.5%) |

**Table 3.** Distribution of systemic mastocytosis subtypes according to the World Health Association classification[11]; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

| Threshold | Specificity | Sensitivity | PPV | NPV |
|---|---|---|---|---|
| **-Inf** | 0.000 | 1.000 | 0.619 | NaN |
| **-3.5** | 0.167 | 1.000 | 0.661 | 1.000 |
| **-2.0** | 0.250 | 0.974 | 0.679 | 0.857 |
| **-0.5** | 0.708 | 0.846 | 0.825 | 0.739 |
| **0.5** | 0.833 | 0.744 | 0.879 | 0.667 |
| **1.5** | 0.917 | 0.692 | 0.931 | 0.647 |
| **3.0** | 1.000 | 0.359 | 1.000 | 0.490 |
| **4.5** | 1.000 | 0.128 | 1.000 | 0.414 |
| **Inf** | 1.000 | 0.000 | NaN | 0.381 |

**Table 4**. Sensitivities, specificities, positive predictive values, and negative predictive values of the different Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score thresholds in differentiating systemic mastocytosis and hereditary alpha-tryptasemia; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

*For this dataset, the area under the curve was 0.869 and the 95% confidence interval was 0.786, 0.953.*

**Abbreviations: PPV:** positive predictive values, **NPV:** negative predictive values, **NaN:** Not able to calculate

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## Financial Disclosures

**P.V.:** None declared.
**M.J.:** None declared.

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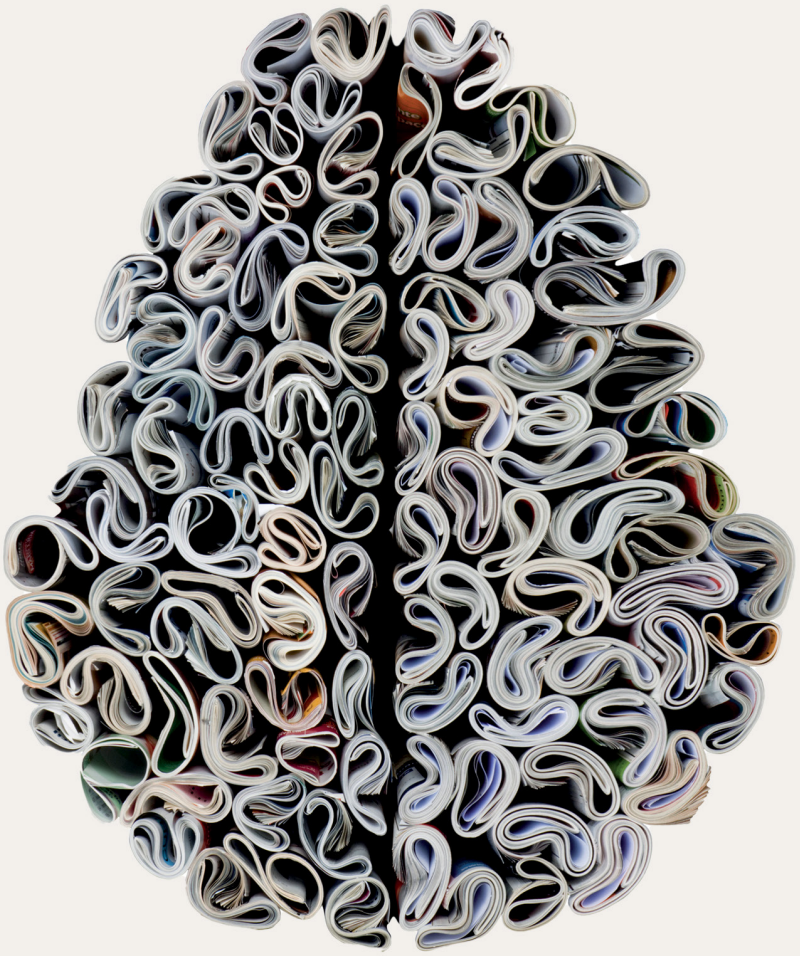

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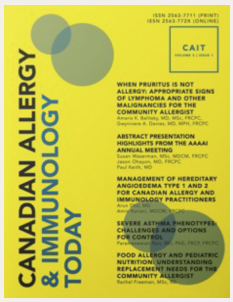






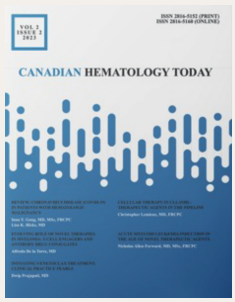




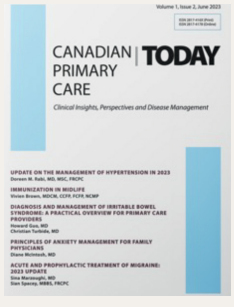


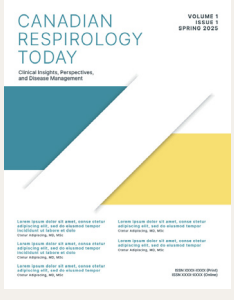



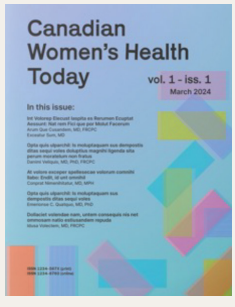

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# The Evolving Therapeutic Landscape for Hereditary Angioedema in Canada: Clinical Advances and Unmet Needs

**Dawn Goodyear, MD**

*Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent, potentially life-threatening episodes of swelling due to bradykinin overproduction. Advances in the understanding of molecular pathophysiology, coupled with the development of innovative therapies, are transforming the management of HAE. This underscores the need for strategic planning to incorporate emerging treatment modalities into the Canadian therapeutic framework for HAE.*

## Introduction

HAE typically presents with recurrent episodes of non-pitting, non-pruritic swelling, commonly involving the skin, gastrointestinal tract, and upper airway. Symptoms generally start in childhood or adolescence and can have a significant impact on quality of life and mental health. Cutaneous attacks can be disfiguring and painful, often affecting the face, extremities, or genitals. Abdominal attacks present with bloating, severe cramping, vomiting, and diarrhea, and may be mistaken for an acute surgical abdomen. Laryngeal attacks necessitate immediate medical attention due to the risk of asphyxiation. Although HAE is estimated to affect 1 in 50,000 individuals,[1] it is likely underdiagnosed in Canada.

## Pathophysiology of Hereditary Angioedema

HAE is primarily driven by bradykinin overproduction due to dysregulation of the contact system. Unlike histamine-mediated angioedema, bradykinin-mediated HAE does not respond to antihistamines, corticosteroids, or epinephrine, making accurate differentiation essential for appropriate diagnosis and treatment.[2] In HAE Types I and II, mutations in the *SERPING1* gene lead to either reduced (Type I) or dysfunctional (Type II) C1 esterase inhibitor (C1-INH), resulting in uncontrolled plasma kallikrein activation and excessive bradykinin release. Bradykinin, a potent vasodilator, increases vascular permeability. In HAE with normal C1-INH (nC1-INH), mutations in genes such as *F12, PLG, ANGPT1, KNG1, MYOF,* and *HS3ST6* have been implicated, though the underlying mechanisms are not fully elucidated.[3] Advances in understanding HAE pathophysiology have enabled the development of targeted therapies that inhibit bradykinin synthesis or activity.

## Current Standard of Care in Canada

Hereditary angioedema presents a unique clinical challenge due to its unpredictable and debilitating attacks, limited conventional treatment options, and frequent misdiagnosis. The International/Canadian Hereditary Angioedema Guideline (2019) emphasizes the importance of individualized patient care, advocating for the use of on-demand treatments to treat acute attacks and consideration of long-term prophylaxis for patients with frequent or severe episodes.[4] The selection of a treatment strategy is influenced by various factors, including the patient's history of attack location, severity and frequency, HAE subtype, access to emergency care and individual preferences.

### On-Demand Therapies Currently Available in Canada:

Icatibant (Firazyr) acts as a selective competitive antagonist of the bradykinin B2 receptor, preventing the binding of bradykinin to its receptor. Icatibant is approved for self-administration during acute HAE attacks. The FAST-3 trial demonstrated that icatibant significantly reduced the time to symptom relief in acute HAE attacks, with a median time of two hours to achieve a 50% reduction in symptoms versus 19.8 hours with placebo (P<0.001).[5] Icatibant is well tolerated, with mild and transient injection-site reactions being the most common side effect.

Plasma-derived C1-INH (Berinert) is used to replenish deficient or dysfunctional C1-INH, administered through intravenous infusion to rapidly increase intravascular C1-INH levels. Berinert is widely used and available for home infusion in Canada. In a randomized, double-blind, placebo-controlled trial, Berinert (20 U/kg) significantly accelerated symptom relief in acute abdominal or facial HAE attacks, with a median time to onset of relief of 0.5 hours versus 1.5 hours with placebo (P=0.0025).[6] Berinert also reduced the median time to complete symptom resolution from 7.8 to 4.9 hours (P=0.0024).[6] While Berinert is generally well tolerated, its intravenous administration may pose challenges for some patients, particularly those with difficult venous access or needle phobia. Additionally, home infusion of Berinert may be inappropriate for patients with infrequent attacks due to limited opportunities to maintain self-administration proficiency.

Fresh frozen plasma (FFP) contains C1-INH and may be used for treating acute attacks when other HAE-specific therapies are unavailable. However, FFP cannot be used for home administration and may be associated with an increased risk of adverse effects, including volume overload and worsening angioedema since FFP contains substrates that may further activate complement.

### Prophylactic Therapies Currently Available in Canada:

Lanadelumab (Takhzyro) is a recombinant, fully human monoclonal antibody that inhibits plasma kallikrein and is administered subcutaneously every 2 to 4 weeks. During the HELP trial, lanadelumab significantly reduced HAE attack rates, with the most effective dose (300 mg every 2 weeks) achieving a mean of 0.26 attacks/month versus 1.97 attacks/month with placebo (p<0.001).[7] Up to 76.9% of lanadelumab-treated patients remained attack-free, and quality-of-life scores improved significantly during the study period.[7] The most common side effects consist of mild, self-limited injection-site reactions.

Subcutaneous plasma-derived C1-INH (Haegarda) is a volume-reduced pdC1-INH concentrate that provides sustained C1-INH levels.

In a phase 2 open-label study, twice-weekly administration of Haegarda resulted in dose-dependent increases in functional C1-INH activity, with mean modelled trough levels of 31.7%, 44.3%, and 80.5% for the 1500 IU, 3000 IU, and 6000 IU doses, respectively.[8] Higher doses achieved protective C1-INH levels (>40%), were associated with fewer breakthrough attacks, and demonstrated a favourable safety profile.[8]

Berotralstat (Orladeyo) is an oral kallikrein inhibitor that is taken once daily, offering a convenient administration option. In the APeX-2 Part 3 trial, a daily dose of 150 mg of berotralstat reduced the mean monthly HAE attack rates by 90.8% at 96 weeks (2 years).[9] Berotralstat is generally well tolerated, although mild transient gastrointestinal side effects can occur. Patient-reported outcomes indicated improved quality of life and increased treatment satisfaction.[9]

A systematic review of 63 studies has confirmed that attenuated androgens (e.g., danazol, stanozolol) are effective for long-term prophylaxis. Placebo-controlled trials have shown that these treatments can reduce attack rates from over 90% with placebo to as low as 2% with danazol.[10] However, long-term use of these androgens is associated with dose- and duration-related adverse effects, including weight gain, menstrual irregularities, virilization, hepatic enzyme changes, and rare cases of hepatic tumours. This warrants cautious, individualized use and regular monitoring. Due to the high rate of adverse effects, androgens are now only considered for selected patients, at the lowest effective dose, as a second-line therapy.

Antifibrinolytics (e.g., tranexamic acid) are not recommended for long-term prophylaxis in HAE. However, they have been shown to reduce the frequency and severity of HAE attacks in small cohorts of patients.[11] Tranexamic acid is a less potent but better-tolerated alternative to attenuated androgens in select patients with HAE and may be considered when other HAE-specific therapies are unavailable.

## Emerging Therapies

Emerging treatments for HAE are designed to enhance efficacy, improve ease of use, and provide sustained disease control. While some therapies are in the advanced stages of clinical development, they are currently only accessible in Canada through clinical trials. The commercial availability of these therapies will expand treatment options and support personalized HAE management, in line with the International/Canadian HAE Guidelines. The emergence of oral therapies, extended-interval therapies, and gene editing holds promise for optimizing disease control and reducing the healthcare burden for individuals with HAE in Canada.

Garadacimab is a subcutaneously administered monoclonal antibody that targets activated Factor XII, thereby inhibiting the kallikrein-kinin cascade. In the phase 3 VANGUARD trial, garadacimab (200 mg monthly) reduced the mean monthly hereditary angioedema attack rate by 87% compared to placebo (0.27 versus 2.01 attacks; P<0.0001). Additionally, 62% of garadacimab-treated patients remained attack-free over 6 months.[12] Garadacimab is currently under review by Health Canada and the Canada Drug Agency.

Donidalorsen is an antisense oligonucleotide that reduces the production of plasma prekallikrein by inhibiting prekallikrein mRNA and is administered subcutaneously. In a phase 2 open-label extension study, donidalorsen achieved a 96% reduction in attack rates over 2 years, with favourable quality of life outcomes.[13] The treatment was well tolerated and demonstrated flexible dosing, allowing administration every 4 or 8 weeks.[13]

Deucrictibant (PHVS416) is an oral bradykinin B2 receptor antagonist currently under investigation for both on-demand and long-term prophylactic use. The phase 2 RAPIDe-1 trial indicated significantly improved HAE symptoms across all doses of deucrictibant (10, 20, and 30 mg), with a median time to ≥30% symptom reduction of 2.1–2.7 hours compared to 8.0 hours with placebo (p<0.0001).[14] In the CHAPTER-1 trial, which evaluated deucrictibant for prophylaxis, daily doses of 20 mg and 40 mg reduced monthly attack rates by 79.3% and 84.5%, respectively, compared with placebo.[15]

Sebetralstat (KVD900) is an oral plasma kallikrein inhibitor with the potential to be the first oral on-demand therapy for HAE. In a phase 3 trial, oral sebetralstat at doses of 300 mg and 600 mg significantly shortened the median time to symptom relief during HAE attacks to 1.61 and 1.79 hours, respectively, compared to 6.72 hours with placebo (P<0.001 and P=0.001).[16] Additionally, it demonstrated higher complete resolution rates at 24 hours (42.5% [300 mg dose]

and 49.5% [600 mg dose] versus 27.4% [placebo]) with a favourable safety profile.[16]

Navenibart (STAR-0215) is a long-acting monoclonal antibody administered subcutaneously that inhibits plasma kallikrein. A recently published phase 1a study indicated that navenibart was well tolerated in healthy adults and achieved up to 85% inhibition of plasma kallikrein activity ($P<0.001$).[17] The study also demonstrated a mean half-life of 82–106 days for doses ≥300 mg, supporting the feasibility of subcutaneous administration every 3 to 6 months.[17]

ATN-249 is an orally-administered prekallikrein inhibitor being developed for prophylactic use in HAE. Preclinical studies have demonstrated that ATN-249 provides 10-fold greater relative plasma kallikrein inhibition compared to C1-INH.[18]

NTLA-2002 is a CRISPR/Cas9-based gene-editing therapy that targets the *KLKB1* gene, aiming to disrupt the hepatic expression of plasma prekallikrein by inactivating the gene encoding kallikrein B1. A single intravenous dose of NTLA-2002 led to dose-dependent reductions in plasma kallikrein levels ranging from 67% to 95%, and a mean 95% reduction in monthly angioedema attack frequency, with no serious adverse events observed in the phase 1 trial.[19] In the phase 2 trial, NTLA-2002 at doses of 25 mg and 50 mg reduced the mean monthly angioedema attack rate by 75% and 77%, respectively, compared to placebo. Notably, 73% of patients receiving the 50 mg dose remained attack-free over the 16-week treatment period.[20]

BMN 331 is an AAV5-based gene therapy designed to transduce the *SERPING1* gene into hepatocytes, enabling patients to produce functional C1-INH. A phase 1/2, single-arm, open-label, dose-escalation and dose-expansion study of BMN 331 is currently under way.[21]

## Unmet Needs In HAE Management in Canada

Despite significant therapeutic advancements, critical gaps in the management of hereditary angioedema persist. Addressing these challenges is essential to optimizing outcomes and achieving high-quality care that aligns with current clinical guidelines.

- Many patients experience a diagnostic delay of approximately 10 years from symptom onset, often experiencing multiple misdiagnoses, including allergic, gastrointestinal, or psychiatric conditions, which can lead to unnecessary suffering, inappropriate treatment, and avoidable morbidity.[22]
- While the adoption of virtual care can improve access to HAE expertise, physical access to infusion services, emergency care, or trained healthcare providers remains a challenge, particularly in rural and northern regions.
- The absence of robust data and standardized treatment strategies for certain subpopulations, such as pediatric HAE patients and HAE with normal C1-INH, has led to limited therapeutic options for these groups.
- The unpredictability of attacks and the burden of living with a complex, congenital disease contribute to anxiety, depression, and social isolation for HAE patients. Mental health support for HAE is often lacking, potentially leading patients to feel misunderstood or dismissed by healthcare providers.
- Not all patients are eligible or able to access the currently available HAE-specific therapies due to cost or coverage limitations.
- National data on HAE prevalence, treatment patterns, and outcomes are scarce. A centralized patient registry and prospective real-world evidence initiatives would support better clinical understanding and inform health policy decisions for Canadian patients with HAE, particularly in the era of novel therapies.

## Conclusion

The therapeutic landscape for HAE is expanding beyond traditional intravenous and subcutaneous therapies. Emerging therapies hold promise for more effective, convenient, and personalized care for HAE patients in Canada. Patient-centric innovations such as oral agents, gene editing, and quarterly or biannual injections may transform care. However, these advancements will require shared decision-making and patient engagement. Additionally, real-world and long-term safety data will be required to guide the integration of emerging and novel therapies into routine HAE practice.

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# An Update on Biologics in Pediatric Asthma: A Canadian Perspective

**Jacob McCoy, MD**
**Padmaja Subbarao, MD**

## Introduction

Asthma is one of the most common chronic diseases in Canada, affecting approximately 11% of Canadians.[1] Severe asthma, estimated to affect 5–10% of patients with asthma, is associated with a significant burden of disease-related morbidity.[2] In adults, typical management strategies include using combinations of inhaled corticosteroids, long-acting beta agonists, leukotriene receptor antagonists, long-acting muscarinic antagonists, and oral corticosteroids. However, in pediatric cases, particularly young children, our medication options are more limited. Although inhaled corticosteroids are effective for the majority of mild-to-moderate asthma cases, their efficacy in non-atopic asthma is limited. Furthermore, using inhaled corticosteroids at moderate-to-high doses can impair linear growth and lead to adrenal suppression. Given our growing recognition of asthma as a heterogenous disease, with multiple disease endotypes driven by distinct inflammatory pathways, there is an increasing demand for targeted therapies, particularly for patients with ongoing, uncontrolled disease (**Figure 1**). Type 2 (T2) high inflammation, characterized by elevated levels of IgE, interleukin (IL)-4, IL-5, and IL-13, alongside eosinophilia and atopy, remains the most well-defined endotype in school-age children and youth.[3] With the advent of biologic medications, targeting T2-high inflammatory pathways has become a critical component for managing uncontrolled, moderate-to-severe asthma in children. This approach aims to improve treatment response and reduce adverse effects. This review will explore the biologic therapies currently available in Canada for moderate-to-severe pediatric asthma, discuss key considerations in selecting the optimal biologic, and outline future research directions to inform the optimal timing for initiating and discontinuing biologic treatments.

## Biologics in Canada

In Canada, four biologics are currently available for use in pediatric patients with asthma, as mentioned above, all are for T2 high asthma: omalizumab, dupilumab, mepolizumab, and tezepelumab (**Table 1**).

### Omalizumab

Omalizumab is an anti-IgE monoclonal antibody that binds to free IgE, thereby preventing further interaction with mast cells, basophils, and eosinophils. It is approved for use in moderate-to-severe persistent asthma that remains uncontrolled despite inhaled corticosteroids. This approval is for children ≥6 years of age who have a positive skin prick test to a perennial aeroallergen and elevated IgE levels.

Several studies have demonstrated the clinical effectiveness of omalizumab in children. In the Inner-City Anti-IgE Therapy for Asthma study, which included children aged 6–20 years with persistent, allergic asthma, omalizumab led to a decrease in the number of participants with an asthma exacerbation by 40% (30% in the omalizumab arm versus 49% in the placebo arm). Additionally, there was a reduction in the mean number of days with symptoms per two-week period (1.48 days in the omalizumab arm versus 1.96 days in the placebo arm).[4] In the Preventative Omalizumab or Step-up Therapy for Fall Exacerbations study, children aged 6–17 years with asthma were randomized to receive omalizumab, placebo, or a doubled dose of inhaled corticosteroid (ICS).[5] Omalizumab led to a reduction in the fall season exacerbation rate compared with placebo (11% versus 21%), with an even more prominent effect in patients who had an exacerbation during the run-in period (6% versus 36%). Although there was no overall difference compared with the ICS 'boost' group, a significant reduction was observed in patients who had an exacerbation in the run-in

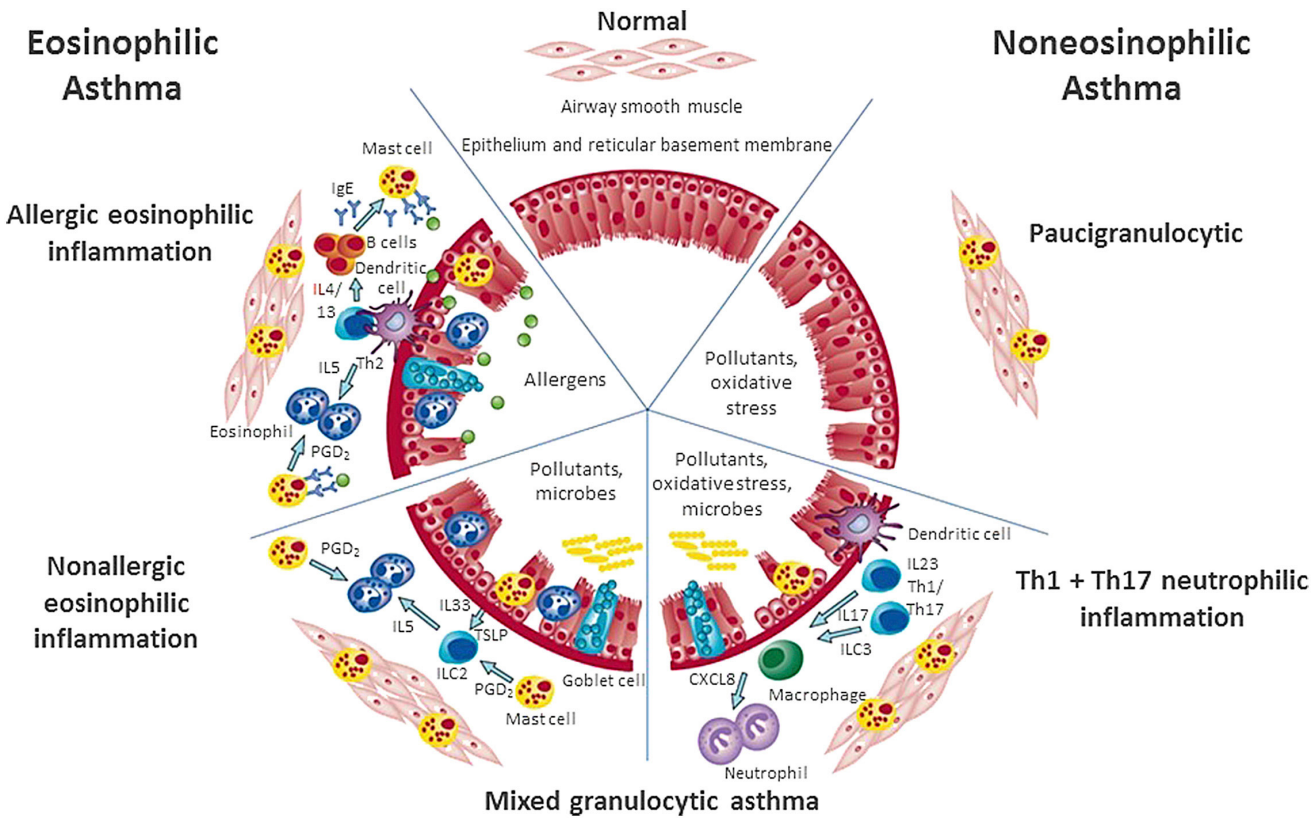


**Figure 1.** Inflammatory pathways involved in asthma immunopathology; *reproduced from William Busse, Biological treatments for severe Asthma: A major advance in asthma care, Allergology International, 2019, with permission from the Japanese Society of Allergology.*[20]

period (2% versus 28%). Additionally, omalizumab improved the mean asthma symptom days compared with placebo, but not compared to the ICS 'boost' group. A pooled *post hoc* analysis of these trials showed that the beneficial effect of omalizumab on exacerbations was higher in patients with frequent exacerbations, previous hospitalizations, lower baseline forced expiratory volume (FEV1) and a baseline blood eosinophil count ≥300 cells/uL.[6] Some trials have shown a reduction in ICS dose in patients on omalizumab compared with placebo, while others have not.[4,7] In adolescents, omalizumab has also been associated with a 12% increase in percent predicted FEV1.[8] Overall, these findings suggest that patients starting omalizumab may expect a reduction in asthma exacerbations, improved symptom control, and an improvement in FEV1.

In Canada, omalizumab is also approved for use in chronic idiopathic urticaria in patients ≥12 years of age, as well as chronic rhinosinusitis with nasal polyposis (CRSwNP) in patients ≥18 years of age. Recently, the Food and Drug Administration (FDA) in the United States has also approved omalizumab for IgE-mediated food allergies to reduce the risk of anaphylaxis. Patients with these comorbid conditions may be suitable candidates for omalizumab therapy.

## Dupilumab

Dupilumab, an anti-IL-4 receptor alpha-subunit monoclonal antibody, is currently approved for treating severe asthma with a T2-high phenotype, or for asthma that is dependent on oral corticosteroids in children ≥6 years of age.

Dupilumab has been shown to improve asthma symptoms and FEV1 in children. In the Liberty Asthma VOYAGE trial, children aged 6-11 years with moderate-to-severe asthma were randomized to receive dupilumab or placebo.[9] Patients on dupilumab had a 59% relative risk reduction in the annualized rate of severe exacerbations, and a 5% higher increase in FEV1 percent predicted than those on placebo. Additionally, the Asthma Control Questionnaire

| Biologic | Mechanism of Action | Age for Asthma Indication | Alternative Indications |
|---|---|---|---|
| **Omalizumab** | Anti-IgE | ≥6 years | • CRSwNP (≥18 years)<br>• CIU (≥12 years)<br>• FDA: Food allergy (≥1 year) |
| **Dupilumab** | Anti-IL-4Ra | ≥6 years | • AD (≥6 months)<br>• EOE (≥6 year)<br>• CRSwNP (≥18 years)<br>• PR (≥18 years) |
| **Mepolizumab** | Anti-IL-5 | ≥6 years | • CRSwNP (≥18 years)<br>• EGPA (≥18 years)<br>• HE (≥18 years) |
| **Tezepelumab** | Anti-TSLP | ≥12 years | |

**Table 1.** Biologic agents approved by Health Canada for the treatment of severe asthma in children; *courtesy of Jacob McCoy, MD and Padmaja Subbarao, MD.*

**Abbreviations: AD:** Atopic dermatitis, **CRSwNP:** Chronic rhinosinusitis with nasal polyposis, **CIU:** Chronic idiopathic urticaria, **EGPA:** Eosinophilic granulomatosis with polyangiitis, **EOE:** Eosinophilic esophagitis, **HE:** Hypereosinophilic syndrome, **IL:** interleukin, **PR:** Prurigo nodularis, **TSLP:** thymic stromal lymphopoietin

(ACQ) score was statistically significantly lower in the dupilumab group. For patients aged ≥12 years, dupilumab led to a 47% relative risk reduction in the annualized rate of severe exacerbations compared to placebo, with a greater effect observed in patients with elevated blood eosinophil levels and fractional exhaled nitric oxide (FENO).[10] Dupilumab also led to an improvement in FEV1 of approximately 320-340 mL, which was a 130–140 mL greater improvement than that observed with placebo.

Considering that dupilumab is also approved for treating atopic dermatitis (for individuals ≥6 months of age), eosinophilic esophagitis (for those ≥12 months of age), and CRSwNP (for those ≥18 years of age), patients with asthma who have these comorbid conditions may experience additional benefit.

## Mepolizumab

Mepolizumab is an anti-IL-5 monoclonal antibody that is currently approved for treating severe eosinophilic asthma, in children aged ≥6 years. It is indicated for patients with inadequate control despite moderate-to-high doses of ICS along with an additional controller, and is recommended for those with blood eosinophil levels of ≥150 cells/uL at initiation of treatment, or ≥300 cells/uL in the last year.

Mepolizumab has been shown to reduce severe exacerbations and improved FEV1 in children. In the MUPPITS-2 trial, mepolizumab led to a 27% relative risk reduction in the mean number of annual asthma exacerbations compared with placebo in children aged 6–17 years.[11] However, no difference was found in FEV1 or symptom scores between the groups.

For all patients aged ≥12 years in the MENSA trial (aged 12–82 years), mepolizumab reduced the rate of exacerbations by 53% compared with placebo. An even greater reduction of 61% was found for exacerbations requiring an ER visit or hospitalization.[12] Additionally, mepolizumab led to a 100 mL greater improvement in FEV1 compared with placebo, as well as improvements in asthma quality of life and symptom scores. Similar findings were uncovered in the MUSCA trial, which included patients aged ≥12 years. The trial reported improvements in quality of life scores, annual exacerbations requiring an ER visit or hospitalization, and in pre-bronchodilator FEV1.[13]

Overall, these findings suggest that children treated with mepolizumab may experience a reduction in asthma exacerbations. Further

research is needed to better determine whether symptoms and lung function may also improve.

Mepolizumab has also been approved for adults with CRSwNP, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome. Patients who have eosinophil-predominant disease may be good candidates for mepolizumab.

### Tezepelumab

Tezepelumab is a monoclonal antibody that targets thymic stromal lymphopoietin (TSLP), a cytokine positioned upstream in the inflammatory cascade, which may help disrupt airway inflammation. Tezepelumab is approved for treating severe asthma in children aged ≥12 years.

Tezepelumab has limited published evidence specifically for the pediatric population. However, in adult studies that included patients aged ≥12 years, tezepelumab has shown greater improvements in pre-FEV1, annualized rate of exacerbations (with a relative risk reduction of approximately 55%), asthma symptom scores, and quality of life scores than placebo.[14,15] These findings suggest potential benefits, however, they require further confirmation with studies specific to pediatric patients.

## Selecting the Right Biologic

### Comorbidities

Until further research is available to guide the selection of biologics based on patient clinical phenotype or biomarkers, providers should be keenly aware of patient comorbidities when selecting an appropriate biologic medication. **Table 1** shows current alternative indications for each biologic agent. Comorbidity-guided selection of biologics may provide an opportunity to improve patient quality of life and reduce symptom burden in addition to improving their asthma control.

### Practical Considerations – Injections, Medication Coverage, and Early Initiation

All four biologic medications are administered via subcutaneous injection every 2 to 4 weeks, depending on the specific medication, the patient's weight, and/or biomarker levels. Pediatric providers should be aware of the frequency of medication administration and the number of injections required for each dose, as these may be important considerations for children and their families.

In Canada, public coverage for biologic therapies varies from province to province, which can significantly impact equitable access. Asthma providers should be familiar with their provincial access programs to ensure efficient initiation and ongoing, uninterrupted provision of medication.

Currently, biologics are reserved for pediatric patients with severe or difficult-to-treat asthma. However, as generic versions become available in the near future, the reduced costs may improve access and shift the focus of biologic treatments. Instead of being used only in the most severe patients with asthma refractory to all other therapeutic options, patients with active, ongoing eosinophilic inflammation, at higher risk for deterioration and long-term lung damage, may also be a target for treatment.

Until further research is available, providers may consider treatment with biologic agents for a period of 2–5 years. During this time, it is important to monitor treatment success by measuring rates of exacerbations, standardized symptom control scores, quality of life, lung function, FENO, and sputum cell counts.

## Future Research Directions

Many questions remain unanswered regarding the use of biologic medications in children: How can we predict which patients will benefit most from which biologic? Does the earlier introduction of biologic therapy improve long-term outcomes? Additionally, how and when should biologics be discontinued? Finally, are there any patients that may benefit from dual-biologic therapy?

Head-to-head studies are needed to determine the relative efficacy of each biologic medication, particularly between subgroups of patients with various asthma phenotypes. Regarding the timing of initiation, adult patients with a longer duration since asthma diagnosis demonstrated lower odds of achieving asthma remission after biologic initiation.[16] This finding warrants further investigation in pediatric patients, but it may suggest that early use of biologics in high risk patients may improve the likelihood of treatment success. Studies investigating the discontinuation of biologics have shown varying results in adults, with many revealing an increase in significant exacerbations, and a worsening of asthma control.[17-19] Pediatric studies are needed that will assess outcomes after discontinuation, particularly among subgroups defined by duration

of treatment, degree of response, or biomarkers. Finally, further studies on biomarker-guided asthma treatment are necessary to identify symptomatic patients with ongoing, targetable airway inflammation despite using a single biologic agent. This could help inform which patients might benefit from dual-biologic therapy.

## Conclusions

Biologic therapies have significantly advanced the treatment of children with severe asthma by improving our ability to directly target the underlying inflammatory pathways driving the disease. These medications have demonstrated improvements in reducing the rate of exacerbations, enhancing symptom control, and improving lung function in children with moderate-to-severe uncontrolled asthma. This progress has minimized our reliance on oral or high-dose inhaled steroids. Selecting the most appropriate biologic medication for patients requires thoughtful consideration of patient biomarkers, comorbidities, and practical factors, including coverage and patient preferences. Before initiating treatment, clinicians should establish goals for therapy and obtain measurable outcomes to determine treatment success. Further research in pediatrics is crucial to guide the optimal timing for biologic initiation and to develop evidence-based protocols for discontinuing therapy when appropriate.

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## Financial Disclosures

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