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


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# Secondary Hypogammaglobulinemia


**Vy H.D. Kim, MD**


## Introduction

Secondary hypogammaglobulinemia (SHG) is characterized by reduced immunoglobulin levels due to extrinsic causes, such as a medication or an acquired disease process, resulting in decreased immunoglobulin production or increased immunoglobulin loss. Most published reports of SHG refer to IgG hypogammaglobulinemia and data on isolated IgA or IgM hypogammaglobulinemia is limited. The common causes of SHG include medications, hematological malignancies, and conditions associated with protein loss. Hypogammaglobulinemia can increase the risk of infection, morbidity and mortality, particularly in patients who may already be immunocompromised due to their associated condition or use of immunosuppressive therapies.[1,2] With growing use of immunosuppressive or immunomodulatory treatments that affect B-cells, it is increasingly important to assess and monitor for SHG. Treatment of the underlying condition or removal of the extrinsic factor often results in resolution of the SHG. A subset of patients presenting with autoimmune or malignant conditions can have a primary immunodeficiency (PID) or primary immune regulatory disorder. It is therefore important to consider both primary and secondary causes when assessing hypogammaglobulinemia. This article will review these common causes and discuss an approach to assessment and management of SHG.

## Medications

Many classes of medications can cause hypogammaglobulinemia. The most commonly implicated therapies include immunosuppressive or immunomodulatory medications, such as B-cell targeted therapies (BCTT), corticosteroids, and antiepileptic drugs.

BCTT are increasingly used for treatment of malignant, autoimmune and inflammatory conditions. Most literature regarding BCTT-associated SHG exists for rituximab, a chimeric anti-CD20 monoclonal antibody. Rituximab results in B-cell depletion within 72 hours with persistence of B-cell lymphopenia for 2–6 months after treatment. B-cell levels usually return to those of pre-treatment within 12 months.[3] B-cell impairment is limited primarily to depletion of pre-plasma B cells, halted differentiation from naïve to memory B-cell, increased B-cell apoptosis, and altered T-cell homeostasis. Hypogammaglobulinemia has been identified in up to 40–50% of patients who received rituximab.[4,5] Significantly delayed B-cell recovery is associated with persistent

hypogammaglobulinemia. A low IgG level prior to or at the time of rituximab use is a risk factor for development of hypogammaglobulinemia after rituximab use.[4] Low IgG levels at any time after rituximab use has been associated with a higher risk of serious infections.[5] Risk factors for moderate persistent hypogammaglobulinemia post-rituximab use include prior cyclophosphamide use, lower nadir IgG in the first 12 months, corticosteroid use at 12 months and female sex.[6] Anti-CD19 chimeric antigen receptor (CD19 CAR)-T-cell therapy causes B-cell aplasia and SHG as its "on target" "off tumor" effect. SHG occurs frequently and can persist for months or years.[7] The association between hypogammaglobulinemia and risk of infection in CD19 CAR-T-cell therapy is variable and complicated by additional risk factors including corticosteroid or other immunosuppressive medication use, cytokine release storm, underlying malignancy, neutropenia, and prior infection history.

Corticosteroid use primarily affects IgG levels and has less impact on IgA and IgM, which can be helpful in distinguishing between primary hypogammaglobulinemia and hypogammaglobulinemia secondary to corticosteroids.[8,9] Prolonged or high-dose use of oral corticosteroids has a greater effect on IgG levels than short-term use. Specific antibody responses are usually preserved and therefore corticosteroid-induced SHG is not associated with significant increased frequency or severity of infectious complications. The infections associated with corticosteroid use are usually due to its associated CD4 T-cell lymphopenia. However, use of corticosteroids in combination with other immunosuppressive therapies can result in more significant hypogammaglobulinemia. High-dose inhaled corticosteroid use has not been associated with SHG.[9]

Antiepileptic drugs (AEDs) can carry an increased risk of hypogammaglobulinemia. Although panhypogammaglobulinemia has been associated with AEDs, IgG is the most commonly reported immunoglobulin class involved[10] Phenytoin, carbamazepine, and lamotrigine have been associated with low IgA. Topiramate has not been associated with a significant risk of SHG. AEDs are thought to have an effect on B-cell maturation or regulatory T-cells, which can affect immunoglobulin isotype production. There is an exposure-response relationship with a trend of increased odds of hypogammaglobulinemia with increasing duration of AED exposure. Hypogammaglobulinemia tends to normalize after AEDs cessation. Most patients have not had significant demonstrated antibody deficiency and it is unclear what the infection risk is for these patients.

## Malignancies

Hematological malignancies, such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) are common causes of SHG. Hypogammaglobulinemia is present in up to 85% of patients with CLL and up to 83% of patients with MM.[11] SHG in CLL is thought to be due to the underlying disease process, such as defective B-cell maturation and dysfunction of nonclonal CD5-negative B-cells, as well as immunomodulatory treatments. The frequency of infection correlates with hypogammaglobulinemia and contributes significantly to morbidity and mortality. SHG is more pronounced with advanced disease stage or longer disease duration in CLL.

## Transplantation

Hypogammaglobulinemia occurs commonly in solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). It has been observed in approximately 60% of lung transplant recipients, 50% of heart transplant recipients, 40% of renal transplant recipients, 16% of liver transplant recipients,[2] and 50–77% of allogeneic HSCT recipients[12,13] at 1 year. Severe hypogammaglobulinemia (IgG level less than 4 g/L) in the first year post-SOT is associated with increased risk of infections, particularly cytomegalovirus and fungal and respiratory infections, as well as mortality.[14] B-cell recovery after HSCT takes 3–6 months but can be delayed by the presence of graft-versus-host disease (GVHD), conditioning and immunosuppressive medications, and type of donor cells. Risk factors for SHG post-HSCT include younger age, lower pre-transplant IgG level, diagnosis of malignant disease, development of acute GVHD, and receiving an unrelated HSCT.[13]

## Conditions Associated with Protein Loss

Protein-losing states can be due to renal (e.g., nephrotic syndrome), gastrointestinal (e.g., protein-losing enteropathy) or cutaneous (e.g., severe burn) loss. Patients with loss of IgG often have retained specific antibody production

and may have a lower risk of infection compared to those with a failure to produce antibodies. However, the use of immunosuppressive therapies and urinary loss of complement (in nephrotic syndrome) can contribute to an immunocompromised state and risk of infection. One study of pediatric patients who received rituximab for complicated nephrotic syndrome did not find a significant association between severity of hypogammaglobulinemia and infection rate.[15] Management is usually targeted at the underlying condition and there is limited data on the efficacy of immunoglobulin replacement therapy.

## Assessment and Management Considerations

When assessing patents with hypogammaglobulinemia, it is important to consider primary immunodeficiency (PID) as many conditions that require immunosuppressive or immunomodulatory treatments may also be presentations of PID. For example, patients with PID can present with immune dysregulation and autoimmunity, such as autoimmune cytopenias and rheumatologic presentations and malignancies, which frequently require treatment with immunosuppressive medications. Often, baseline immunoglobulin levels are not routinely established at the time of diagnosis of the initial condition or before treatment with immunosuppressive medications. When the concern for hypogammaglobulinemia arises, the immune evaluation may be affected by the current immunosuppressive therapy, thus hampering the assessment of primary versus secondary immunodeficiency. Two studies demonstrated that a significant subset of children who received rituximab for autoimmune cytopenia and experienced persistent hypogammaglobulinemia were subsequently diagnosed with PID.[5,16] Another study identified variants in PID genes in approximately half of adult patients with rheumatic diseases who had persistent hypogammaglobulinemia after immunomodulatory therapy.[17] Red flags for PID in the context of hypogammaglobulinemia after immunosuppressive or immunomodulatory therapy are listed in **Table 1**.

Ideally, a clinical immunologist should be involved as part of the multidisciplinary team and patients would have baseline immune testing done. Patients who present with red flags or additional features concerning for PID should undergo more extensive immune evaluation by a clinical immunologist, which often includes genetic testing.

There is significant variation in practice regarding screening and management of SHG.[18-20] Society guidelines and expert recommendations have been published for specific populations or conditions, such as CLL and SOT.[21,22] Patients with secondary antibody deficiency have been shown to experience delays in diagnosis similar to those with PID.[23] Therefore, increased awareness, screening and monitoring are essential for timely diagnosis and management. Most recommendations suggest that baseline immunoglobulin levels be measured either at diagnosis or prior to initiation of treatment for at-risk patients. The frequency of immunoglobulin monitoring ranges from 3 to 12 months, depending on the treatment, underlying condition and frequency or severity of infections. For patients in whom hypogammaglobulinemia is identified or with a history of frequent infections, further evaluation of humoral immune function includes IgG, IgA and IgM levels, lymphocyte subsets and B-cell immunophenotyping, and measurement of specific antibody responses to vaccines. Interpretation of specific antibody titres may be complicated by the effect of immunosuppression on vaccine responses.

Management of SHG is complex. While removal of the treatment or condition causing SHG is preferred, it is often not easily accomplished or possible. Many patients with hypogammaglobulinemia may not develop infections and there is limited evidence regarding what is clinically meaningful SHG or when immunologic intervention should be initiated, particularly in the absence of symptoms. Supportive treatment options for SHG include immunization, antimicrobial prophylaxis and immunoglobulin replacement therapy (IGRT).

Immunizations with non-live vaccines are recommended according to routine immunization schedules, including influenza and pneumococcal vaccines, although the response may be suboptimal.[24] When possible, immunizations should be completed before immunosuppression. Live vaccines are generally not recommended for patients with malignant disorders, post-transplantation, or in those receiving immunosuppressive medications. In addition to providing protection against infection, immunizations can help assess humoral function through the measurement of antibody responses post-vaccination.

- Previous history of infections, autoimmunity, or lymphoproliferation
- Immune abnormalities prior to immune suppression: low immunoglobulin levels, low antibody responses to vaccines, low memory B cells
- Positive family history for immunodeficiency
- Young age (<10 years)
- Persistent hypogammaglobulinemia
- Abnormal B-cell subsets

**Table 1.** Red flags for PID in patients with hypogammaglobulinemia after immunosuppressive or immunomodulatory therapy; *courtesy of Vy H.D. Kim, MD.*

Evidence supporting the use of prophylactic antibiotics or IGRT for SHG is limited. The choice of antibiotics for prophylaxis should be based on the history of infections, allergies, spectrum of infection risk, and local resistance patterns. Most guidelines recommend a trial of IGRT when IgG levels are less than 4 g/L or when IgG levels are less than 7 g/L and there are suboptimal responses to vaccination, a history of recurrent or severe infections and/or failure of antibiotic prophylaxis.[21] The dosing used for IGRT is usually similar to that used for patients with primary antibody deficiency, starting at 400–600 mg/kg/month. IGRT use has been associated with significant reduction in rates of serious bacterial infections and antimicrobial use.[1] As the SHG may be transient, periodic assessments to evaluate if IGRT should be paused or discontinued should be completed every 6 to 12 months; if immunosuppression has been discontinued; or when the SHG-associated condition has been successfully treated. Re-evaluation of immune function after IGRT has been discontinued is often done following a period of 4–6 months, to allow for exogenous IgG to be cleared.

## Summary

Many conditions and treatments can cause SHG. Increasing use of novel immunomodulatory or BCTT therapies contribute to increasing incidence of SHG. As hypogammaglobulinemia may be an indicator for PID and is associated with increased risk of infection, it is important to assess and monitor for hypogammaglobulinemia and antibody deficiency in at-risk patients. Baseline immune evaluation can be helpful to stratify the risk of recurrent or severe infections in patients who may have PID. Patients with SHG should have periodic assessments for infection and immune function. Shared decision-making is important for the initiation of supportive therapy in SHG, such as IGRT. More research is needed to identify optimal laboratory evaluations for screening and monitoring, what is clinically significant SHG, and which patients would benefit from IGRT.

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## Financial Disclosures

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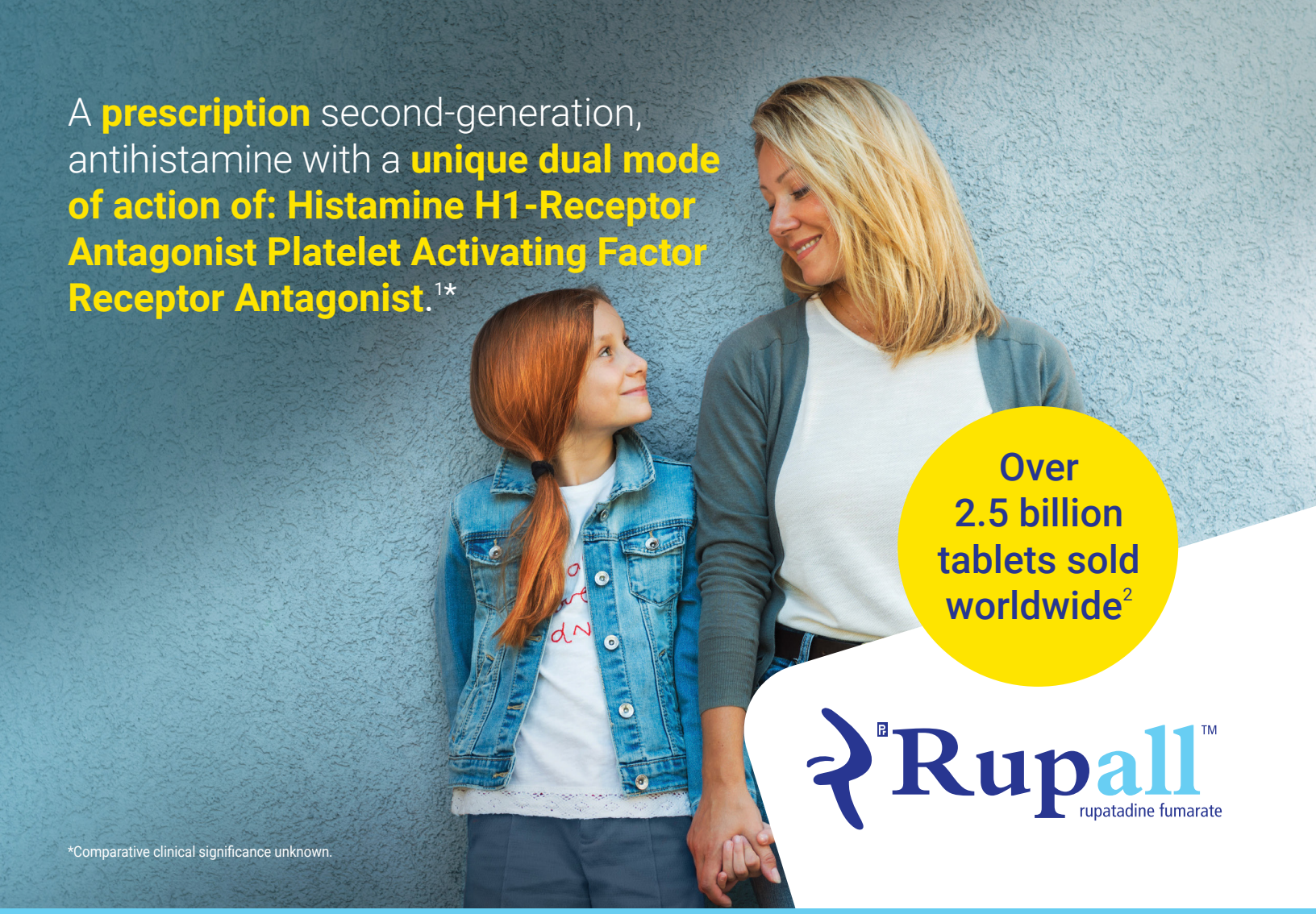
## References


1. Monleón Bonet C, Waser N, Cheng K, et al. A systematic literature review of the effects of immunoglobulin replacement therapy on the burden of secondary immunodeficiency diseases associated with hematological malignancies and stem cell transplants. Expert Rev Clin Immunol. 2020;16(9):911-21.
2. Lichvar AB, Ensor CR, Zeevi A, et al. Detrimental association of hypogammaglobulinemia with chronic lung allograft dysfunction and death is not mitigated by on-demand immunoglobulin G replacement after lung transplantation. Prog Transplant. 2019;29(1):18-25.
3. Kimby E. Tolerability and safety of rituximab (MabThera®). Cancer Treat Rev. 2005;31(6):456-73.
4. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun. 2015;57:60-5.
5. Labrosse R, Barmettler S, Derfalvi B, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol. 2021;148(2):523-32.e8.
6. Tieu J, Smith RM, Gopaluni S, et al. Rituximab associated hypogammaglobulinemia in autoimmune disease. Front Immunol. 2021;12:671503.
7. Kampouri E, Walti CS, Gauthier J, et al. Managing hypogammaglobulinemia in patients treated with CAR-T-cell therapy: key points for clinicians. Expert Rev Hematol. 2022;15(4):305-20.
8. Wirsum C, Glaser C, Gutenberger S, et al. Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. J Clin Immunol. 2016;36(4):406-12.
9. Kawano T, Matsuse H, Obase Y, et al. Hypogammaglobulinemia in steroid-dependent asthmatics correlates with the daily dose of oral prednisolone. Int Arch Allergy Immunol. 2002;128(3):240-3.
10. Perrott S, Macleod A. Associations between antiepileptic use and hypogammaglobulinaemia: findings from a population-based case-control study using data linkage. J Neurol Neurosurg Psychiatry. 2022;93(9):e2.
11. Na I, Buckland M, Agostini C, et al. Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies. Eur J Haematol. 2019;102(6):447-56.
12. Karakulska-Prystupiuk E, Dwilewicz-Trojaczek J, Drozd-Sokołowska J, et al. Prevalence of hypogammaglobulinemia and its management with subcutaneous immunoglobulin supplementation in patients after allogeneic hematopoietic stem cell transplantation—a single-center analysis. Ann Hematol. 2021;100(12):3007-16.
13. Frangoul H, M, Frangoul H, Min E, et al. Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT. Neoplasia. 2013;48(11):1456-59.
14. Florescu DF, Kalil AC, Qiu F, et al. What Is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant. 2013;13(10):2601-10.
15. Inoki Y, Nishi K, Sato M, et al. The association between hypogammaglobulinemia severity and infection risk in rituximab-treated patients with childhood-onset idiopathic nephrotic syndrome. Pediatr Nephrol. 2023;38(2):451-60.
16. Ottaviano G, Marinoni M, Graziani S, et al. Rituximab unveils hypogammaglobulinemia and immunodeficiency in children with autoimmune cytopenia. JACI (Cambridge, MA) 2020;8(1):273-82.
17. Sogkas G, Dubrowinskaja N, Adriawan IR, et al. High frequency of variants in genes associated with primary immunodeficiencies in patients with rheumatic diseases with secondary hypogammaglobulinaemia. Ann Rheum Dis. 2021;80(3):392-9.
18. Ar MC, El Fakih R, Gabbassova S, et al. Management of humoral secondary immunodeficiency in hematological malignancies and following hematopoietic stem cell transplantation: Regional perspectives. Leuk Res. 2023;133:107365.
19. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol. 2019;10:33.
20. Bourassa-Blanchette S, Knoll G, Tay J, et al. A national survey of screening and management of hypogammaglobulinemia in Canadian transplantation centers. Transpl Infect Disease. 2017;19(4).
21. Otani IM, Lehman HK, Jongco AM, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol. 2022;149(5):1525-1560.
22. Jolles S, Michallet M, Agostini C, et al. Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus. Eur J Haematol. 2021;106(4):439-49.
23. Duraisingham SS, Buckland M, Dempster J, et al. Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. PloS one 2014;9(6):e100324.
24. Public Health Agency of Canada. Immunization of immunocompromised persons: Canadian Immunization Guide. 2018; Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a13. Accessed June 15, 2024.



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**References: 1.** Rupall Product Monograph, Pediapharm Inc. January 3, 2017. **2.** Data on file.

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# Understanding and Managing Adenotonsillar Hypertrophy in Pediatric Otolaryngology

**Ivry Zagury-Orly, MD, MMSc**
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## Introduction

Adenotonsillar hypertrophy (ATH) is a common pediatric condition marked by the growth of lymphoid tissues within the Waldeyer's ring, which includes adenoids, palatine tonsils, and lingual tonsils. These tissues surround the upper airway and food passage, and play an immunological role, enlarging until about age 12, before gradually reducing during adolescence and adulthood.[1,2]

Untreated or poorly managed ATH can severely impact multiple health aspects of children.[3] It is the primary cause of upper airway obstruction and obstructive sleep apnea (OSA) syndrome in children, which disrupts sleep and can severely impair cognitive development, school performance and behaviour. Chronic mouth breathing from ATH can alter dental arches and facial growth, known as adenoid facies. More severe outcomes include increased pulmonary pressures and the potential development of pulmonary hypertension and cor pulmonale due to chronic hypoxia and $CO_2$ retention.

As a result, tonsillectomy, with or without adenoidectomy (T&A), has become one of the most frequently performed surgeries in North America, with over 530,000 operations performed annually on children under age 15.[4] This paper discusses the significant impact of ATH on pediatric health and the frequent need for surgical intervention. It covers the immunophysiology, influence of atopy, community-based assessments prior to specialist referrals, and an overview of available medical and surgical treatment options. Additionally, it outlines general indications for referring patients to otolaryngology.

## Immunophysiology and Role of Atopy in Adenotonsillar Disease

The tonsils and adenoids, key components of the Waldeyer's ring, are central to immune defence in the aerodigestive tract.[5] Unlike other secondary lymphoid tissues, they lack afferent lymphatic vessels and are exposed directly to antigens via epithelial crypts that trap foreign materials, populated with immune cells like B and T lymphocytes, macrophages, and dendritic cells. This arrangement allows local and systemic immune responses by generating effector and memory lymphocytes. As children age, the immunological activity of these tissues gradually declines.

The specific role of atopy in ATH and associated disorders like OSA remains debated. Carr *et al.'s* study[6] using radioallergosorbent (RAST) tests, suggests that systemic atopy may not significantly influence ATH in pediatric sleep apnea, hinting at potential localized allergic reactions undetectable by systemic IgE assays. Costa *et al.*[7] found no direct link between atopy and ATH severity in mouth breathers, while Alexopoulos *et al.*[8] saw no significant correlation between eczema and either ATH or OSA prevalence, challenging the direct impact of atopy on these conditions.

In contrast, Cho *et al.*[9] provided evidence that local allergic reactions in adenotonsillar tissues might significantly contribute to ATH. They found that 68.6% of children had sensitization to at least one allergen in these tissues, higher than the 53.9% in serum, with inhalant allergens more common in adenoids and food allergens in tonsils. Children with local atopy also had a higher incidence of respiratory symptoms such as asthma and allergic rhinitis, highlighting the potential role of localized allergic inflammation in ATH and its symptoms. These findings illustrate the complex

relationship between atopic conditions and ATH, suggesting that localized immune responses in adenotonsillar tissues may be pivotal, requiring further focused research.

## Clinical Evaluation

The initial assessment of adenotonsillar disease primarily depends on a thorough history and physical examination, as polysomnography (PSG)—the gold standard for diagnosing OSA—is often not readily accessible. Clinicians should collect detailed histories to detect symptoms such as snoring, mouth breathing and hyponasal speech, indicative of upper airway obstruction. Physical examinations focus on signs of ATH and features such as adenoid facies, including an open mouth, elongated face, high-arched palate, and dental malocclusion, which develop from chronic mouth breathing in children with prolonged adenoid hypertrophy.

Due to PSG's limited availability, alternative diagnostics like overnight pulse oximetry, and parental audio and video recordings during sleep can be used. These help identify desaturation patterns and capture episodes of apnea, aiding in quicker diagnosis and management of OSA or adenotonsillar hypertrophy. Before performing tonsillectomy and adenoidectomy, PSG is recommended for those with sleep-disordered breathing, under age 2, or with contributing conditions such as obesity or craniofacial abnormalities.

Routine labs, blood biomarkers and most radiographic evaluations, including lateral neck radiographs, are not typically advised for screening OSA or ATH due to their limited utility. However, specific imaging might be necessary for children with anatomical risks (e.g., craniofacial abnormalities). Management will depend on severity of symptoms, physical examination, age, and comorbidities.

## Management Overview

Management of adenotonsillar disease and OSA in children entails both medical and surgical approaches, guided by the underlying cause. Acute adenotonsillar infections often require antibiotics effective against beta-lactamase-producing organisms, addressing symptoms through medication. Chronic conditions are generally managed surgically after other treatments fail.

For sleep-disordered breathing or confirmed OSA, anti-inflammatory treatments such as intranasal steroids and leukotriene receptor antagonists are used, targeting increased leukotriene activity noted in children with OSA. Studies demonstrate significant reductions in apnea-hypopnea index with treatments such as montelukast (from 9.2 to 4.2 events/hour),[10] and intranasal budesonide (from 3.7 to 1.3 events/hour).[11] There is no evidence for use of systemic steroids.[9] See **Table 1** for an overview of medical therapy.

Acute tonsillitis is managed with rapid strep antigen screening for accurate diagnosis, treating identified infections with penicillin or a clavulanic acid to combat beta-lactamase-producing pathogens.

Aside from medication, continuous positive airway pressure is the primary nonsurgical treatment for pediatric OSA. It involves delivering airway pressure through a mask to prevent airway obstruction, reduce sleep disturbances and ease breathing efforts. While adherence can be challenging, it can be improved with appropriate mask fitting, pressure adjustments and behavioural support interventions, such as desensitization or motivation enhancement programs led by specialists such as child psychologists or behavioural developmental pediatricians.[13]

Surgical interventions like tonsillectomy and adenoidectomy are generally reserved for recurrent infections or significant hypertrophy causing airway obstruction (see **Table 2** for general surgical indications and reasons for referral to otolaryngologist). T&A has shown significant improvements in behavioural and neurocognitive function, school performance and quality of life for up to 2 years post-surgery.[14]

Finally, environmental controls are imperative, including avoiding tobacco smoke, indoor pollutants and allergens to prevent airway issues. Weight loss is recommended for obese children with OSA but not for those with normal or low body weight. Overall, the approach to managing adenotonsillar disease and OSA involves a combination of targeted medical therapies and surgical intervention based on the severity of symptoms and underlying causes, with a focus on improving both nighttime and daytime clinical outcomes.

| Medication | Primary Indication | Usage Details | Key Considerations |
|---|---|---|---|
| **Intranasal Corticosteroids (INCS)** | Mild-to-moderate OSA with nasal obstruction<br><br>Adjunct or alternative to surgical intervention, or temporizing measure while awaiting other measures | Evaluate effectiveness after 4-6 weeks[13,15]<br><br>Consider long-term use if beneficial (up to 6 months if prompt improvement[15]) | Direct spray laterally inside the nostril to minimize contact with the nasal septum and reduce irritation. |
| **Montelukast (Singulair)** | | | Monitor for potential neuropsychiatric side effects, as outlined in medication warnings |
| **Combination Therapy** | Enhanced treatment effect for nasal obstruction and OSA | Follow individual medication guidelines; adjust based on therapeutic response | Combines the benefits of corticosteroids and montelukast for a synergistic effect on adenotonsillar reduction and symptom improvement |

**Table 1.** Medical therapy for mild-moderate adenotonsillar disease; *courtesy of Ivry Zagury-Orly, MD, MMSc and Jonathan MacLean, MD.*

| Surgery Type | Indication | Details and Specifics |
|---|---|---|
| **Tonsillectomy (with or without adenoidectomy)** | Obstructive sleep apnea (OSA) | First-line treatment for children over age 2 with adenotonsillar hypertrophy.[16] Associated with cardiovascular and cognitive morbidities if untreated.[17] |
| | Recurrent throat infection | Recommended for severely affected children (Paradise criteria[18]: ≥7 episodes in one year, ≥5 episodes in two years, or ≥3 episodes in three years), with each episode characterized by symptoms such as fever, cervical lymphadenopathy, tonsillar exudate, or positive culture for streptococci |
| | Peritonsillar abscess (PTA) | Recurrent PTA (>1) or severe recurrent pharyngitis in the context of a first episode of PTA, or persistent PTA (despite I&D)[19] |
| **Adenoidectomy alone** | Nasal obstruction | Indicated for severe obstruction due to adenoidal hypertrophy causing symptoms like mouth breathing and hyponasal speech. Moderate cases treated if symptoms present for ≥1 year unresponsive to conservative measures (i.e., 6-week trial of INCS).[15] |
| | Chronic sinusitis | Reasonable for children refractory to medical therapy, especially if considering endoscopic sinus surgery[20] |
| | Otitis media | Suggested in addition to tympanostomy tube (TT) placement for recurrent acute otitis media or chronic otitis media with effusion, who have previously had TT insertion. |

**Table 2.** Common indications for surgical adenotonsillar treatment and referral to otolaryngologist; *courtesy of Ivry Zagury-Orly, MD, MMSc and Jonathan MacLean, MD.*

## Conclusion

ATH not only impacts sleep quality in children but also affects their overall health and development, making timely and effective management crucial. This review underscores the importance of a comprehensive approach encompassing both medical and surgical strategies to address the multifaceted effects of ATH. By understanding the immunophysiology and exploring the role of atopy, as well as improving community-based assessments and referrals, clinicians can better identify and manage this prevalent condition. Surgical interventions such as tonsillectomy and adenoidectomy remain vital options, particularly in cases of significant obstruction or recurrent infections, demonstrating the need for tailored treatments based on individual patient characteristics and the severity of symptoms.

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## Financial Disclosures

**None declared.**

## References

1. Niedzielski A, Chmielik LP, Mielnik-Niedzielska G, et al. Adenoid hypertrophy in children: a narrative review of pathogenesis and clinical relevance. BMJ Paediatr Open. 2023;7(1):e001710.
2. Winkelmann A. Wilhelm von Waldeyer-Hartz (1836-1921): An anatomist who left his mark. Clin Anat N Y N. 2007;20(3):231-4.
3. Nelson R. Adenotonsillar disease has a detrimental effect on children's quality of life. The Lancet. 2002;360(9338):1002.
4. Hall MJ, Schwartzman A, Zhang J, et al. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. Natl Health Stat Rep. 2017;(102):1-15.
5. van Kempen MJ, Rijkers GT, Van Cauwenberge PB. The immune response in adenoids and tonsils. Int Arch Allergy Immunol. 2000;122(1):8-19.
6. Carr E, Obholzer R, Caulfield H. A prospective study to determine the incidence of atopy in children undergoing adenotonsillectomy for obstructive sleep apnea. Int J Pediatr Otorhinolaryngol. 2007;71(1):19-22.
7. Costa EC, Sabino HAC, Miura CS, et al. Atopy and adenotonsillar hypertrophy in mouth breathers from a reference center. Braz J Otorhinolaryngol. 2013;79(6):663-7.
8. Alexopoulos EI, Bizakis J, Gourgoulianis K, et al. Atopy does not affect the frequency of adenotonsillar hypertrophy and sleep apnoea in children who snore. Acta Paediatr. 2014;103(12):1239-43.
9. Cho KS, Kim SH, Hong SL, et al. Local atopy in childhood adenotonsillar hypertrophy. Am J Rhinol Allergy. 2018;32(3):160-6.
10. Kheirandish-Gozal L, Bandla HPR, Gozal D. Montelukast for children with obstructive sleep apnea: results of a double-blind, randomized, placebo-controlled trial. Ann Am Thorac Soc. 2016;13(10):1736-41.
11. Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. Pediatrics. 2008;122(1):e149-55.
12. Al-Ghamdi SA, Manoukian JJ, Morielli A, et al. Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy? The Laryngoscope. 1997;107(10):1382-7.
13. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130(3):e714-55.
14. Mitchell RB, Kelly J. Quality of life after adenotonsillectomy for SDB in children. Otolaryngol Head Neck Surg. 2005;133(4):569-72.
15. Zhang L, Mendoza-Sassi RA, César JA, et al. Intranasal corticosteroids for nasal airway obstruction in children with moderate to severe adenoidal hypertrophy. Cochrane Database Syst Rev. 2008;2008(3):CD006286.
16. Mitchell RB, Archer SM, Ishman SL, et al. Clinical Practice Guideline: Tonsillectomy in Children (Update). Otolaryngol Head Neck Surg. 2019;160(1_suppl):S1-S42.
17. Guilleminault C, Khramsov A, Stoohs RA, et al. Abnormal blood pressure in prepubertal children with sleep-disordered breathing. Pediatr Res. 2004;55(1):76-84.
18. Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. N Engl J Med. 1984;310(11):674-83.
19. Schraff S, McGinn JD, Derkay CS. Peritonsillar abscess in children: a 10-year review of diagnosis and management. Int J Pediatr Otorhinolaryngol. 2001;57(3):213-8.
20. Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2014;151(4):542-53.

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* Clinical significance is unknown.

**References: 1.** DUPIXENT® Product Monograph, sanofi-aventis Canada Inc., July 12, 2023. **2.** Data on file, sanofi-aventis Canada Inc., September 1, 2023.



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# Abstract Presentation Highlights from the 2024 EAACI Annual Meeting

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**Paul Keith, MD**

## Introduction

Many oral abstracts, posters and case reports were presented at The European Academy of Allergy and Clinical Immunology (EAACI) Annual Meeting which was held in June 2024 in Valencia, Spain. We have selected the following 13 articles due to their relevance to Canadian allergy and immunology clinical practice and research.

## Long-term efficacy and safety of remibrutinib in patients with chronic spontaneous urticaria in the phase 3 REMIX-1 and REMIX-2 studies

***Metz, M et al. (2024, June).***
***Presented as a late-breaking oral abstract.***

Despite treatment with up-dosing of second-generation antihistamines, up to 4 times the standard dose, 75% of patients will experience no or only partial relief. Remibrutinib is a novel, highly selective oral bruton tyrosine kinase (BTK) inhibitor, which inhibits activation of human masT-cells and basophils, and the production of IgG autoantibodies against IgE or the high affinity IgE receptor. Metz M demonstrated the long-term (52-week) efficacy and safety of remibrutinib 25 mg po bid vs placebo for patients with at least 6 months of chronic spontaneous urticaria (CSU), uncontrolled on H1-antihistamines (H1-AH).[1] REMIX-1 and REMIX-2 were identically designed global, multicentre, randomized, double-blind, placebo-controlled (DBPC) Phase 3 studies. Remibrutinib demonstrated statistically significant superiority in both primary endpoints [urticaria activity score (UAS7) and the itch severity and hive severity scores (ISS7/HSS7) at week 12]. REMIX-1 included 470 adult participants, while REMIX-2 had 455 adult participants.

### Key Takeaways:

1. ***Rapid Onset of Action:*** Symptom improvement was observed as early as one week after treatment initiation. Significantly more patients achieved well-controlled disease (UAS<6) with remibrutinib vs placebo at Weeks 2, 12 and 24. Approximately 30% of patients achieved complete response (UAS7=0) with remibrutinib vs 10% of those on placebo at Week 12. Patients who switched from placebo to remibrutinib at Week 24 also showed significant symptom improvement within the first week after switching.

2. ***Sustained Efficacy:*** Patients treated with remibrutinib experienced significant improvements in weekly urticaria activity scores (UAS7) through Week 52. By Week 52, almost half of the patients achieved complete relief from itch and hives (UAS7 score of 0).

3. ***Safety Profile:*** Adverse events were balanced between remibrutinib and placebo during the treatment period with a consistent safety record over the 52 weeks. Petechiae were more common in remibrutinib vs placebo, but all cases were mild-to-moderate without clinically significant platelet decreases. Newly occurring liver transaminase elevations were infrequent and balanced between the treatment and placebo groups. No serious adverse events were related to study medication.

**Key Takeaways:**

Remibrutinib is a new oral treatment for CSU where improvements occurred as early as Week 1, and sustained relief was noted over 52 weeks of treatment. There was overall favourable safety and tolerability with no increase in adverse events up to 52 weeks. Remibrutinib may be especially helpful in individuals with low total IgE and autoantibodies, where omalizumab is less efficacious. These results support remibrutinib's potential as a new, effective, fast-acting oral treatment option for CSU patients uncontrolled by first-line H1-antihistamines.

## Dupilumab improves urticaria activity, health-related quality of life, and disease perception and severity in patients with CSU: results from the LIBERTY-CSU CUPID A study

***Maurer, M (2024, June).***

This study evaluated the efficacy and safety of dupilumab in patients with CSU unresponsive to H1-AH. The study design was a DBPC trial including 138 patients (70 dupilumab, 68 placebo) aged six years and older, diagnosed with CSU for over six months, and symptomatic despite standard H1-AH treatment.[2] Participants were omalizumab-naive and were excluded if they had active atopic dermatitis (AD). There was a 24-week treatment period with dupilumab vs placebo and 12 weeks of post-treatment follow-up. The primary and key secondary outcomes were the change in baseline at week 24 of UAS7 and ISS7 respectively.[2]

**Key Takeaways:**

1. ***Reduction in urticaria activity (efficacy):*** A higher proportion of patients treated with dupilumab achieved well-controlled urticaria (UAS7 ≤6) and urticaria-free status (UAS7 = 0) from Week 1 to Week 36.
2. ***Symptom Improvement:*** Dupilumab effectively reduced the severity of itch and hives, as measured by the Urticaria Activity Score over seven days (UAS7) and the Itch Severity Score (ISS7) at Week 24. Improvements persisted through the 12-week post-treatment follow-up, indicating sustained efficacy even after discontinuing dupilumab.
3. ***Health-Related Quality of Life:*** Patients experienced significant improvements in health-related quality of life and disease perception.
4. ***Safety/Adverse Events:*** Dupilumab was well-tolerated with a safety profile consistent with that of previous studies. Treatment-emergent adverse events (TEAEs) were similar between the dupilumab (54.3%) and placebo (58.8%) groups. Serious adverse events (SAEs) were lower in the dupilumab group (2.9%) compared to placebo (7.4%). Injection site reactions were the most common adverse events, and were generally mild and more frequent in the dupilumab group. Of note, no dupilumab-treated patients reported conjunctivitis.

**Key Takeaways:**

The LIBERTY-CSU CUPID A Study provides evidence supporting dupilumab as an effective and well-tolerated treatment for CSU patients unresponsive to H1-AH therapy. These findings show that dupilumab has the potential to improve disease control and quality of life for CSU patients and may be a valuable therapeutic addition for managing CSU in both adults and children. There was also sustained efficacy over the 12-week follow-up when dupilumab was discontinued.

Another presentation at EAACI 2024 reported on the "Efficacy and Safety of Therapy with Omalizumab in Children with Chronic Spontaneous Urticaria."[3] The study was a retrospective and observational analysis. It included 235 CSU patients, with a subset of 26 patients aged under 12 (range 4 to 11 years) treated with at least three omalizumab injections over an average

treatment duration of 3.4 months. Most patients (98.7%) responded to omalizumab treatment by the end of week 12. A total of 91.1% achieved a complete response (CR), indicating no symptoms of urticaria. Omalizumab was also well-tolerated among pediatric patients with no serious adverse events related to the treatment.

### Key Takeaways:

This study demonstrated that omalizumab is a safe and effective treatment option for CSU in children, including those under 12 years of age. It supported the addition of omalizumab to the treatment regimen for pediatric CSU patients who do not respond adequately to antihistamines.

## Patients With moderate-to-severe asthma treated with dupilumab are more likely to meet clinical remission criteria: results from the VESTIGE trial

***Lugogo, NL (2024, June).***

VESTIGE, a Phase 4 clinical trial, included 109 adult patients aged 21 to 70 years with uncontrolled moderate-to-severe asthma and increased Type 2 biomarkers. Patients were randomized 2:1 to receive 300 mg of dupilumab (n=72) or matched placebo (n=37) every two weeks for 24 weeks.

The VESTIGE study evaluated several key endpoints. The primary endpoint was the proportion of patients achieving clinical remission, as defined by meeting all four specified criteria, at Week 24. Additionally, the study assessed changes from baseline over time in three important measures: Fractional Exhaled Nitric Oxide (FeNO) levels, Asthma Control Questionnaire-7 (ACQ-7) scores, and pre-bronchodilator Forced Expiratory Volume in 1 second ($FEV_1$), to provide a more comprehensive assessment of treatment efficacy.

In this study, remission was defined by four specific criteria that patients needed to meet over a 24-week period. First, patients had to experience no severe asthma exacerbations during the entire study duration. Second, they were required to abstain from using systemic corticosteroids throughout the 24 weeks. Third, patients needed to achieve an Asthma Control Questionnaire-5 (ACQ-5) score below 1.5 at Week 24. Last, they had to demonstrate either a pre-bronchodilator percentage predicted $FEV_1$ greater than 80% at Week 24 or show an improvement from baseline in pre-bronchodilator $FEV_1$ of more than 100 mL at Week 24. The results at the 6-month mark revealed that patients receiving dupilumab were significantly more likely to meet clinical remission criteria, with 38.9% achieving remission compared to 18.9% in the placebo group.

### Additional VESTIGE endpoints:

1. ***Reduction in airway inflammation:*** 56.9% of patients treated with dupilumab achieved a significant reduction in airway inflammation measured by fractional exhaled nitric oxide (FeNO) <25 parts per billion (ppb) compared to 10.8% of patients on placebo (P <0.001).
2. ***Mucus reduction:*** Dupilumab led to numerically more significant decreases in mucus plug scores and volume than placebo. The difference in mucus scores (range 0 to 20) between dupilumab and placebo was -4.9 (P<0.001).
3. ***Notable improvement in lung function:*** Patients treated with dupilumab showed numerically greater improvements in lung function from baseline compared to placebo as defined by airway volumes and airway resistance at total lung capacity.
4. ***Safety profile:*** The safety results were consistent with the known safety profile of dupilumab in moderate-to-severe asthma.

### Key Takeaways:

Clinical remission has emerged as an important outcome in asthma treatment. These results affirm that dupilumab leads to significant improvements in airway inflammation, mucus plugging, and lung function, and demonstrate that patients on dupilumab are more likely to meet clinical remission criteria for moderate-to-severe asthma.

## Dupilumab reduces FeNO levels and exacerbations and improves asthma control with inhaled corticosteroid withdrawal: A Phase 2 study.

***Soliman, M. (2024, June).***

The objective of the study was to assess the impact of withdrawing inhaled corticosteroids and long-acting beta-agonists (ICS-LABA) on exacerbations, asthma control, and fractional exhaled nitric oxide (FeNO) levels in adults treated with dupilumab who had a baseline blood eosinophil count ≥300 cells/μL, a key indicator of eosinophilic inflammation in asthma. The interventions in Phase 2a were: dupilumab 300 mg weekly and for Phase 2: dupilumab 300 mg every two weeks. Both studies lasted 12 weeks. In the last 3 weeks, patients were on no ICS-LABA.

### Key Takeaways:

1. ***Exacerbation Reduction:*** In Phase 2a, there was a substantial 60% reduction in severe exacerbations compared to placebo (adjusted annualized severe exacerbation rate relative risk: 0.39, 95% CI: 0.18-0.88). In Phase 2, this reduction was even more pronounced, with a 75% decrease in severe exacerbations compared to placebo. These results provide strong evidence of the drug's effectiveness in reducing severe exacerbations (adjusted annualized severe exacerbation rate relative risk: 0.62, 95% CI: 0.22-1.76).

2. ***Asthma Control:*** By Week 12, patients treated with dupilumab showed a significant improvement in ACQ-5 scores vs placebo in both Phase 2 and 2a studies.

3. ***FeNO Levels:*** In Phase 2 and 2a studies, at Week 12, dupilumab-treated patients demonstrated a more significant decrease in FeNO levels from baseline compared to placebo.

### Key Takeaways:

Dupilumab effectively reduces severe exacerbations, improves asthma control, and decreases FeNO levels, even after the withdrawal of ICS-LABA treatment, a common practice among patients. Longer term studies of ICS-LABA tapering/withdrawal are required.

### Summary

Promising new therapies for adults and children are emerging for CSU, a prevalent condition with significant impacts on quality of life.

Clinical remission, a controversial term, has been increasingly adopted as a goal of therapy in many disease states. A significant proportion of moderate-to-severe asthmatics on dupilumab met predefined criteria for remission compared to placebo. The benefits of dupilumab were maintained over 12 weeks, in spite of ICS-LABA withdrawal in the latter treatment period.

## Efficacy and safety of epicutaneous immunotherapy (EPIT) for peanut allergy in subjects aged 1-3 with and without atopic dermatitis in the EPITOPE study.

***Scurlock, M. et al. (2023).***

In a follow-up to Greenhawt et al's NEJM publication on epicutaneous immunotherapy (EPIT), Scurlock *et al.* continue the work on peanut transdermal immunotherapy. In this Phase 3, DBPC trial, 362 children aged 1–3 were treated over 1 year (in a 2:1 ratio drug: placebo) to a maximum dose of 250 mcg of peanut EPIT.[6] All children received entry peanut Double-blind, placebo-controlled food challenge (DBPCFC) with a repeat challenge at the end of 1 year of EPIT. Treatment responders fell into 2 groups. Group A, with eliciting peanut protein dose of anaphylaxis less than 10 mg; and Group B, with eliciting peanut protein doses of anaphylaxis between 10 mg and 300 mg. Unique to this publication was AD as a variable both for safety and efficacy. There were 4 times more toddlers with AD than without AD. Treatment responder rates after 12 months of EPIT were similar in the AD and non-AD group, with a slightly greater risk difference in the AD group (**Figure 1**). There was no change in SCORAD over time regardless of treatment group or AD status. There was no difference in safety in either the AD or non-AD groups.

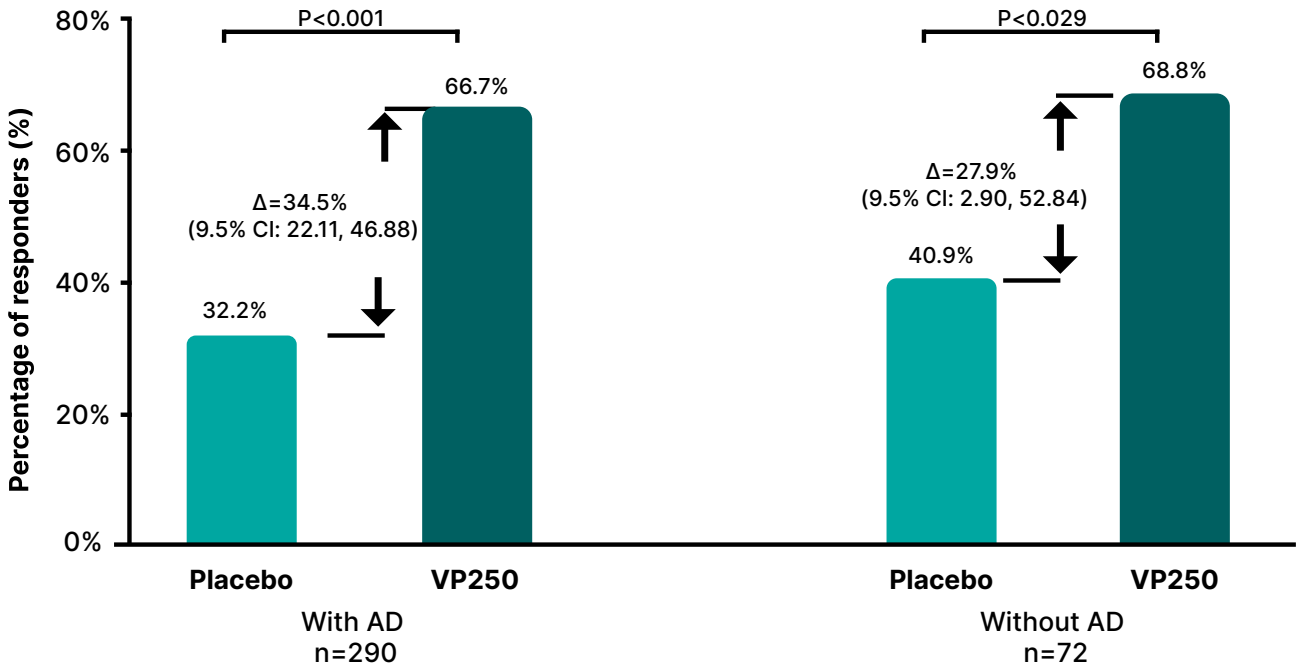


**Figure 1.** Treatment responder rates at month 12 DBPCFC; *adapted from Scurlock, M. et al., 2023; from abstract at EAACI Congress 2024, Valencia, Spain.*

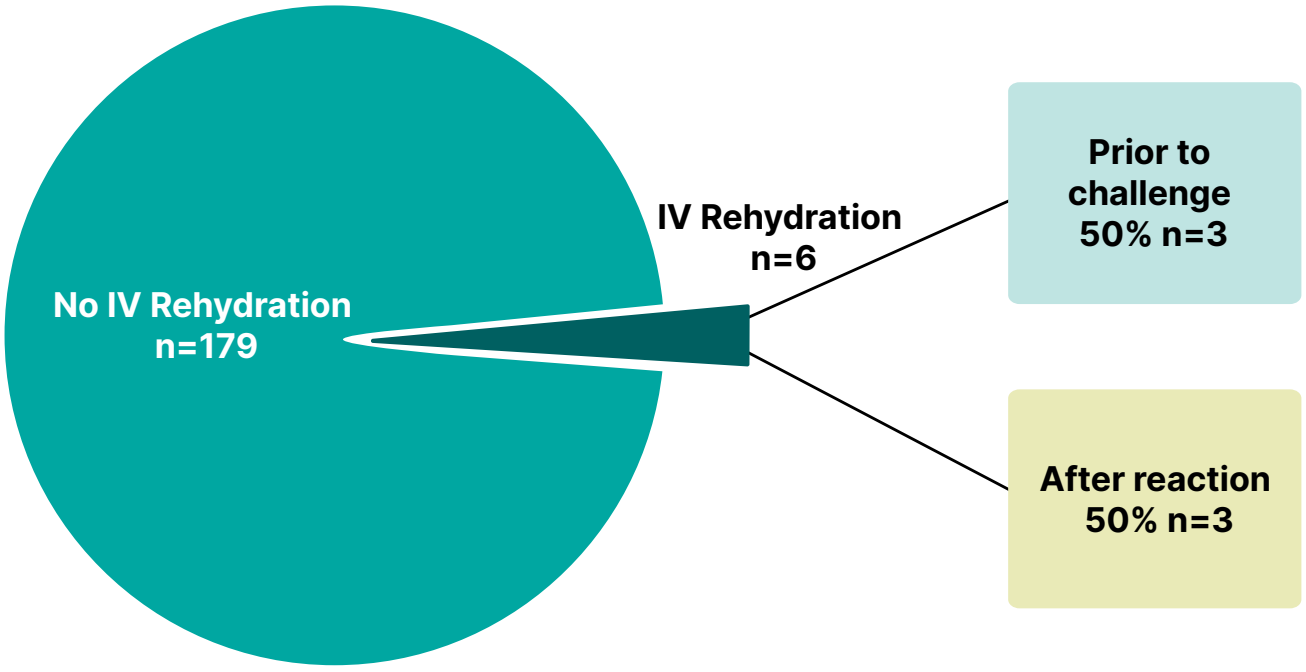


**Figure 2.** IV placement in patients treated with IV rehydration; *adapted from Patel, G. et al., 2023; from abstract at EAACI Congress 2024, Valencia, Spain.*

### Key Takeaways:

Early peanut EPIT for toddlers is a safe and effective form of immunotherapy with peanut allergy and signifies a future alternative to oral immunotherapy (OIT). AD, a common co-morbidity in this group of early peanut allergic toddlers, was more commonly represented, but unaffected throughout the EPIT treatment program. EPIT will likely become an impactful and safe go-to form of immunotherapy for peanut-sensitized toddlers in our community.

## Intravenous access is rarely necessary in food protein-induced enterocolitis syndrome oral food challenges

***Patel, G et al. (2023).***

In this 12-year retrospective chart review of 185 pediatric food protein-induced enterocolitis syndrome (FPIES) patients, the authors from UT Southwestern Medical Center reviewed the frequency, and utilization of intravenous (IV) access in children undergoing FPIES challenges.[7] In 44 of the patients, IV was established before their ondansetron delivery. Positive FPIES reactions occurred in 29 (16%) of patients. IV access for either ondansetron delivery (6/29) or fluids and ondansetron in (6/29) was utilized. The remaining (17/29) positive FPIES challenges were treated with oral or intramuscular (IM) ondansetron and oral fluids or no intervention at all. IV access was established in 3/6 patients before the oral challenge (OC) and 3/6 patients after symptom development (**Figure 2**). No ER transfers were needed. Variable foods were challenged. The low amount of IV usage (3%) from the initial 44/185 IV pre-OC preparation suggests that FPIES challenges in children are generally safe and can be managed without IV and need for ER transfer.

### Key Takeaways:

For clinicians who diagnose and follow children with FPIES, this retrospective review on the safety of overseeing FPIES challenges without IV access is reassuring and confirms that the overwhelming majority of FPIES challenges may continue safely in the community.

## Dupilumab improves histologic, symptomatic and endoscopic outcomes in children with eosinophilic esophagitis in the EoE KIDS study, regardless of history of elimination diet or concomitant food allergy

***Spergel, J et al.(2024).***

The KIDS study involved children with EoE aged 1–12 years, randomized to either dupilumab or placebo for 16 weeks extending to 1 year on open label dupilumab dosed by weight.[8] The primary outcome was histological changes/regression of eosinophils less than 6/hpf. Observations compared children in both groups who maintained food elimination diet or had a history of concomitant food allergy. Dosing in this pediatric EoE trial was reduced to alternate weeks in children between 15–30 kg (200 mg) and also alternate weeks between 30 to 40 kg, (300 mg) as compared to those above 40 kg, adopting the weekly adult dosing (300 mg). Dupilumab improved both groups of children with EoE, although a higher proportion of children were found with histologic remission by 52 weeks in the co-treated food elimination diet cohort (**Figure 3**).

### Key Takeaways:

Having alternate week dosing regimens in the management of pediatric EoE population is highly welcomed along with the reassurances that dupilumab is effective even in those children/families who find food elimination diets prohibitive.

## Pregnancy in hereditary angioedema: a single centre experience

***Tan, KL. et al. Frimley Park, UK; EAACI 2024***

Hormonal factors, including estrogen, have been associated with exacerbations for hereditary angioedema (HAE); however, the impact of pregnancy has not been reported on specifically as a risk factor within the HAE community. A United Kingdom Allergy Group performed a 65-year review at their immunology center in addition to a literature search to determine whether pregnancy is a trigger for HAE attacks.[9,10] Despite the small sample size, approximate 70% of patients reported their pregnancies were either “better” or “similar” to their pre-pregnancy

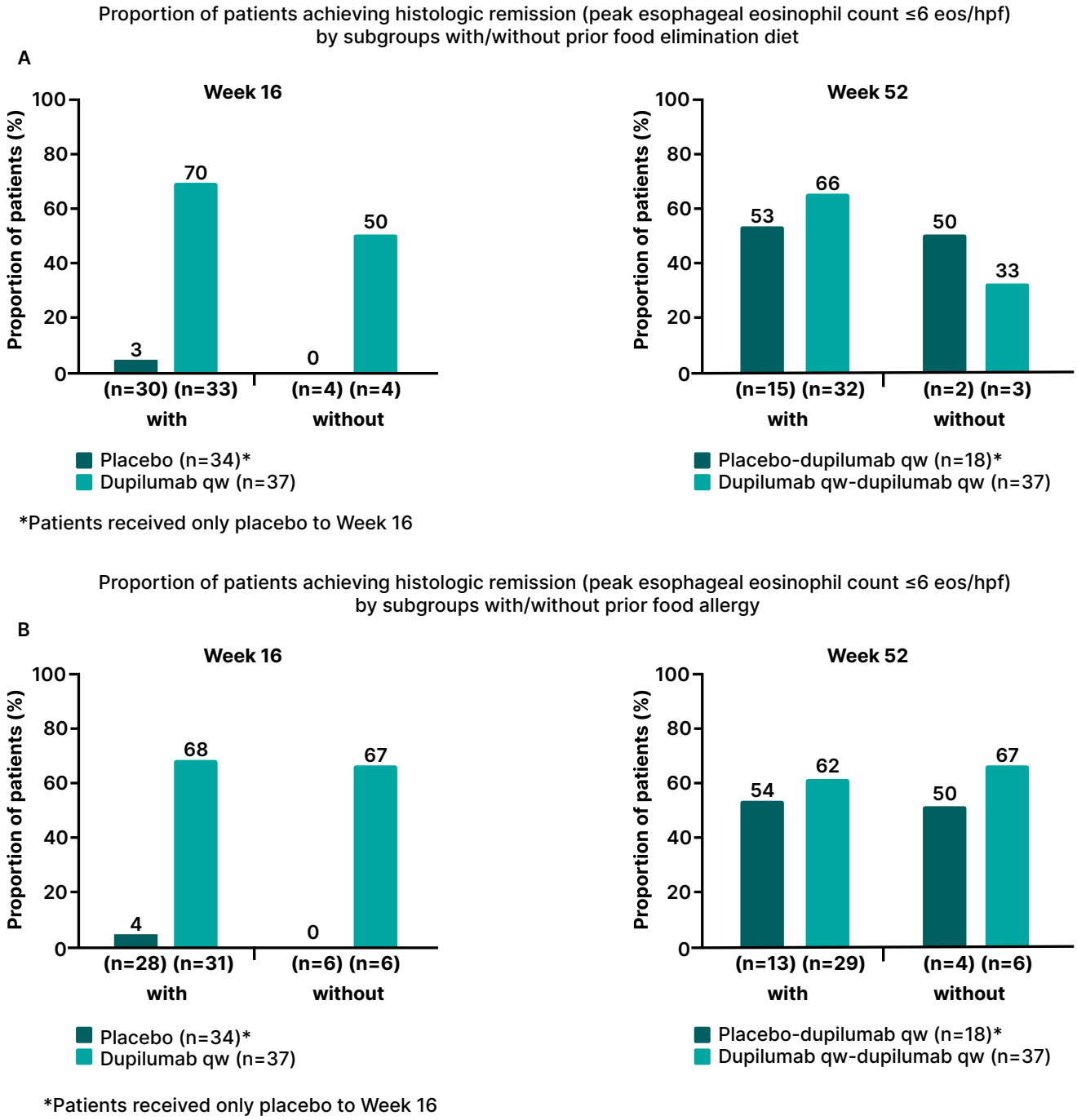


**Figure 3.** Improvements in achieving histologic remission (peak esophageal eosinophil count ≤6 eos/hpf) were observed in patient subgroups treated with dupilumab HE vs placebo regardless of history of **(A)** food elimination diet or **(B)** food allergy, with efficacy maintained to Week 52, and improvements observed in patients who switched from placebo to dupilmab HE at Week 16.; *adapted from Spergel, J. et al., 2024; from abstract at EAACI Congress 2024, Valencia, Spain.*

**17 pregnancies**  **7 patients**

**Timeframe: 1957–2022**

| Symptoms compared to pre-pregnancy baseline | Percentage (%) |
|---|---|
| Better | 53 |
| Similar | 17.6 |
| Worse | 29.4 |

**Common affected sites: Abdomen and extremities**

**Figure 4.** Pregnancy in hereditary angioedema: a single centre experience; *adapted from Tan, KL. et al.; from abstract at EAACI Congress 2024, Valencia, Spain.*

HAE state. Furthermore, vaginal delivery was not identified as a trigger for a HAE attack. Vaginal deliveries were pre-treated with prophylactic C1-esterase inhibitor in 1 out of every 4 deliveries; the remainder without prophylaxis or treatment. Six months post-delivery, patients stated that they had returned to their pre-pregnancy baseline of HAE activity (**Figure 4**).

### Key Takeaways:

In this small but important cohort of patients with HAE, pregnancy was not found to increase the risk of HAE activity, including vaginal delivery. The hormonal changes of pregnancy do not appear to increase HAE attacks in the majority of females with HAE.

## A randomized trial of penicillin skin testing versus direct challenge in pregnancy

### *Mustafa, SS et al., Rochester NY; EAACI, 2024*

Pregnant women with a history of penicillin allergy have been increasingly evaluated for their penicillin allergy during pregnancy to increase their eligibility for amino-penicillin treatment if they are Group B streptococcus (GBS) positive at delivery. Over the last few years, an increasing number of publications have cited the safety of both skin testing (ST) and direct challenges (DC) during pregnancy. The authors of this trial randomized mothers with a history of cutaneous only, GI or unknown reactions to penicillin allergy greater than 5 years to either (A) ST followed by amino-penicillin in-office challenge or (B) DC to amino-penicillin without ST. The patients selected were considered "low risk" for true penicillin allergy. Total consulting time was measured for both groups. A total of 64 pregnant patients were evaluated at a mean age of 28 weeks and 24 weeks' gestation in the ST vs DC group, respectively. Four of 35 ST group were identified as positive; they did not proceed to amino-penicillin challenge. None of the 29 DC patients reacted to amoxicillin at 40 mg and 400 mg dosing followed by a 30-minute observational period. An average savings of 6 minutes was identified in the DC group (**Figure 5**).[11,12]

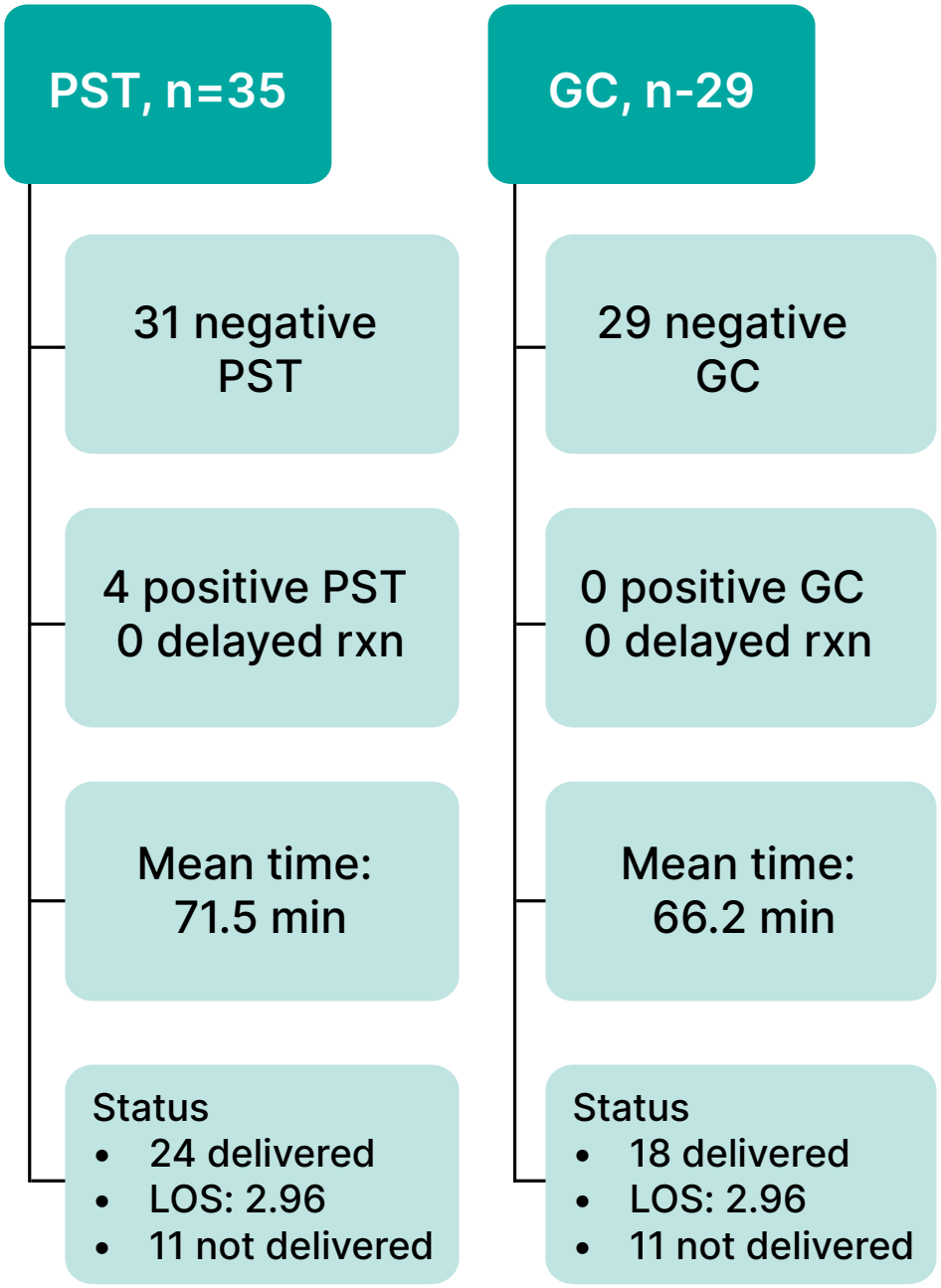


**Figure 5.** Penicillin skin testing and graded challenge results; *adapted from Mustafa, SS et al.; from abstract at EAACI Congress 2024, Valencia, Spain.*

**Abbreviations: PST:** penicillin skin testing, **GC:** graded challenge, **LOS:** length of stay

**Key Takeaways:**

De-labelling of penicillin allergy is increasing in the pregnancy population. Identifying pregnant patients who are low risk allowed for safe direct challenge, without skin testing. Skin testing remains an option for this population as well, followed by a DC to ensure full tolerance of amino-penicillins. The ability to ensure pregnant patients are offered complete treatment for GBS carriage through de-labelling of penicillin allergy is now a practice that community allergists should embrace to aid our obstetrical colleagues.

## Sublingual immunotherapy (SLIT) for allergic rhinitis. The SQ House dust mite SLIT-tablet is effective and well-tolerated in children (5–11 years) with house dust mite allergic rhinitis/rhinoconjunctivitis – results from a global phase III clinical trial (MT-12).

***An oral presentation by Dr. Antje Schuster***

House dust mites (HDM) are a prominent cause of inhalant allergy and the burden of HDM allergic rhinitis (AR) is often hidden. The efficacy and safety of the HDM SLIT tablet (12 SQ HDM dose) for the treatment of HDM AR has been demonstrated in phase III clinical trials in adults and adolescents.

The objective of the study was to demonstrate efficacy and safety of the HDM SLIT tablet (12 SQ HDM dose) over 1 year of therapy vs placebo in children (5–11 years) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C), with or without asthma. Subjects had high symptom and medication scores and normal lung function; 38% had concomitant asthma. A total of 52% of the children were polysensitized.

**Key Takeaways:**

1. Study participants showed 22% improvement in the total combined rhinitis score which combines rhinitis symptom scores and medication reduction scores vs placebo (P<0.0001).
2. The onset of effect of symptom improvement was demonstrated after only 8 weeks of therapy (P=0.011).
3. Statistically significant improvements were seen in rhinitis symptom scores, need for rhinitis medication scores, and quality of life questionnaire scores, further confirming the efficacy of the treatment.
4. 95% of subjects completed the trial.

The majority of treatment-related adverse events were transient local application site reactions that were mild or moderate in severity, and few subjects discontinued treatment due to adverse events.

The safety profile of the 12-SQ HDM dose was similar to that of the already established safety profile in adolescents and adults with HDM AR/C. The 12-SQ HDM SLIT-tablet was well-tolerated and had a favourable safety profile in children with HDM AR/C with and without asthma.

## The SQ tree SLIT-tablet is effective and well-tolerated during the tree pollen season (birch homologous group) in children (5-17 years) – results from a global phase III clinical trial (TT-06)

***An oral presentation by Dr. Monika Gappa***

The prevalence of birch/tree pollen sensitization causing nasal and ocular symptoms increases through childhood. Pollen allergies can significantly impair quality of life. Sleep quality, daily activities (e.g., sports/outdoor activities) and school attendance can all suffer.

The SQ tree SLIT-tablet has previously been demonstrated as efficacious and safe in the TT-04 phase III trial including adults (n=574) and adolescents (n=60) with tree pollen allergy.

The objective of this study was to demonstrate efficacy and safety of the SQ tree SLIT-tablet (12 SQ-Bet dose) in children (5–17 years) with moderate-to-severe ARC-induced by pollen from birch and trees belonging to the birch homologous group.

### Key takeaways:

1. 94% of 952 children aged 5–17 with moderate-to-severe tree pollen allergic rhinitis/conjunctivitis with and without asthma completed the trial.
2. There was a 22% improvement in total combined score (combining symptom score with medication reduction score) during the birch pollen season vs placebo (P=0.0004).
3. Daily symptom scores, medication scores and quality of live questionnaire scores all significantly improved, further supporting the efficacy of the SLIT-tablet.
4. The SQ tree SLIT tablet was generally well-tolerated and had a favourable safety profile in children with tree pollen AR/C with or without asthma, similar to the already established safety profile in adults.

## Rilzabrutinib reduces IgG anti-thyroid peroxidase (anti-TPO), soluble mas-related G protein-coupled receptor X2 (sMRGPRX2) and eosinophils at 12 weeks in patients with chronic spontaneous urticaria

***An oral presentation by Dr. Marcus Maurer***

Chronic spontaneous urticaria (CSU) is a common immunologic skin disease. Bruton's tyrosine kinase (BTK), expressed in B-cells, masT-cells and other immune cells, plays a critical role in immune-mediated diseases. Rilzabrutinib (SAR444671), an oral reversible covalent BTK inhibitor, was administered for a 12-week period of the RILECSU Phase 2 study evaluating the efficacy and safety of the drug in adults with moderate-to-severe CSU not adequately controlled with antihistamines.

### Key takeaways:

Serum levels of IgG anti-TPO autoantibodies, sMRGPRX2 (a masT-cell receptor), and blood eosinophils were all reduced with rilzabrutinib 400 mg TID treatment compared with placebo over 12 weeks; however, there was no change in total serum IgE levels. Reduction of these biomarkers aligned with the clinical efficacy results. The effect of various therapies on a variety of biomarkers in CSU may help clinicians better understand the cause of this common condition.

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## References

1. Metz, M. Long-term efficacy and safety of remibrutinib in patients with chronic spontaneous urticaria in the Phase 3 REMIX-1 and REMIX-2 studies. Presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024, Valencia, Spain.
2. Maurer, M. Dupilumab improves urticaria activity, health-related quality of life, and disease perception and severity in patients with CSU: results from the LIBERTY-CSU CUPID A study. Presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024, Valencia, Spain.
3. Galimova, A. Efficacy and safety of therapy with omalizumab in children with chronic spontaneous urticaria. Presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024, Valencia, Spain.
4. Lugogo, NL. Patients with moderate-to-severe asthma treated with dupilumab are more likely to meet clinical remission criteria: results from the VESTIGE trial presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024, Valencia, Spain.
5. Soliman, M. Dupilumab reduces FeNO levels and exacerbations and improves asthma control with inhaled corticosteroid withdrawal: a phase 2 study. Presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024, Valencia, Spain.
6. Greenhawt M, Sindher SB, Wang J, et al. Phase 3 trial of epicutaneous immunotherapy in toddlers with peanut allergy. N Engl J Med. 2023;388:1755-66.
7. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-workgroup report of the adverse reactions to foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2017 Apr;139(4):1111-26.e4.
8. Chehade M, Dellon ES, Spergel JM, et al. Dupilumab for eosinophilic esophagitis in patients 1 to 11 years of age. N Engl J Med. 2024 Jun 27;390(24):2239-51.
9. Riedl MA. Hereditary angioedema during pregnancy: considerations in management. Immunol Allergy Clin North Am. 2023 Feb;43(1):145-57.
10. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update, Allergy. 2022 Jul;77(7):1961-90.
11. Atkinson A, Poliquin V, Elwood C. Penicillin allergy de-labelling in pregnancy CMAJ. 2023 Mar 27;195(12):E452-53.
12. Blumenthal KG, Shenoy E. Penicillin allergy in pregnancy. JAMA. 2020 Mar 24;323(12):1216.

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# Allergen Immunotherapy and Atopic Dermatitis: Updated Guidance

**Derek K. Chu, MD**

## Introduction

Atopic dermatitis (AD), also commonly referred to as atopic eczema, is the most common chronic inflammatory skin disease. Research over the past 30 years has revealed that it affects approximately 13% of children and 7% of adults worldwide.[1,2] Among the growing number of treatment options for AD, the role of allergy to aeroallergens, such as house dust mite (HDM) pollens or animal dander, in driving this condition has remained uncertain for a long time. Consequently, so too has been the therapeutic role of allergen immunotherapy (AIT) for AD. The American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force (JTF) on Practice Parameters recently updated their AD guidelines.[3] This update included a systematic review of the effectiveness and safety of AIT, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) versus no AIT for patients with AD.[4] This article summarizes the systematic review findings, guideline update, and future directions.

## Evidence

The previous practice parameter noted that AIT could be effective for treating AD. This guideline's linked systematic review evaluated 23 randomized controlled trials (RCTs; 11 SCIT trials and 12 SLIT trials) that included 1,957 adult and pediatric patients, with a median of study mean ages of 19 years, and a range of means of 4–34 years,[4] with, on average, a mostly baseline moderate-to-severe AD, with a median on the SCORing Atopic Dermatitis [SCORAD] scale[5] of 42, [0–103, indicating higher worse; a corresponding higher end of moderate severity using EASI being roughly 20], and a range of means of 12–64 (i.e. upper end of mild disease to middle range of severe disease, or roughly an EASI of 7 to 40). **Figure 1** presents the graphical abstract.

SCIT and SLIT comprised an approximately equal proportion of the included RCTs. Most studies focused on desensitized patients to HDMs; specifically, *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*. whereas 4 of the studies also included other inhaled allergens (e.g. pollens). Patients were mostly treated with standard topical therapy including topical corticosteroids and moisturizers with AIT added to the standard topical

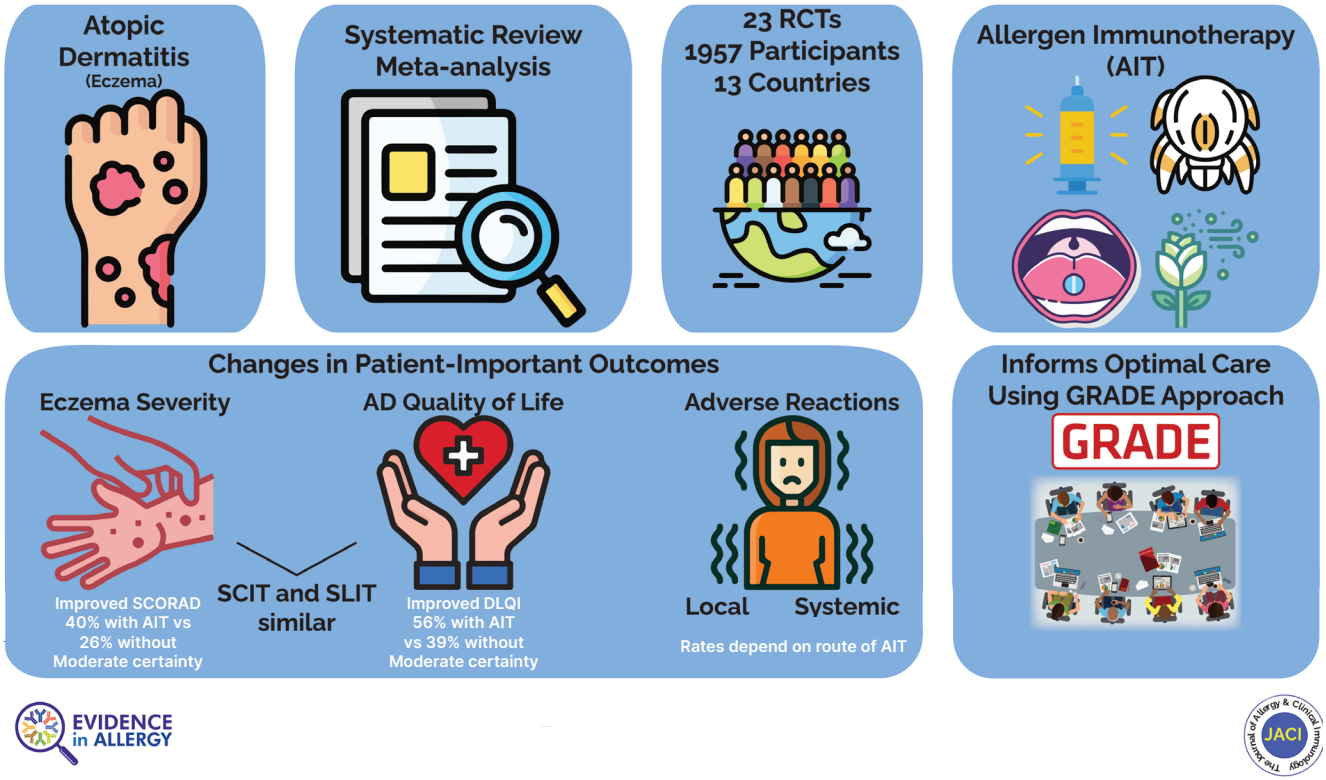


**Figure 1.** Systematic review and meta-analysis: allergen immunotherapy and atopic dermatitis; *reproduced with permission from Yepes-Nuñez JJ, et al. 2022.*

therapy. Furthermore, most studies included polysensitized patients in addition to those sensitized to HDMs. The studies added either AIT or no AIT (e.g. placebo) to standard care with topical treatments. AIT was administered for a median (range) of mean duration among studies of 12 (3–36) months. The trials were conducted in 13 countries across 4 continents (Asia, Europe, North America, and South America).

Based on a combination of clinician- and patient-reported AD severity (SCORAD), AIT likely improved AD severity by 50% or more from baseline compared with no AIT (40% with AIT vs 26% without AIT), with similar estimates of effect for SCIT and SLIT. AIT also likely improves quality of life (56% with AIT vs 39% without AIT, with a relative risk of 1.44 [95% confidence interval, 1.03-2.01], indicating a moderate certainty of evidence). Crude estimates of the median time-to-effect were 5 (range 1–12) months, and effects sustained over the duration of follow up stated above. The main adverse effects for this therapy were similar to those of AIT for allergic rhinitis and asthma, which are often transient.[6-10] In terms of common adverse reactions to AIT, which are also transient and usually minor, SCIT tends to increase local injection site reactions (mean of 66% of individuals) and SLIT tends to increase oropharyngeal itching (mean of 13% of individuals). Less common though more serious systemic reactions, or those severe enough to cause discontinuation of treatment, occurred in approximately 10% of those receiving SCIT, and rarely occurred in those receiving SLIT (0.14% of patients with a systemic reaction, 1.2% of patients discontinued SLIT).

Subgroup and sensitivity analyses were conducted using various statistical approaches to demonstrate that the results were consistent with the main findings. These variables included stratification by age, duration of AIT, the country where the study was conducted, the species of dust mite the patient was desensitized to, and whether the AIT was targeted at a monoallergen or a multiallergen, among others.

## Mechanism

Allergens, such as HDM, may drive both innate and adaptive inflammatory processes and contribute to epidermal barrier disruption (e.g., intrinsic allergen enzymatic activity). These mechanisms stimulate the production of multiple cytokines including interleukin (IL)-4 and IL-13 from T-cells and local production of thymic stromal lymphopoietin (TSLP), IL-25, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) to collectively promote skin inflammation and itch.[11-13] Conversely, AIT works through several mechanisms including induction of IL-10 production by innate cells, epithelial repair, and modulation of the Janus Kinase Signal Transducer and Activator of Transcription (JAK-STAT) pathway. These mechanisms, along with other multiple anti-inflammatory, immunomodulatory, and protolerogenic effects, might explain the clinical benefits observed in the meta-analysis.[14-16]

## Updated Guidelines

The JTF on Practice Parameters of the AAAAI and the ACAAI released updated guidelines for AD in December 2023.[3] The multidisciplinary guideline panel consisted of patients and caregivers, AD experts (dermatology and allergy/immunology), primary care practitioners (family medicine, pediatrics, internal medicine), and allied health professionals (psychology, pharmacy, nursing). The panel prioritized equity, diversity, and inclusiveness, and implemented management strategies to minimize the influence of conflicts of interest. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to inform the rating of the certainty of the evidence and the strength of the recommendations. Evidence-to-decision frameworks, subjected to public comment, translated evidence into recommendations using trustworthy guideline principles. The guideline's 25 evidence-based recommendations address the optimal use of **(1)** topical treatments, including barrier moisturization devices, corticosteroids, calcineurin inhibitors,[17] phosphodiesterase 4 (PDE4) inhibitors (crisaborole), topical JAK inhibitors, occlusive (wet wrap) therapy, adjunctive antimicrobials, application frequency, and maintenance therapy,[18] **(2)** dilute bleach baths,[19] **(3)** dietary avoidance/elimination,[20] **(4)** allergen immunotherapy,[4] and **(5)** systemic treatments, including biologics/monoclonal antibodies, small molecule immunosuppressants (cyclosporine, methotrexate, azathioprine, mycophenolate, JAK inhibitors), systemic corticosteroids, and ultraviolet (UV) phototherapy (light therapy).[21] The eAppendix of the guidelines provide practical information and implementation considerations for each treatment, presented in the form of 1–2 page handouts.[3]

In addressing one of the core questions in the guideline "Question 4. Should allergen immunotherapy be used for atopic dermatitis?", the panel agreed on 2 conditional recommendations. **Table 1** summarizes the implications of the conditional recommendations using the GRADE approach.[22] Likewise, each guideline recommendation is accompanied by the following: some common conditions that might influence whether the recommended course of action might be optimal, or not, for the patient; the systematically reviewed evidence for benefits and harms; the systematically reviewed patient values and preferences[23]; direct patient and family input addressing treatment of AD; factors that might affect accessibility, equity, and feasibility; implementation considerations; and a summary.

### Recommendation 14

In patients with moderate-severe atopic dermatitis refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel suggests adding allergen immunotherapy to standard topical treatment over not adding (conditional recommendation, moderate-certainty evidence).

**Conditions to consider:**

1. Allergic comorbidities that will likely be responsive to immunotherapy (e.g., allergic rhinitis, or asthma with relevant sensitization) may lead to benefits for multiple diseases and therefore favour AIT.
2. Values and preferences regarding SCIT vs SLIT (e.g., convenience, age, travel plans).
3. The plausibility of allergen sensitization to reflect allergy. For example, a patient sensitized to horse dander with no further plausible exposure to horse dander will unlikely benefit from AIT to horse. In contrast, a patient with dust mite sensitization and dust mite exposure might benefit from AIT to dust mite.

| Implications for | Strong recommendation | Conditional recommendation |
|---|---|---|
| **Patients** | Most individuals in this situation would want the recommended course of action, and only a small proportion would not. | Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences. |
| **Clinicians** | Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences. | Different choices, whether a conditional recommendation for or against a certain course of action, will be appropriate for individual patients (ie, the alternative strategy, in many scenarios, may be appropriate); clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences. |
| **Policymakers** | The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate. |
| **Researchers** | The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations. | The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps. |

**Table 1.** Interpretation of Strong and Conditional Recommendations; *adapted from Maleki-Yazdi KA, et al., 2023.*

**Summary of Rationale:** The panel inferred that most well-informed patients would value moderate-certainty benefits over little to no harms with SLIT, and their corresponding upsides and downsides (e.g. time commitment, resource use). With SCIT, the balance between benefits and harms is closer. With both interventions, the burdens and anticipated variability in values and preferences, particularly with age, severity of disease, and allergic comorbidities, contributed to the conditional recommendation.

**Implementation Considerations:** The available SLIT studies addressed SLIT in the form of drops, whereas most allergists in the United States may be most familiar with SLIT tablets. In Canada, SLIT tablets are marketed for dust mites, pollen from birch, grass, and ragweed pollen for allergic rhinitis. The age indications are as follows: dust mite tablets for 12 years to 65 years of age, birch tablets for 18 to 65 years of age, and grass and ragweed tablets for 5 years to 65 years of age. Separate AIT practice parameters state that there is no specific upper or lower age limit for initiating AIT if indications are present and after considering the absence of significant comorbid conditions and the patients' ability to complete AIT.[8] The guideline eAppendix[3] provides additional practical information and implementation considerations in the form of 1–2 page handouts.

### Recommendation 15

In patients with mild atopic dermatitis, the JTF panel suggests against adding allergen immunotherapy to standard topical treatment (conditional recommendation, moderate-certainty evidence).

**Conditions to consider:**

1. Patients with allergic comorbidities with relevant sensitization that will likely be responsive to AIT (e.g., allergic rhinitis, asthma) may be more likely to pursue this treatment even if their AD is mild if it means that multiple conditions will improve. In contrast, most individuals with mild AD and no other allergic comorbidities will likely not pursue this treatment.

2. Values and preferences regarding SCIT vs SLIT (e.g., convenience, age, travel plans).

While the summarized evidence for benefits, harms, and contextual factors remained similar to those presented in Recommendation 14, the panel inferred that most well-informed patients would value avoiding the inconvenience of SCIT or SLIT. This preference is despite the moderate certainty for small benefits to AD outcomes in patients with mild AD. The anticipated variability in values and preferences, particularly with age and allergic comorbidities (e.g., mild AD but has indications for allergen immunotherapy due to indications for allergic rhinitis), contributed to the conditional recommendation.

The AAAAI/ACAAI JTF guidelines, as living guidelines, will continue to be updated and responsive to practice-changing evidence.

## Future Directions Regarding Allergen Immunotherapy for Atopic Dermatitis

The impact of immunotherapy on some outcomes such as itch, sleep, and flares are less certain due to sparse data. Future studies should ensure that all patient-important outcomes are reported and that when collected, all measures are fully reported. Time-to-effect analyses are crude estimates, and future studies must formally address this issue. Future studies should clearly document whether systemic reactions after AIT for AD are immediate (e.g., anaphylaxis) or delayed (e.g., eczematous eruption or AD flare). No study has addressed AIT's potential long-term immunomodulatory effects (seen over 3–5 years of treatment). The systematic review provided sample size estimates that can be taken under consideration for planning future RCTs to address these now open questions. Additional research is also needed to better understand the mechanisms by which allergens and AIT affect AD, and how they might interact with the other factors to drive improvements and worsening of disease.

## Conclusions

These findings support AIT's role in optimal AD outcomes and support a multidisciplinary model of care for patients with AD.

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## References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251-1258.e1223. doi:10.1016/j.jaci.2009.10.009
2. Bridgman AC, Fitzmaurice C, Dellavalle RP, Karimkhani Aksut C, Grada A, Naghavi M, et al. Canadian burden of skin disease From 1990 to 2017: results from the Global Burden of Disease 2017 Study [Formula: see text]. J Cutan Med Surg. 2020;24(2):161-173. doi:10.1177/1203475420902047
3. AAAAI/ACAAI JTF Atopic Dermatitis Guideline Panel, Chu DK, Schneider L, Asiniwasis RN, Boguniewicz M, De Benedetto A, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. Ann Allergy Asthma Immunol. 2024;132(3):274-312. doi:10.1016/j.anai.2023.11.009
4. Yepes-Nuñez JJ, Guyatt GH, Gómez-Escobar LG, Pérez-Herrera LC, Chu AWL, Ceccaci R, et al. Allergen immunotherapy for atopic dermatitis: systematic review and meta-analysis of benefits and harms. J Allergy Clin Immunol. 2023;151(1):147-158. doi:10.1016/j.jaci.2022.09.020
5. Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. J Allergy Clin Immunol. 2013;132(6):1337-1347. doi:10.1016/j.jaci.2013.07.008
6. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007
7. Cox L, Li JT, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol. 2007;120(3):S25-S85. doi:10.1016/j.jaci.2007.06.019
8. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55. doi:10.1016/j.jaci.2010.09.034
9. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol. 2017;118(3):276-282 e272. doi:10.1016/j.anai.2016.12.009
10. de Blay F, Gherasim A, Casale TB, Doyen V, Bernstein D. Which patients with asthma are most likely to benefit from allergen immunotherapy? J Allergy Clin Immunol. 2022;149(3):833-843. doi:10.1016/j.jaci.2022.01.011
11. Nygaard U, Hvid M, Johansen C, Buchner M, Folster-Holst R, Deleuran M, et al. TSLP, IL-31, IL-33 and sST2 are new biomarkers in endophenotypic profiling of adult and childhood atopic dermatitis. J Eur Acad Dermatol Venereol. 2016;30(11):1930-1938. doi:10.1111/jdv.13679
12. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. J Allergy Clin Immunol. 2013;131(1):187-200 e181-188. doi:10.1016/j.jaci.2012.08.002
13. Marschall P, Wei R, Segaud J, Yao W, Hener P, German BF, et al. Dual function of Langerhans cells in skin TSLP-promoted TFH differentiation in mouse atopic dermatitis. J Allergy Clin Immunol. 2021;147(5):1778-1794. doi:10.1016/j.jaci.2020.10.006
14. Traidl S, Werfel T. [Allergen immunotherapy for atopic dermatitis]. [Article in German] Hautarzt. 2021;72(12):1103-1112. doi:10.1007/s00105-021-04909-y
15. Caminiti L, Panasiti I, Landi M, De Filippo M, Olcese R, Ciprandi G, et al. Allergen immunotherapy in atopic dermatitis: light and shadow in children. Pediatr Allergy Immunol. 2020;31 Suppl 26:46-48. doi:10.1111/pai.13390

16. Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. Immunity. 2021;54(2):291-307.e297. doi:10.1016/j.immuni.2020.12.013
17. Devasenapathy N, Chu A, Wong M, Srivastava A, Ceccacci R, Lin C, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2023;7(1):13-25. doi:10.1016/S2352-4642(22)00283-8
18. Chu DK, Chu AWL, Rayner DG, Guyatt GH, Yepes-Nuñez JJ, Gomez-Escobar L, et al. Topical treatments for atopic dermatitis (eczema): systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023;152(6):1493-1519. doi:10.1016/j.jaci.2023.08.030
19. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: a systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. Ann Allergy Asthma Immunol. 2022;128(6):660-668.e669. doi:10.1016/j.anai.2022.03.024
20. Oykhman P, Dookie J, Al-Rammahy H, de Benedetto A, Asiniwasis RN, LeBovidge J, et al. Dietary elimination for the treatment of atopic dermatitis: a systematic review and meta-analysis. Journal of Allergy and Clinical Immunology: In Practice. 2022;10(10):2657-2666.e2658. doi:10.1016/j.jaip.2022.06.044
21. Chu AWL, Wong MM, Rayner DG, Guyatt GH, Martinez JPD, Ceccacci R, et al. Systemic treatments for atopic dermatitis (eczema): systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023;152(6):1470-1492. doi:10.1016/j.jaci.2023.08.029
22. Chu DK, Golden DBK, Guyatt GH. Translating Evidence to Optimize Patient Care Using GRADE. J Allergy Clin Immunol Pract. 2021;9(12):4221-4230. doi:10.1016/j.jaip.2021.09.035
23. Maleki-Yazdi KA, Heen AF, Zhao IX, Guyatt GH, Suzumura EA, Makhdami N, et al. Values and preferences of patients and caregivers regarding treatment of atopic dermatitis (eczema): a systematic review. JAMA Dermatol. 2023;159(3):320-330. doi:10.1001/jamadermatol.2022.6045

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AD=atopic dermatitis; JAK1=Janus kinase 1.
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**Reference:** CIBINQO Product Monograph, Pfizer Canada ULC.

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Dr. Sowers led a team of PhDs and MDs as the lead research scientist at ALK's allergen research lab in the US, where she spearheaded translating bench science to clinical practice. Her work focused on characterizing allergen extracts for their use in both human and veterinary allergy immunotherapy. Dr. Sowers presently serves as a clinical and scientific consultant, lecturer, educator, and a strategist in scientific and clinical fields.

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# Pollen Cross-Reactivity: A Primer for Allergy Specialists

**Tricia Sowers, PhD**

## Introduction

There are over 400,000 land-based plant species that comprise our biodiverse habitat. Only a small subset of those plant species satisfies Thommen's postulates, classifying them as allergens. The number of allergenic species, however, remains so vast that it is prohibitive to both test and treat for all relevant species within a geographical region. Allergy specialists have a valuable tool that can be used to help simplify the management of allergic patients: cross-reactivity.

Cross-reactivity is the ability for an allergen to induce an IgE-mediated response, regardless of previous exposure.[1] Allergens are a complex milieu of proteins, some of which have allergic potential while others do not. A number of proteins are conserved across allergen species. When exposure to these conserved proteins occurs, the immune system recognizes them in a similar manner. For homologous or cross-reactive allergenic proteins, this conserved molecular recognition initiates the allergic cascade. Allergen characterization is critical to the understanding of cross-reactivity. Characterization, in this context, refers to the protein make-up of a particular allergen. The process of allergen characterization began in 1962 with the discovery of antigen E, the first identified allergenic protein.[2] Antigen E, commonly known as Amb a 1, is an allergenic protein in ragweed, and is the primary sensitizing protein for ragweed allergy sufferers. These primary sensitizers are referred to as major allergens and can be defined as such when >50% of the allergic patient population is sensitized to them. An entire branch of research arose from this discovery, which has allowed for major advances to be made in the understanding of cross-reactive relationships among allergen species. Cross-reactivity is not limited to homologous major allergen expression. Rather, minor allergens and panallergens, though less clinically relevant, play a similar role in cross-reactive relationships.[3] This primer will explore the science behind cross-reactivity, as well as provide a general overview of the cross-reactive relationships that have been defined for plant allergens found across North America.

## Techniques for Determining Cross-Reactive Relationships

A number of techniques have been used to better understand and define cross-reactive allergens, both *in vitro* and *in vivo*, each providing a varying quality of evidence. Protein sequencing

has elucidated conserved proteins among both related and seemingly unrelated allergens, which can explain the cross-reactions observed in clinical practice. In general cross-reactivity appears to occur when there is >70% homology between protein sequences.[4] Proteins with the same cellular function, if allergenic, can induce similar IgE responses, despite coming from dramatically different species. An example of this is the conserved group 1 proteins found in birch (Bet v 1) and apple (Mal d 1). This ability is not only related to function, but also to relative conformation. The 3D structures of cross-reactive allergenic proteins are often very similar. The epitopes can be recognized by the same IgE molecules and provoke the allergic cascade.[5] Cross-referencing allergen databases that include protein sequences, 3D conformations, protein functions, and isoform information has drastically expanded the current knowledge base. It has allowed for a more in-depth characterization of allergens and their cross-reactive relationships.

IgE and IgG inhibition studies enable further evaluation of cross-reactivity. This *in vitro* technique demonstrates how one allergen can inhibit IgE or IgG binding with another allergen. When conducted with maximum rigour, IgE and IgG competitive binding studies evaluate each species independently as the inhibitor. High inhibition suggests cross-reactivity, whereas lower inhibition rates imply less shared IgE or IgG affinity and binding. This methodology has been used extensively to define cross-reactive relationships among grass species and in a more limited capacity with tree and weed species.[6-9]

*In vivo* methods for evaluating cross-reactivity are largely limited. Comparing skin prick testing results and serum IgE levels across species allows for possible cross-reactivity correlations to be made. However, this approach has limitations, given the vast variability in antigen strength, testing sensitivity and specificity, and the diverse nature of the allergenic components contained within. Positive testing correlations could be attributed to panallergens, rather than allergen-specific proteins, which could lead to the overreporting of cross-reactive relationships.[10] Pan allergens and their contribution to cross-reactivity will be discussed further. Allergen provocation testing can also be used to evaluate cross-reactivity, with a level of rigour that exceeds skin and serum testing correlations. With this approach, atopic patients are exposed to an allergen they have not previously been exposed to, and symptom provocation is recorded.[11] Clinical symptoms can be specifically attributed to the non-sensitizing allergen, demonstrating (or not demonstrating) cross-reactivity.

While these *in vitro* and *in vivo* approaches have greatly advanced our understanding of cross-reactivity, a large number of allergenic species still require characterization. Without an understanding of the protein make-up of an allergen, cross-reactive relationships can only be defined using taxonomy. This approach has been shown to be accurate in the majority of instances. Two assumptions must be made when using taxonomic relationships to define cross-reactivity: **1)** the botanical classification accurately reflects the biological relationship between species; and **2)** cross-reactivity is greatest among plants within the same genus, proceeded by those in the same family (**Figure 1**).[12] This implies that distantly related plants exhibit minimal cross-reactivity. Of course, exceptions do exist, likely driven by panallergens.

## Panallergens

Approximately 20% of pollen-allergic patients are polysensitized across tree, weed, and grass species.[3] These patients are not truly sensitized to the diverse array of allergens, rather, they are sensitized to panallergens. Panallergens are ubiquitously expressed proteins that are critical to cellular function. Given their purpose in general organismal processes, their structure and epitope binding capabilities are highly conserved. The presence of panallergens across allergen species complicates testing and treatment of allergic patients. If a patient develops a sensitivity to a panallergen, a multitude of false positive reactions may develop during skin or serum IgE testing.[10] Test interpretation may be further complicated by the disproportionate expression of panallergens across allergenic plant species – concentrations may be low in one species and high in another, resulting in variable test reactivity.[13] Cross-reactivity can also extend beyond pollens to include plant-based foods.

Panallergens are categorized into several protein families, each with varying levels of distribution and cross-reactivity. These families include profilin, polcalcin, pathogenesis-related class 10 (PR-10) related proteins, and non-specific lipid transfer proteins (LTPs).[10] Component-resolved diagnostic testing can help tease apart the role panallergens play in the

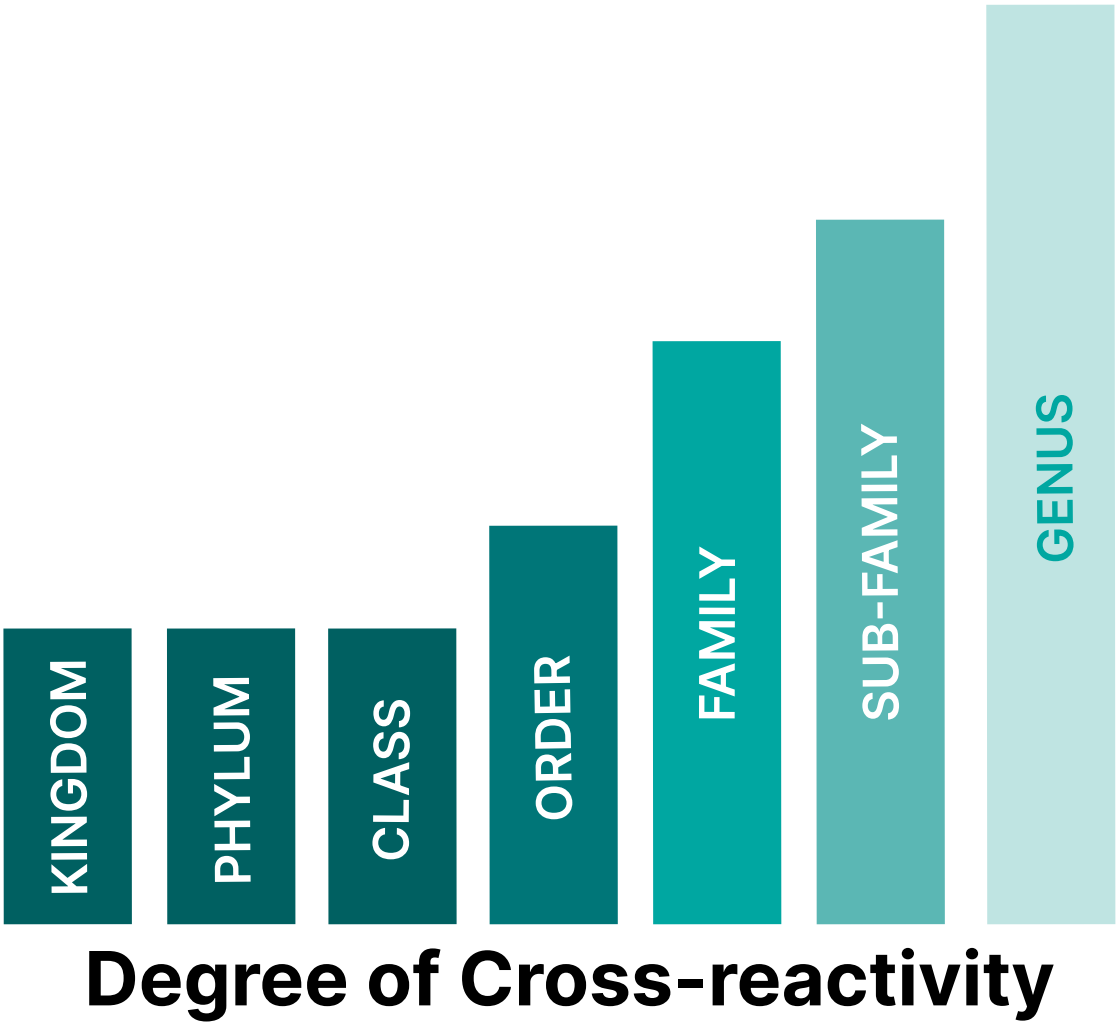


**Figure 1.** Cross-reactivity as it related to taxonomic relationships. Species that are more closely related are more cross-reactive. Distantly related species typically have little to no cross-reactivity, with the exception of panallergen expression. Little cross-reactivity is observed among plant species in the same Order; *courtesy of Tricia Sowers, PhD*.

sensitization status of allergic patients. Molecular diagnostic panels contain panallergen proteins that are expressed across multiple allergen species. An example is profilin-related proteins, which include Bet v 2 (birch), Pho d 2 (palm), Phl p 12 (Timothy grass) and Amb a 8 (ragweed). When a patient is panallergic, component-resolved diagnostic testing results will be consistently positive for the panallergen-related protein, regardless of the plant species. While component-based testing is becoming commonplace for food allergy diagnosis, it is less frequently employed for pollen-allergic patients.

As an alternative to component-resolved diagnostic testing, queen palm extract can be used as a diagnostic tool to screen for panallergy, specifically profilin sensitization. Queen palm extract contains a high concentration of profilin. If a patient without prior exposure produces a positive reaction to queen palm and most other pollens used for testing, it can be surmised that the patient is profilin sensitized. Theoretically, patient treatment can be significantly simplified, using an extract with high profilin expression (e.g., Timothy grass).[13] Integrating knowledge of panallergens and their relative expression into clinical practice is important when diagnosing

and treating allergic patients. Inclusion of a large number of species into patient treatment can create a dilution effect and compromise patient outcomes. Ruling out panallergen involvement can allow for the use of individual species, rather than comprehensive pollen mixes. Further refining treatment formulations by considering cross-reactive relationships can enhance the effectiveness of allergy treatments.

## Grass Cross-Reactivity

There is a high degree of cross-reactivity among many grass species – particularly among those grasses that are considered temperate or Northern pasture grasses (e.g., Timothy, perennial ryegrass, orchard, Kentucky bluegrass). These grass species are the most highly abundant species across Canada and are the most clinically relevant. IgE and IgG inhibition studies have demonstrated a 98–100% homology among temperate grass species, meaning that a single species can serve as a representative for both allergen screening and allergy immunotherapy.[6,7] This high degree of homology is likely attributed to the conservation of both group 1 and group 5 proteins, across members of this Pooideae sub-family (**Table 1**). While there is a high degree of cross-reactivity, the major allergen concentration does vary, making certain species more favourable for use in clinical diagnosis and treatment. Although concentrations vary among extract manufacturers, in general, Timothy and orchard grass report the most robust group 5 concentrations.[14]

Southern grasses are less predominant in Canada; however, Bermuda and Johnson grass can be found in multiple provinces. Group 1 proteins, which are homologous to those found in temperate grass species, are the major allergens associated with subtropical grass sensitization. Several studies have demonstrated a high prevalence of co-sensitization when evaluating temperate grass and Southern grass species, particularly with perennial ryegrass and Timothy grass.[11,15,16] Furthermore, treatment with temperate grasses has been shown to reduce clinical symptoms associated with Bermuda grass pollen exposure in co-sensitized patients, suggesting that cross-reactivity does occur among temperate and subtropical grass species.[15] The degree to which cross-reactivity is observed is limited, largely due to the exclusion of group 5 proteins from the Southern grass species.

## Tree Cross-Reactivity

While cross-reactivity among grass species is quite extensive, tree species present a more complex landscape. In general, tree allergens are not as well characterized, resulting in greater dependence on taxonomical associations and less in-depth knowledge of major and minor allergen homologies. **Table 1** summarizes tree cross-reactivity using the current body of literature. Species within the same family are generally assumed to be cross-reactive. Intrafamilial cross-reactivity has been well-established, using multiple *in vivo* and *in vitro* methods, for both the *Cupressaceae* (e.g., cedar, cypress, juniper) and *Oleaceae* (e.g., olive, ash, privet) families.[12] Given these findings, a single representative species can be used for both testing and treatment. Some evidence for interfamilial cross-reactivity has been elucidated; however, further allergen-specific characterization is generally required to alter clinical approaches to testing and treatment. The exception to this is among members of the *Betulaceae* and *Fabaceae* families.

The cross-reactive relationship among birch-homologous species is the most well-documented. Birch and alder have long been classified as cross-reactive within the *Betulaceae* family. Recent studies have extended this cross-reactivity to include members of the *Fabaceae* family (e.g., beech, oak).[8] IgE inhibition studies have demonstrated a high degree of homology across these species. In addition, provocation studies have also shown that oak pollen-related symptoms can be alleviated using birch-specific immunotherapy.[17] With both birch-related and oak species being prevalent across Canada, this finding has significant clinical impact.

Of note, there is conflicting evidence in the literature concerning box elder and maple cross-reactivity. Earlier research suggests that these species might have unique, unrelated allergens; however, more recent literature indicates that cross-reactivity is sufficient to allow for the selection of individual species for treatment.[12,18] Until further characterization studies produce conclusive results, it remains at the discretion of the allergy specialist to determine rules for inclusion or exclusion of *Acer* family members.

| Grasses | Trees | Weeds |
|---|---|---|
| **Pooideae Sub-Family** | **Aceraceae Family** | **Asteraceae Family** |
| *Agrostideae Tribe* | Box Elder | *Iva-Xanthium Genera* |
| Redtop | Maple | Marshelder |
| Timothy | **Betulaceae Family** | Cocklebur |
| *Poceae Tribe* | Alder | *Artemisia Genus* |
| Brome | Birch | Mugwort |
| Orchard | Hazelnut | Sagebrush |
| Meadow Rescue | **Fagaceae Family** | Prairie Sage |
| Perennial Ryegrass | Beech | *Eupatorium Genus* |
| *Tritceae Tribe* | Oak | Dog Fennel |
| Quack Grass | **Cupressaceae Family** | Baccharis |
| Wheat Pollen | Cedar | *Ambrosia Genus* |
| *Phalarideae Tribe* | Cypress | Ragweed |
| Sweet Vernal | Juniper | Rabbit Bush |
| Canary-Reed | **Juglandaceae Family** | Burrobush |
| *Aveneae Tribe* | Hickory | *Solidago Genus* |
| Oat Grain | Pecan | Goldenrod |
| **Panicodieae Sub-Family** | Walnut | *Polygonaceae Genus* |
| *Paniceae-Andropogoneae Genera* | **Moraceae Family** | Sheep Sorrel |
| Bahia | Mulberry | Yellow Dock |
| Johnson | **Oleaceae Family** | *Plantaginacea Genus* |
| Corn | Ash | English Plantain |
| **Chloridoideae Sub-Family** | Olive | **Amaranthaceae Family** |
| *Cynodonteae Tribe* | Privet | *Amaranthus Genus* |
| Bermuda | **Plantanaceae Family** | Careless Weed |
| | Sycamore | Pigweed |
| | **Saliaceae Family** | W. Waterhemp |
| | Aspen | *Atriplex-Chenopodium-Kochia-Salsola Genera* |
| | Cottonwood | Wingscale |
| | Poplar | Lenscale |
| | Willow | Allscale |
| | **Fabaceae Family** | Saltbrush |
| | Acacia | Lamb's Quarters |
| | Locust | Kochia |
| | Mesquite | Russian Thistle |
| | **Ulmaceae Family** | |
| | Elm | |
| | **Cannabaceae Family** | |
| | Hackberry | |
| | **Fabaceae Family** | |
| | Bottlebrush | |
| | Eucalyptus | |
| | Melaleuca | |
| | **Arecaceae Family** | |
| | Queen Palm | |
| | **Pinaceae Family** | |
| | Pine | |
| | **Atingiaceae Family** | |
| | Sweetgum | |

**Table 1.** Cross-reactive relationships among grass, tree, and weed species. Related species are grouped accordingly; *courtesy of Tricia Sowers, PhD.*

## Weed Cross-Reactivity

Cross-reactivity among weed species is better defined than the cross-reactive relationships among tree species. This is largely due to enhanced characterization of relevant allergenic proteins. Generally speaking, intrafamilial cross-reactivity exists among members of the common weed families such as *Asteraceae, Amaranthaceae*, and *Polygonaceae*. The degree of cross-reactivity is enhanced at the genus level (**Table 1**).[12]

A significant body of research has been dedicated to the characterization of ragweed and ragweed-related species. Proteins within the *Ambrosia* genus are highly conserved, with 12 identified allergenic proteins that contribute to patient sensitization.[19] Clinically, a single representative ragweed species can be used for both testing and treatment. Mugwort shares many homologous proteins with ragweed and numerous studies report high levels of cross-reactivity. However, it is important to note that Art v 1, the mugwort major allergen, is not homologous with Amb a 1, the ragweed major allergen.[20] While this does not negate cross-reactivity, there are likely patients who would benefit from mugwort-specific immunotherapy, rather than relying upon ragweed and cross-reactivity for desensitization. Significant cross-reactivity has been demonstrated between ragweed and cocklebur using inhibition assays.[21]

Cross-reactivity among members of the *Amaranthaceae* family is also well-documented, particularly with respect to lamb's quarters, kochia, and Russian thistle.[22,23] Russian thistle is the most highly characterized of the allergens, however, there are a number of conserved proteins across the three aforementioned species. Profilin and an Ole e-1 like protein appear to be conserved across the *Amaranthaceae* family members.[23] This homology extends to carelessweed and pigweed as well, and likely accounts for the high degree of cross-reactivity that is observed clinically.

## Conclusion

Understanding cross-reactive relationships among grass, tree and weed species can provide substantial opportunities for simplifying the clinical approach to allergy testing and treatment. Cross-reactivity is extensive within allergen families and is even further enhanced at the genus level. The evolution of proteomic research has greatly enhanced our understanding of allergic sensitization and advanced our knowledge concerning cross-reactivity. This research has led to the characterization of both major and minor allergens, as well as elucidating the role of panallergens. In addition, panallergen sensitization should be carefully considered when diagnosing and treating allergic patients. While the clinical relevance of panallergens appears to be less significant, ignorance of panallergen contributions to skin and serum testing results can potentially complicate patient treatment. When component-resolved diagnostic testing is added to the diagnostic process, immunotherapy prescriptions are changed in >50% of patients, often leading to significant treatment simplification.[24] It is important to remember that allergen sensitization is patient-specific. Cross-reactivity will only translate when the relevant, sensitizing allergenic proteins are conserved across species.

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## Financial Disclosures

**Consulting:** ALK-Abello

## References


1. Aalberse RC. Assessment of allergen cross-reactivity. Clinical and molecular allergy : CMA. 2007;5:2. doi:10.1186/1476-7961-5-2
2. Pomes A, Davies JM, Gadermaier G, Hilger C, Holzhauser T, Lidholm J, et al. WHO/IUIS Allergen Nomenclature: providing a common language. Mol Immunol. 2018;100:3-13. doi:10.1016/j.molimm.2018.03.003
3. Kleine-Tebbe J, Ackermann-Simon J, Hanf G. Molecular allergy diagnosis using pollen marker allergens and pollen panallergens: five patterns seen in multiple test reactions to pollen extracts. Allergol Select. 2021;5:180-186. doi:10.5414/alx02238e
4. Bublin M, Breiteneder H. Cross-reactivities of non-homologous allergens. Allergy. 2020;75(5):1019-1022. doi:10.1111/all.14120
5. Sharma E, Vitte J. A systematic review of allergen cross-reactivity: translating basic concepts into clinical relevance. J Allergy Clin Immunol Glob. 2024;3(2):100230. doi:10.1016/j.jacig.2024.100230
6. Hejl C, Wurtzen PA, Kleine-Tebbe J, Johansen N, Broge L, Ipsen H. Phleum pratense alone is sufficient for allergen-specific immunotherapy against allergy to Pooideae grass pollens. Clin Exp Allergy. 2009;39(5):752-759. doi:10.1111/j.1365-2222.2008.03195.x
7. Johansen N, Weber RW, Ipsen H, Barber D, Broge L, Hejl C. Extensive IgE cross-reactivity towards the Pooideae grasses substantiated for a large number of grass-pollen-sensitized subjects. Int Arch Allergy Immunol. 2009;150(4):325-334. doi:10.1159/000226233
8. Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol . 2019;143(3):1058-1066 e1056. doi:10.1016/j.jaci.2018.12.1001
9. Zbîrcea LE, Buzan MR, Grijincu M, Babaev E, Stolz F, Valenta R, et al. Relationship between IgE levels specific for ragweed pollen extract, amb a 1 and cross-reactive allergen molecules. Int J Mol Sci. 2023;24(4). doi:10.3390/ijms24044040
10. McKenna OE, Asam C, Araujo GR, Roulias A, Goulart LR, Ferreira F. How relevant is panallergen sensitization in the development of allergies? Pediatr Allergy Immunol. 2016;27(6):560-568. doi:10.1111/pai.12589
11. Ramirez DA, Andrews CP, Rather CG, Jacobs RL. Responsiveness to timothy grass pollen in individuals without known natural exposure in an allergen challenge chamber. Ann Allergy Asthma Immunol. 2015;114(3):226-232. doi:10.1016/j.anai.2014.11.006
12. Weber RW. Assessing cross-reactivity in allergen immunotherapy. Allergy Asthma Proc. 2022;43(4):314-321. doi:10.2500/aap.2022.43.210112
13. Plunkett GA, Barber D, Villalobos EM, Jacobs JS, Hallett JS, Mostofi T, et al. Prevalence of IgE Specific to Profilin in a Texas and California Population. J Allergy Clin Immunol. 2013;131(2):AB111. doi:10.1016/j.jaci.2012.12.1067
14. Nelson HS. The use of standardized extracts in allergen immunotherapy. J Allergy Clin Immunol. 2000;106(1 Pt 1):41-45. doi:10.1067/mai.2000.107197
15. van Nunen SA, Burk MB, Burton PK, Ford G, Harvey RJ, Lozynsky A, et al. 5-grass-pollen SLIT effectiveness in seasonal allergic rhinitis: impact of sensitization to subtropical grass pollen. World Allergy Organ J. 2022;15(2):100632. doi:10.1016/j.waojou.2022.100632
16. Maloney J, Bernstein DI, Nelson H, Creticos P, Hebert J, Noonan M, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol. 2014;112(2):146-153 e142. doi:10.1016/j.anai.2013.11.018
17. Couroux P, Ipsen H, Stage BS, Damkjaer JT, Steffensen MA, Salapatek AM, et al. A birch sublingual allergy immunotherapy tablet reduces rhinoconjunctivitis symptoms when exposed to birch and oak and induces IgG(4) to allergens from all trees in the birch homologous group. Allergy. 2019;74(2):361-369. doi:10.1111/all.13606
18. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020;13(2):100080. doi:10.1016/j.waojou.2019.100080
19. Buzan MR, Zbîrcea LE, Gattinger P, Babaev E, Stolz F, Valenta R, et al. Complex IgE sensitization patterns in ragweed allergic patients: Implications for diagnosis and specific immunotherapy. Clin Transl Allergy. 2022;12(7):e12179. doi:10.1002/clt2.12179
20. Wopfner N, Gadermaier G, Egger M, Asero R, Ebner C, Jahn-Schmid B, et al. The spectrum of allergens in ragweed and mugwort pollen. Int Arch Allergy Immunol. 2005;138(4):337-346. doi:10.1159/000089188
21. Perrick D, Stafford CT, Armstrong E, DuRant RH. Modification of the fluorescent allergosorbent test as an inhibition assay for determination of cross-reactivity among aeroallergens. J Allergy Clin Immunol. 1991;87(1 Pt 1):98-103. doi:10.1016/0091-6749(91)90218-d
22. Tehrani M, Sankian M, Assarehzadegan MA, Falak R, Jabbari F, Varasteh A. Immunochemical characterization of Amaranthus retroflexus pollen extract: extensive cross-reactive allergenic components among the four species of Amaranthaceae/Chenopodiaceae. Iran J Allergy Asthma Immunol. 2010;9(2):87-95.
23. Villalba M, Barderas R, Mas S, Colás C, Batanero E, Rodríguez R. Amaranthaceae pollens: review of an emerging allergy in the mediterranean area. J Investig Allergol Clin Immunol. 2014;24(6):371-381; quiz 372 p preceding 382.
24. Izmailovich M, Semenova Y, Abdushukurova G, Mukhamejanova A, Dyussupova A, Faizova R, et al. Molecular aspects of allergen-specific immunotherapy in patients with seasonal allergic rhinitis. Cells. 2023;12(3). doi:10.3390/cells12030383

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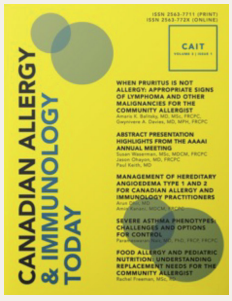






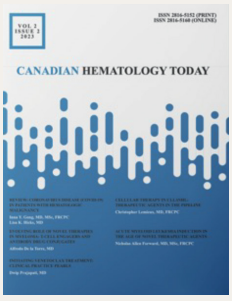



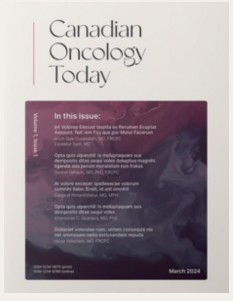


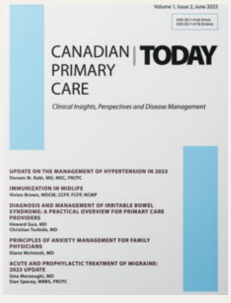




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