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**WHEN PRURITUS IS NOT ALLERGY: APPROPRIATE SIGNS OF LYMPHOMA AND OTHER MALIGNANCIES FOR THE COMMUNITY ALLERGIST**
Amaris K. Balitsky, MD, MSc, FRCPC,
Gwynivere A. Davies, MD, MPH, FRCPC

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# WHEN PRURITUS IS NOT ALLERGY: APPROPRIATE SIGNS OF LYMPHOMA AND OTHER MALIGNANCIES FOR THE COMMUNITY ALLERGIST

**Case**

A 29-year-old woman presented in 2020 with a several-month history of intense pruritus with neck and truncal rash (**Figure 1A**). During the spring, she reported recurrently to health care with intermittent respiratory symptoms, and persistent fever and sweats. X-ray imaging suggested left sided pneumonia with an effusion, for which she received several courses of antibiotics and eventually underwent thoracentesis in June 2020. Concurrently, she noted nodularity in the skin of her upper back and sternum. Past medical history included scoliosis and anemia, initially thought to be related to iron deficiency, though later testing suggested anemia due to inflammation. She had previously developed cutaneous patches, but without a formal dermatologic diagnosis. Of note, she had a family history of psoriasis.

CT imaging in July 2020 demonstrated diffuse opacities within her right lung with partial collapse of her right upper lobe, bilateral pleural effusions, and extensive soft tissue in the mediastinum encasing various venous structures, the pericardium and heart with small pericardial effusion. Mediastinal mass core biopsy demonstrated nodular sclerosing Hodgkin lymphoma. The patient was treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy for six cycles and achieved a complete remission. With treatment, her pruritus and rash resolved within 1-2 months; however, she subsequently developed drug-induced flagellate dermatitis[1], which has slowly faded since treatment completion (**Figure 1B**). She remains in remission at most recent follow up.

**Pruritus**

Pruritus is a common symptom, with 8%-22% of individuals experiencing chronic pruritus defined as an itch lasting longer than six weeks[2-4]. In a prospective study of patients presenting to an outpatient dermatology clinic with chronic pruritus, 22% were diagnosed with an underlying systemic etiology.[5] With some exceptions, the majority of systemic causes are associated with normal appearing skin. Systemic causes of pruritus are extensive, including renal, hepatic, endocrine, hematologic, and iatrogenic (**Table 1**).

Malignancy is an uncommon etiology of pruritus.[6,7] In a population-based cohort of 8,744 patients with chronic pruritus, compared to age- and sex-matched controls, patients with chronic pruritus had higher rates of alcohol use, smoking, higher



*Figure 1A. Demonstration of neck and truncal rash prior to diagnosis; photo courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD*



*Figure 1B. Hyperpigmentation from bleomycin-induced flagellate dermatitis that developed during treatment with ABVD; photo courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD*

| System | Specific Disorder |
|---|---|
| **Dermatologic** | Xerosis<br>Eczematous dermatitis<br>Urticaria<br>Papulosquamous disorders<br>Infections and infestations<br>Scars |
| **Renal** | End-stage renal disease |
| **Liver** | Cholestatic liver disease<br>Cholestasis of pregnancy<br>Primary biliary cholangitis |
| **Endocrine** | Diabetes mellitus<br>Hyperthyroid<br>Carcinoid syndrome |
| **Hematologic** | Myeloproliferative neoplasm (polycythemia vera, essential thrombocytosis, myelofibrosis)<br>Hodgkin lymphoma<br>Non-Hodgkin lymphoma<br>Multiple myeloma<br>Mastocytosis<br>Iron deficiency anemia |
| **Infections** | Scabies<br>HIV<br>Varicella<br>Superficial fungal infection<br>Onchocerciasis |
| **Rheumatologic** | Sjogren syndrome<br>Scleroderma<br>Dermatomyositis |
| **Neurologic** | Brachioradial pruritus<br>Notalgia paresthetica<br>Postherpetic neuralgia<br>Multiple sclerosis |
| **Drug reactions** | Examples include: opioids/analgesics, chemotherapeutic agents, chloroquine, antibiotics |
| **Psychogenic itch** | |
| **Chronic pruritus of unknown origin** | |

*Table 1. Systemic conditions associated with pruritus; courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD*

body mass index and lower socio-economic status. Patients with chronic pruritus also had a higher risk of death[7]. While there was no increase in overall malignancy, increased mortality was attributed to a higher risk of hematologic and bile duct malignancies, HR 2.02 (95% CI 1.48–2.75) and 3.73 (95% CI 1.55 – 8.97), respectively[7]. This study suggests that the search for malignancy in the itching patient should focus on specific etiologies, including hematologic and bile duct malignancies.

**Pathophysiology of pruritus in hematologic malignancy**

Itch receptors, or polymodal C-fibre nerve endings, are stimulated by pruritogens (e.g., histamine, tryptase, etc) to cause the unpleasant itch sensation.[8] Mast cells and their mediators such as histamine, tryptase, prostaglandins and leukotrienes are involved in the pathogenesis of pruritus.[9] Interleukin (IL)-31 signaling has been identified as central to bridging the immune system with neurons, epithelial surfaces and

connective tissue and plays a role in TH2 mediated pruritus and autoimmune disease.[8] This molecular change is produced by a variety of leukocytes including T cells, eosinophils, basophils, mast cells, monocytes and dendritic cells.[10] In malignancy, there is an increase in pruritogens. For example, mast cells in patients with myeloproliferative disorders release more histamine, leukotrienes and IL-31 compared to those of healthy individuals.[11] In other hematologic malignancies, the cancer cell itself can release histamine, leukopeptidases, bradykinins and IL-31. Additionally, numerous hematologic malignancies can visually involve the skin leading to discomfort, either alone or in combination with systemic disease.

**When to consider hematologic malignancy as the cause of pruritus**

**Table 1** outlines various hematologic diagnoses associated with pruritus. Generalized pruritus is seen in only 1%-3% of patients with non-Hodgkin lymphoma, but in up to 19%-30% of those with Hodgkin lymphoma,[12, 13] occurring more often in the nodular sclerosis subtype. Itch can precede the clinical onset of lymphoma, sometimes described as a burning quality occurring at night, or even precipitated by alcohol consumption. Mycosis fungoides and Sezary syndrome are cutaneous hematologic malignancies associated with itch and rash. A skin biopsy can be helpful in these cases. Aquagenic pruritus, a hot bath- or shower-induced itch, is described in 30%-40% of individuals with a myeloproliferative neoplasm called polycythemia vera (PV). These patients may also present with abdominal symptoms and should have a detailed thromboembolic history as they are at risk of venous and arterial thromboembolism

There are no accepted screening tests for hematologic malignancies. However, routine bloodwork abnormalities may be uncovered. There is a wide spectrum of presentations of hematologic malignancies, ranging from an incidental finding on imaging or routine blood work to an aggressive symptomatic presentation. A symptomatic presentation can include enlarged lymph nodes, symptoms of a mediastinal mass including new cough or shortness of breath, symptoms of splenomegaly including early satiety or abdominal fullness, or constitutional symptoms including recurrent fevers, drenching night sweats or unintended weight loss. A physical examination with specific palpation of cervical, axillary and inguinal lymph nodes regions, and abdominal examination for enlargement of the spleen and liver is recommended.

If history and physical exam are suspicious, or if there has been no cause found, a complete blood count (CBC) and lactate dehydrogenase (LDH) can be helpful. For example, PV is characterized by high hemoglobin levels and can be identified on a CBC. Thrombocythemia can result from reactive or inflammatory causes or relating to a specific mutation such as with the myeloproliferative neoplasms. Some hematologic malignancies such as Hodgkin lymphoma can result in a reactive leukocytosis, predominantly displaying as a left shift or neutrophilia, while some patients may have malignant cells circulating that can be detected on their leukocyte differential. If there is suspicion for hematologic malignancy with a lymphocytosis or abnormal blood cells such as blasts present, flow cytometry testing can be sent on a peripheral blood sample to examine for clonal malignant populations. This test is not useful in the setting of reactive neutrophilia alone, and a blood smear review may help guide decision making. The LDH test can be helpful if elevated and is frequently used in prognostic scores for hematologic malignancy, but should be interpreted with caution as a non-specific test for tissue turnover.

If lymphadenopathy is present on exam, consideration should be given to CT or ultrasound imaging, depending on location and other patient factors, such as risk for contrast induced injury, radiation exposure and others. The largest and most easily accessible node should be targeted for an excisional (surgical) or core biopsy (interventional radiology or surgical). Fine needle aspirates are inadequate for pathological confirmation of a lymphoproliferative disorder, necessitating a second biopsy and resulting in a delay in diagnosis and treatment. This should be sent specifically for "lymphoma protocol" or the local correlate, such that part of the tissue is saved fresh for flow cytometry testing. In the case of concern for hepatosplenomegaly, abdominal ultrasound can be performed. If concerns remain from initial workup, then referral to a hematology specialist should occur. **Figure 2** summarizes an initial approach to the work-up of suspected hematologic malignancy in the patient who presents with pruritus.

During the course of workup, providers may wish to treat the unpleasant symptom of pruritus. While first line therapy remains topical treatments (i.e., corticosteroids), emollients and anti-histamines, other therapies with varying efficacy for refractory pruritus can be considered. These include gabapentin, mirtazapine, and SSRIs. A systematic review of itch

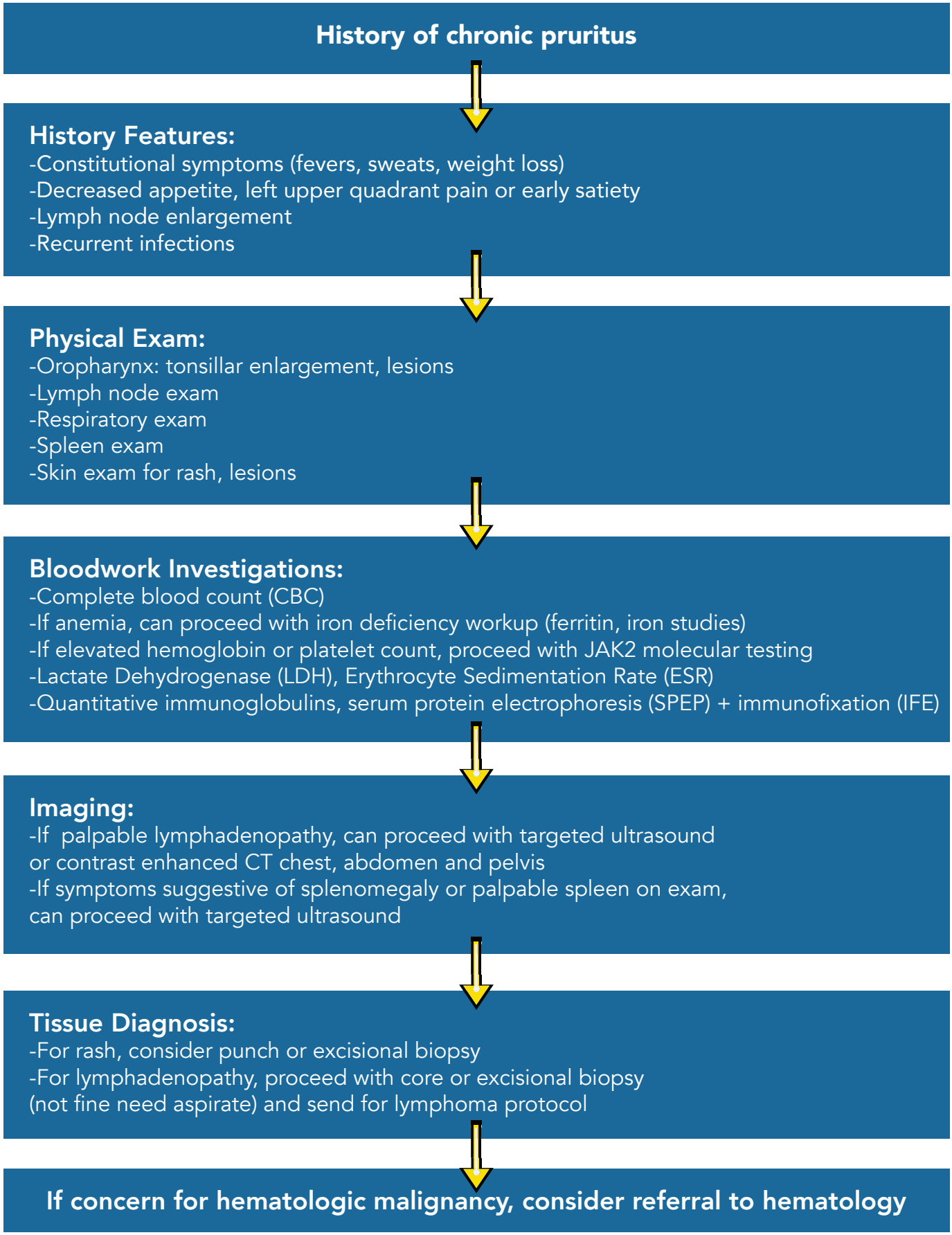



***Figure 2.*** *Suspected hematologic malignancy work-up; courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD*

in cutaneous T cell lymphoma demonstrated efficacy of the antiemetic aprepitant, specifically targeting substance P.[12] For all patients, the potential toxicity of treatment has to be weighed against the patient's discomfort. Definitive treatment of the underlying disorder once identified remains the mainstay of management.

## Conclusion

Pruritus is a common symptom that all individuals have experienced at some time. Although general malignancy is a rare cause of pruritus, there is an increased risk of hematologic malignancy in those with chronic itch. For the allergist assessing chronic itch, we have outlined an approach in the case of suspected hematologic malignancy and steps for an initial work-up.

Patient data and photos obtained with consent.

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# ABSTRACT PRESENTATION HIGHLIGHTS FROM THE 2023 AAAAI ANNUAL MEETING

Many oral abstracts posters and case reports were presented at the American Academy of Allergy Asthma & Immunology (AAAAI) Annual Meeting which was held in February 2023 in San Antonio Texas. We have selected the following seven articles due to their relevance to Canadian allergy and immunology clinical practice and research.

### Sublingual epinephrine as an EpiPen® alternative

Greenhawt, M. et al. (2023). Comparison of the pharmacokinetic and pharmacodynamic profiles of epinephrine delivered by a sublingually absorbed film (DESF), versus 0.3 mg administered by a standard IM injection or the EpiPen. *Journal of Allergy and Clinical Immunology. 151(2): AB4.*

Intramuscular (IM) injection of epinephrine for acute allergic reactions has several limitations, including patient delay in its administration, due to needle phobia and lack of knowledge on proper administration by caregivers and bystanders.

This study compared the pharmacokinetic and pharmacodynamic profiles of epinephrine delivered through a sublingually absorbed film (DESF), through a standard IM injection and via the Epipen®.

In the study, 24 healthy adults received either 12mg of epinephrine via DESF, 0.3mg via manual IM injection, or 0.3mg via the EpiPen®. DESF produced the fastest observed median time to maximum concentration (Tmax), of 12 minutes, versus 45 minutes for manual IM epinephrine, and 23 minutes for the EpiPen®.

The median Cmax of DESF was 294 pg/ml, compared to 411.2 pg/ml for the manual IM administration and 744.2 pg/ml for EpiPen® injection. Within minutes, the mean change in systolic blood pressure and diastolic blood pressure were highest with DESF, compared to both forms of IM injection, despite the higher Cmax with the intramuscular injections **(Figure 1-3)**. The study found no clinically meaningful safety concerns with DESF.

DESF is a novel prodrug of epinephrine. It will undergo a phase 3 trial later this year, with possible FDA approval in 2025.

These preliminary results suggest sublingual epinephrine could be an alternate effective treatment for acute allergic reactions. The ease of carrying and administering sublingual forms of epinephrine could address the challenges with the intramuscular epinephrine leading to its delay in use.

**Figure 1: Mean Change from Baseline in Systolic Blood Pressure**

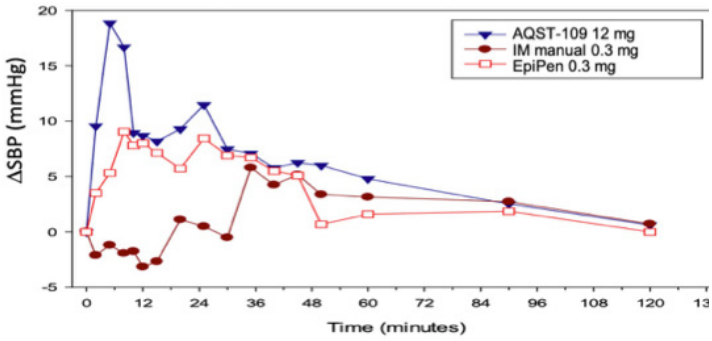



**Figure 2: Mean Change from Baseline in Diastolic Blood Pressure**

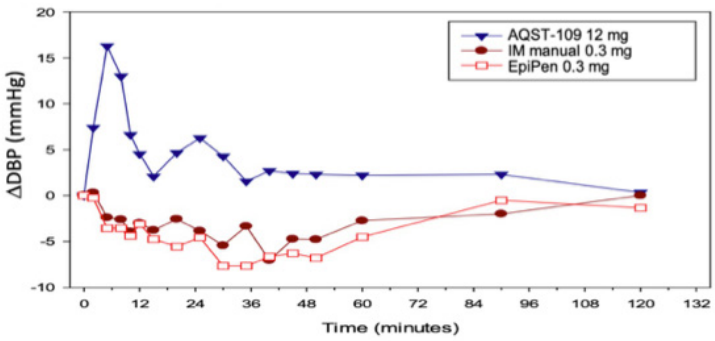
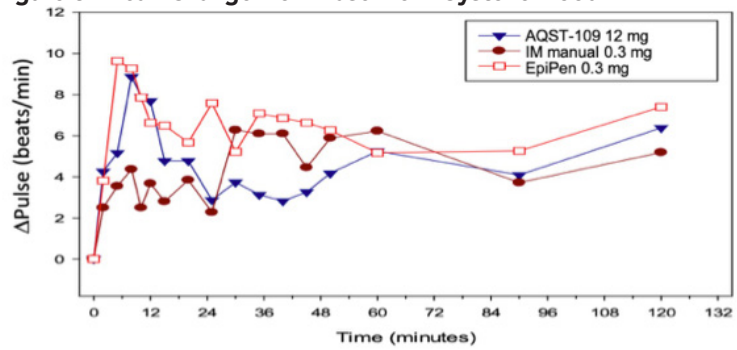



**Figure 3: Mean Change from Baseline in Systolic Blood**



**Nasal epinephrine results in plasma epinephrine concentrations similar as currently injectable available forms**

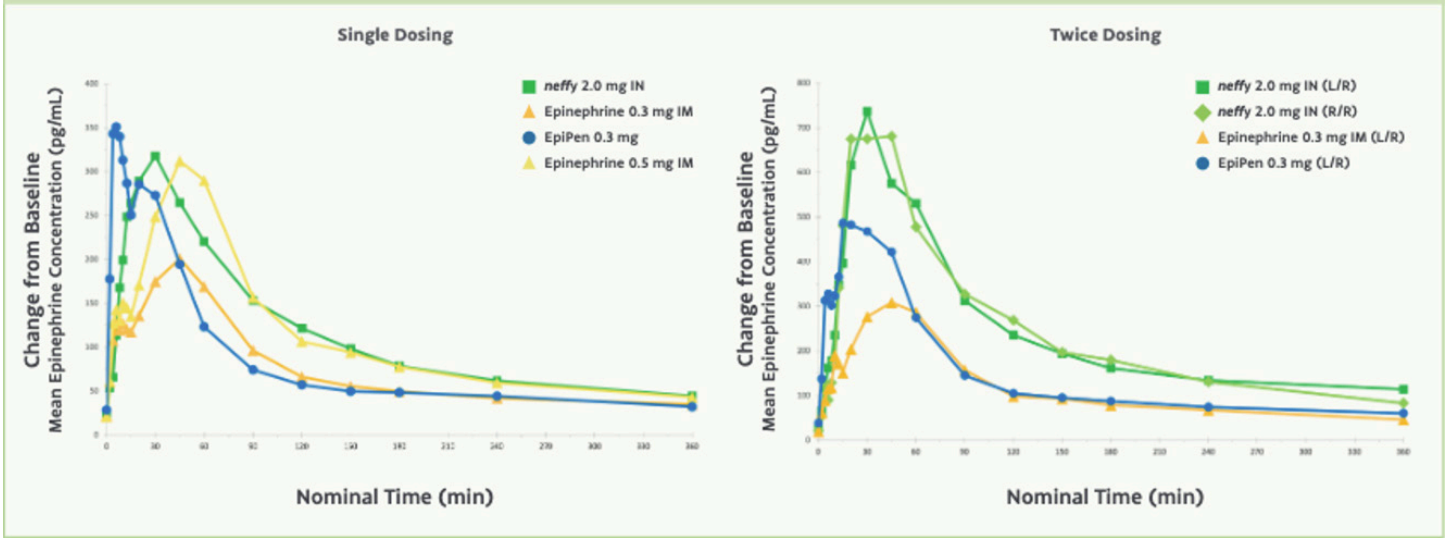
Lieberman, J. et al. ARS-1 (neffy® Nasal Spray) 2.0 mg Versus Epinephrine Injection Products: An Integrated Pharmacokinetic Analysis. *Journal of Allergy and Clinical Immunology. 151(2): AB5.*

Researchers analyzed the pharmacokinetic and pharmacodynamic data from five randomized, open-label phase 1 trials to compare an intranasal epinephrine spray with manual IM and auto-injection forms of epinephrine. The trials enrolled healthy adults; two of the five studies enrolled participants with a history of type I allergies. Patients received single doses as well as two doses, spaced 10 minutes apart, of epinephrine. There were 78 subjects who received 2mg of epinephrine via intranasal spray, 77 who received epinephrine via an auto-injection device EpiPen® (0.3mg), and 178 who received 0.3mg of IM epinephrine (0.3mg).

Both single and twice-dosed treatments for intranasal epinephrine spray (ARS-1) resulted in mean epinephrine plasma concentrations that were in range of the other two currently approved injection products. Following a single dose, mean Cmax values were 485 pg/mL for intranasal spray, 581 pg/mL for auto-injected epinephrine, and 277 pg/mL for IM injection. The median Tmax was 20.5 minutes for the intranasal spray, compared to 10 minutes for the auto-injected form and 45 minutes for IM injection. Systolic blood pressure, diastolic blood pressure, and heart rate values were comparable for all three treatment modes at both single and double dosing.

Based on these results, ARS-1 intranasal epinephrine spray ("neffy") shows promise as a future alternative to IM and auto-injector epinephrine. If approved, intranasal epinephrine could reduce dosing errors and treatment delays that can occur with the injectable forms.

**Figure 1: Change from Baseline - Mean Epinephrine Concentration versus Time Profiles by Treatment**




**Graded oral challenges an effective way to assess cephalosporin allergies in children**

Sillcox, C. et al. Assessing allergic reactions to cephalosporins in children. *Journal of Allergy and Clinical Immunology. 151(2): AB113.*

Patients labelled as having an antibiotic allergy results in substitute antibiotic usage often at greater expense and with risk of increased microbial resistance. These same patients may have ultimately outgrown their antibiotic allergies.

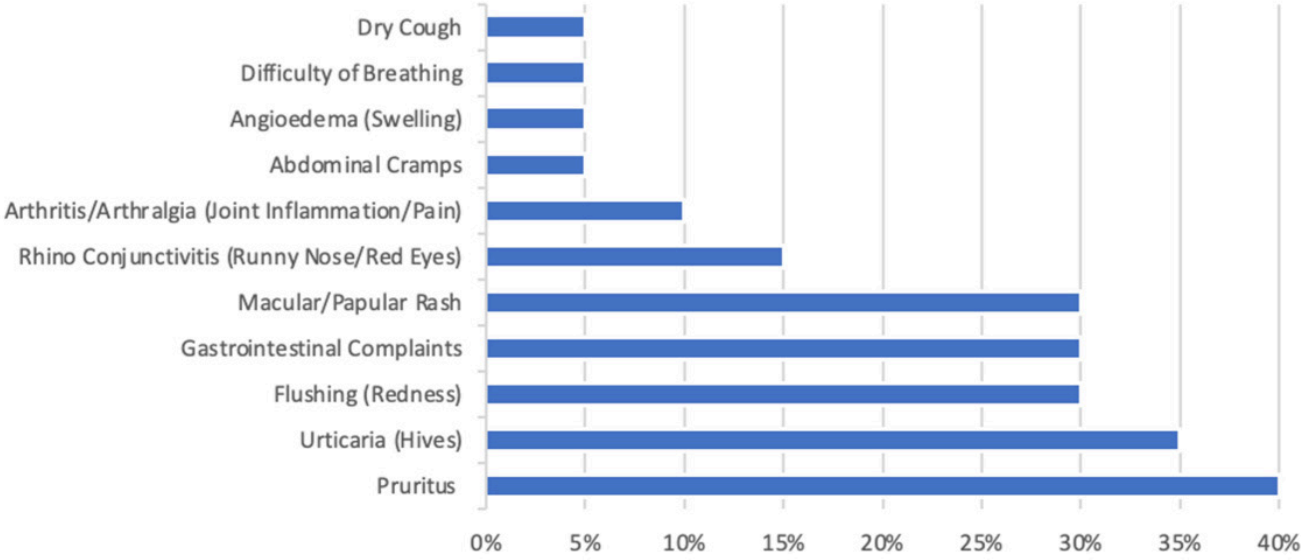
In the case of cephalosporin allergies (CA) in children, there is a need to help address the above concerns to allow their early re-introduction. Testing for cephalosporin allergy in children will likely decrease health care costs and enable children to receive both in the inpatient and outpatient setting safely.

A Canadian study recruited 218 children with suspected cephalosporin allergies across three sites, in Montreal, St. John's, and Winnipeg, from October 2013 to August 2022. As standardized skin testing allergens for oral cephalosporins are lacking, researchers utilized direct graded oral challenges (GOCs) to confirm or rule out CA. All index reactions were mild and cutaneous in nature. Children with anaphylactic histories to cephalosporins were excluded from this trial.

The median age of children in the study was 4.9 years, and cefprozil (Cefzil) was most common cephalosporin identified suspected index reaction. Children received 10% of the suspected cephalosporin dose initially, followed by the remaining 90% of the desired dose after 20 minutes. Patients were asked to report symptoms over the next week. Researchers subsequently contacted patients annually for the next three years, to identify any subsequent reactions to any antibiotic medications.

## Results - Symptoms of Positive Graded Oral Challenges

### Majority are dermal and or GI reactions




There were 22 (10%) reactions to the GOCs, 12 within one hour and 10 after one hour, with 32% of reactions occurring after eight hours. The majority of the reactions were dermal or gastrointestinal in nature. Pruritis (40%) and hives (35%) were the most common reactions, while abdominal cramps (5%) and difficulty breathing (5%) were among the least common reactions. Among those who had a negative response to the GOCs, 8% reported a subsequent adverse reaction to an antibiotic in annual follow-up calls. This longitudinal study supports the use of direct GOCs as an effective and safe tool for diagnosing cephalosporin allergies in children with histories of dermal reactions alone.

Future studies are needed to explore the safety of GOCs in adult populations, assess reactions to IV antibiotics following GOCs, and compare the sensitivity of GOCs to available skin tests.

**Penicillin direct oral challenges may be appropriate in some pregnant women**

Ramsay, A. et al. A Randomized Trial of Penicillin Skin Testing Versus 2-Step Direct Challenge for Penicillin Allergy During Pregnancy. *Journal of Allergy and Clinical Immunology. 151(2): AB207.*

Little is known about the safety of direct penicillin challenges in pregnant women. Given that penicillin is a first-line prophylactic therapy in Group B streptococcal-colonized women, clarification of true penicillin allergy in the pregnant female would result in less use of substitutes that are less effective against GBS and potentially more costly.

To assess the safety of direct penicillin challenges in pregnant women with histories of low-risk penicillin reactions, researchers at Rochester Regional Health in New York enrolled 38 pregnant patients who previously had mild or cutaneous-only reactions to penicillin. These reactions occurred, at minimum, five years prior to enrollment. The mean time since the index reaction was 23 years, and the mean gestation among the women in the study was 28 weeks. Study participants were randomized to receive either standard penicillin skin testing, followed by a dose of amoxicillin if the result was negative (22 patients), or a two-step direct amoxicillin oral challenge (16 patients).

Penicillin skin testing was negative in 20 patients, or 91% of participants, while none of the patients in the direct oral challenge group experienced a reaction. There were no serious adverse events in either group. The cost for the direct oral challenge was $187.46 per patient, compared to $301.73 per patient for penicillin skin testing.

As the direct oral two-step challenge was shown to be as safe as skin testing followed by an oral challenge, it may be clinically appropriate and more cost-effective to choose a two-step direct oral challenge over a penicillin skin test in pregnant patients identified with remote low-risk penicillin histories.

**Food-protein induced enterocolitis oral challenges rarely need intravenous access**

Patel, G. Intravenous Access Is Rarely Necessary For FPIES Oral Food Challenges. *Journal of Allergy and Clinical Immunology. 151(2): AB215.*

There are no established, internationally-accepted protocols for food-protein induced enterocolitis (FPIES) oral food challenges (OFC).

To provide evidence on the need for intravenous placement prior to a FPIES OFC, researchers retrospectively analyzed the medical charts of 108 children (54 male and 54 female) who underwent FPIES OFCs at the Children's Health Food Allergy Center in Dallas, Texas.

Over a two-year period, 108 children underwent 185 FPIES OFCs. The challenges were conducted at least one year after the FPIES allergy diagnosis.

Children had an IV placement in 44 of the challenges, while 141 challenges were conducted without IV access. The OFCs were conducted for peanut, soy, milk, baked egg, wheat and beef allergies.

Reactions occurred in 15.6% of the OFCs (29 of 185). Four of these reactions were treated with oral ondansetron, nine with intramuscular ondansetron, six with IV ondansetron, two with antihistamines, and six with IV fluid along with ondansetron; two of the reactions were not treated.

Of the 185 challenges, six (3%) involved IV rehydration after antiemetics. Of these six, three had an IV placed before the challenge, and three during the reaction. None of the children needed to be transferred to the emergency department.

These results show that FPIES OFC reactions rarely require IV rehydration. Roughly 1 in 7 FPIES children will react on re-challenge one year from diagnosis, with 1 in 5 of those who reacted, receiving IV fluids. Patient outcomes were similar, regardless of whether the IV was placed before or during the reaction.

**Pollen exposure could explain idiopathic anaphylaxis in children**

Nathan, M. Possible pollen induced anaphylaxis during elevated pollen levels in the environment in a cohort of idiopathic anaphylactic children. *Journal of Allergy and Clinical Immunology. 151(2): AB3.*

While anaphylaxis from pollen reactions is thought to be extremely rare, there is little data on the association between high pollen levels and anaphylaxis.

To assess the possible link, researchers gathered data on idiopathic anaphylaxis from the Cross-Canada Anaphylaxis Registry. They queried patients with outdoor idiopathic anaphylaxis on their known pollen allergy types (grass, tree, or weed), as well as the date and the location of their reaction. Additionally, researchers gathered data on average pollen levels for the three days leading up to each reaction. They employed a logistic regression analysis to evaluate the association between epinephrine use and pollen levels.

Of 159 children, aged 1 to 17, who presented to the Montreal Children's Hospital with idiopathic anaphylaxis, 41 children had confirmed pollen allergies. Among these 41 children, epinephrine was administered in 26 of the reactions, or 63% of the time. In the study, anaphylaxis was defined as either a reaction that involved two or more organ systems after exposure to a possible allergen or hypotension after exposure to a known allergen. The most common reaction symptoms were angioedema (63%), urticaria (56%) and breathing difficulties (51%).

The use of epinephrine was 2.49 times as likely during periods of higher tree pollen levels (p-value = 0.038). However, there was no association between reaction severity and the levels of ragweed or grass pollen.

The study suggests that tree pollen may play a role in idiopathic anaphylaxis in children during high pollen season. Larger studies are needed to confirm this link.

## HAE case study reveals challenges with contradictory guidelines in diagnosing HAE in infancy

Maria Fernanda Villavicencio and Timothy Craig
Friday, February 24th, 2023; 3:15 pm to 4:15 pm

The 2020 US Hereditary Angioedema (HAE) Association Medical Advisory Board Guideline does not recommend testing C4 inhibitor and C1 inhibitor antigenic levels before one year of age as they are highly variable. The guideline instead recommends C1-inhibitor functional activity to diagnose HAE during the first year, as it is more sensitive and specific.

However, the International World Allergy Organization/European Academy of *Allergy* and Clinical Immunology (WAO/EAACI) 2021 guideline notes that C1-inhibitor levels and/or functional activity are typically low in children younger than one year, with exceptions. The WAO/EAACI guideline requires at least two matching HAE test results, with the second one performed after one year of life, for a final diagnosis of HAE.

In this case study, a child with a family history of type I HAE underwent HAE screening at one year. The result was minimally low C4 levels at 9 mg/dL (the normal range is 10 to 40 mg/dL) and minimally low C1-inhibitor levels at 17 mg/dL (the normal range is 21 to 39 mg/dL) and with a normal C1-inhibitor function of 76%.

The child remained asymptomatic and was retested at two years of age. At this time, the child's C4 level was 4 mg/dL, the C1-inhibitor was 11 mg/dL, and the C1-inhibitor function level was 45%. Based on these results, the child was diagnosed with HAE Type 1. The child's first HAE attack occurred at four years of age, and presented with erythema marginatum, followed by angioedema of the face. Since then, angioedema episodes have reoccurred with a frequency of fewer than one per month.

This case shows that C1 inhibitor function during the first year of life may be normal and decrease into early toddlerhood, necessitating re-evaluation. This case report highlights the need for unified recommendations in using biochemical tests to diagnose HAE before age one. This is especially important given that genetic tests for HAE are not readily available for all Canadian patients.

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# MANAGEMENT OF HEREDITARY ANGIOEDEMA TYPE 1 AND 2 FOR CANADIAN ALLERGY AND IMMUNOLOGY PRACTITIONERS

**Background**

Hereditary angioedema (HAE) is a rare and debilitating disorder characterized by recurrent episodes of angioedema, without the presence of urticaria. These attacks can occur unexpectedly or as a result of various triggers, such as stress and surgery. The symptoms of HAE can significantly impact the quality of life of those affected; in severe cases, edema of the upper airway can be fatal.[1]

HAE type 1 and 2 are due to mutations in the SERPING1 gene leading to a deficiency in C1 inhibitor (C1- INH) and will be the focus of this article. HAE type 1 (HAE-1) is due to a decrease in the plasma level of C1-INH and type 2 (HAE-2) is due to a decrease in the function of C-INH. Other forms of hereditary angioedema have been identified with normal C1-INH (HAE nC1-INH) and are considerably rarer than HAE-1 and HAE-2. Their pathophysiology is not as well understood but pathogenic variants in certain genes have been identified in some families.

The prevalence of HAE is estimated at approximately 1 in 50,000 individuals and has been reported in all races. Both HAE-1 and HAE-2 are inherited in an autosomal dominant manner, although up to 25% of cases may occur *de novo* without a prior family history.[2,3] HAE-1 is estimated to occur in 80% to 85% of patients and HAE-2 in the remaining 15% to 20%.

A diagnosis of HAE-1 and HAE-2 can be confirmed by measuring levels of complement C4 and C1-INH antigen and functional levels on 2 occasions separated by at least 1 month. In these disorders, C4 levels are reduced as C4 is consumed by dysregulated C1-INH activity. Most HAE-1 and HAE-2 patients will have a reduced C4 level between attacks, and nearly all will have a reduced level during attacks. While C1-INH function will be reduced in both HAE-1 and HAE-2, the conditions are distinguished by a reduced C1-INH antigen level in HAE-1, and a normal or increased level in HAE-2. Genetic testing also plays an important role in confirming the diagnosis and may help identify the heritability of the condition.

It is imperative for allergists and immunologists to accurately confirm the diagnosis of HAE and coordinate individualized, patient-centred treatment. The 2019 International/Canadian Hereditary Angioedema Guideline, provides an evidence-based approach to managing HAE patients.[4] The objective of this article is to further assist healthcare providers in caring for patients with a confirmed diagnosis of HAE by outlining an approach to patient counselling and reviewing the principles of therapy.

We propose 5 essential items to consider in the management of all HAE patients: 1) Patient education; 2) On-demand therapy; 3) Short-term prophylaxis (STP); 4) Long-term prophylaxis (LTP); and 5) Genetic testing. We will also discuss special considerations for pregnant patients.

**1. Patient education**

Patients with HAE-1 and HAE-2 should understand the basic pathophysiology of the disease. Specifically, it is important for practitioners to communicate to them that they have a pathogenic variant in a gene responsible for the production of the C1 INH which, when absent, leads to the accumulation of bradykinin, which produces angioedema.

It is essential to discuss potential triggers with patients, such as trauma, physical pressure, emotional stress, menstruation and pregnancy. Patients should be advised to inform their healthcare team of any planned dental procedures or surgeries. A list of approved therapies to use in outpatient or inpatient procedures follows below.

The use of medication should be carefully reviewed with patients, as several drug classes that affect bradykinin metabolism may exacerbate the symptoms of HAE. Patients should be informed to avoid all angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor-neprilysin inhibitors (ARNIs) such as sacubitril, and dipeptidyl peptidase-4 inhibitors (DPP-4is) such as sitagliptin and saxagliptin. Similarly, oral contraceptive use should be avoided as estrogen can trigger attacks. In follow-up appointments, healthcare providers should inquire about any interim diagnoses of hypertension or diabetes and ensure that potentially triggering medications are avoided.

**2. On-demand therapy**

"On-demand therapy" is a term that refers to the treatment of acute angioedema attacks, either at home or at a local healthcare facility. In Canada, there are several options available for this purpose.

Berinert® (CSL Behring, Ottawa, ON) is a plasma-derived C1-INH (pdC1-INH) agent approved for use in adults and children. It replaces the deficient C1-INH protein in patients and is administered as a single intravenous push at a dose of 20 U/kg (rounded to the nearest 500 mg). Berinert may be administered by patients, caregivers or healthcare professionals. Patient and caregiver training may be required to establish and use an intravenous line.[5]

Icatibant (Firazyr® [Takeda, Minneapolis, MN]) is a bradykinin 2 receptor antagonist approved for use in Canada in patients 2 years and older. Dosing is 30 mg subcutaneously. The product is supplied in pre-loaded syringes.[6]

Cinyrze (Takeda, Minneapolis, MN) is a plasma-derived C1-INH agent approved for use in Australia and the European Union for the treatment of acute HAE. It is approved in Canada for long-term prophylaxis only. However, it may be used off-label for rescue in Canada if supply issues are present.[7] Initial dosing is 1,000 U intravenously initially, followed by an additional 1,000 U if there is no response.[8]

Ecallantide (Kalbitor® [Takeda, Minneapolis, MN])) is a selective, reversible inhibitor of plasma kallikrein. This agent is not currently licensed in Canada; it can be requested by the Special Access Program of Health Canada if required. Dosing is 30 mg subcutaneously, administered as three 10 mg pre-filled syringes.[9]

Frozen plasma should not be used for HAE attacks as the evidence for its effectiveness is limited.[10] Although plasma contains C1-INH, the protein that is deficient in patients with HAE, the level of C1-INH in frozen plasma is not sufficient to provide effective treatment. In Canada, frozen plasma is not widely available and the process of obtaining it can be time-consuming. As such, guidelines do not recommend this as treatment unless other evidence-based therapies are not available. Additionally, other proteins that are present in plasma may have negative effects on patients with HAE.

Based on the agent selected, a care plan should be created and implemented at a local healthcare facility.

**3. Short-term prophylaxis**

Short-term prophylaxis (STP) reduces the risk of an angioedema attack in response to an anticipated trigger, such as medical or dental procedures. It is essential for patients to be educated about the potential triggers of an attack, and to be aware that even with the administration of STP, an attack may still occur within 72 hours of the procedure. Patients should also be informed about other potential triggers, such as emotional stress.[4]

Guidelines recommend considering STP for any medical, surgical, or dental procedure.[4] Furthermore, HAE-specific acute treatment should be made available during and after any procedure. The decision to initiate STP should be made collaboratively between the patient and their healthcare team. In cases where STP is not used, two doses of on-demand therapy should be readily available.

Intravenous plasma-derived C1-INH agents (Berinert or Cinryze) are recommended for STP, administered at a dose of 20 U/kg IV within an hour before a procedure.[4] If plasma-derived C1-INH is not accessible, attenuated androgens or frozen plasma can be considered, particularly in situations where on-demand therapies are not available.

**4. Long-term prophylaxis**

Patients with recurrent angioedema attacks may benefit from regular treatment with long-term prophylaxis (LTP) to reduce the frequency and severity of attacks. Even with LTP, patients should continue to have access to at least two doses of on-demand therapy, as breakthrough symptoms may occur.

There are no set criteria regarding the initiation of LTP. The decision to initiate LTP should be made collaboratively between the patient and their healthcare team, considering factors such as the number and frequency of attacks, the severity of previous attacks, access to emergency treatment (particularly in remotely located patients), and the impact of the attacks on the patient's quality of life.

In patients with HAE-1 and HAE-2, plasma-derived C1-INH administered intravenously or subcutaneously is an effective therapy for LTP. Subcutaneous administration may be preferred as it offers patients greater convenience; additionally, recent literature has proven it to be more efficacious.[11] Options available in Canada include Haegarda, Cinryze, and Berinet (off-label).[5]

Haegarda® (CSL Behring, King of Prussia, PA), a form of subcutaneous (human) C1-INH, is approved in Canada for use in patients 12 years of age and older at a dosage of 60 U/kg subcutaneously every 3-5 days.[12]

Cinryze® (Takeda, Minneapolis, MN), is a form of plasma-derived C1-INH approved for patients 12 years and older at a dosage of 1,000 U intravenously every 3-4 days.[8] Although it is not approved for LTP,

Berinet® (CSL Behring, Ottawa, ON) may also be used in a similar fashion at a dose of 20 U/kg.[4,5]

Lanadelumab (Takhzyro® [Takeda, Minneapolis, MN]) is a fully humanized anti-active plasma kallikrein monoclonal antibody that is approved in Canada as LTP. Funding for lanadelumab is available for patients who have had at least three HAE attacks requiring injectable on-demand treatment within any 4-week period in their disease.[13] Dosing is 300 mg subcutaneously every 2 weeks. This is reassessed at the 6-month mark, at which time the interval can be prolonged to up to every 4 weeks if the patient is stable.[14]

Berotralstat (Orladeyo [BioCryst®, Durham, NC) is an oral plasma kallikrein inhibitor approved by Health Canada in 2022 for LTP in adults and pediatric patients 12 years of age and older. The dosage is one 150 mg tablet daily. Abdominal side effects associated with this product typically subside following the first 2 weeks.[15] Public funding has not yet been approved but the product is available through the manufacturer's patient support program or private payers.[16]

Historically, androgens such as danazol (Cyclomen®, Sanofi, Bridgewater Township, NJ) have been used for LTP. Although it is not first-line therapy, danazol may be used as LTP at a low dose of 200 mg or less per day. Routine bloodwork and repeated abdominal ultrasounds are required for patient monitoring. Further guidance regarding monitoring is outlined in the 2019 International/Canadian HAE guideline.[4]

Currently there are no guidelines for LTP in patients with HAE nC1-INH, due to a lack of sufficient data.

**5. Genetic testing**

Patients with HAE-1 and HAE-2 should be informed that their condition is inherited in an autosomal dominant manner, with the explanation that the offspring of individuals with this condition have a 50% chance of inheriting the condition. It is important for all family members, including the extended family, to have screening bloodwork performed. Due to the unreliability of biochemical testing in children,[17] C1-INH testing should be performed after 1 year of age. At our center, patients interested in family planning are referred to a genetic counsellor.

**Pregnancy**

Patients with HAE may experience varying attack frequency during pregnancy, with no definitive pattern. Due to ethical concerns, no randomized trials have been conducted in this population. The recommended treatment for acute symptoms in pregnant HAE-1 and 2 patients is plasma-derived C1-INH.[4] Routine short-term prophylaxis (STP) is not recommended for uncomplicated vaginal deliveries, as clinical studies have not shown an increased attack frequency in pregnant HAE patients. However, STP may be considered for patients with recurrent attacks in their third trimester or a history of genital angioedema due to mechanical trauma. Additionally, STP is recommended for patients undergoing a C-section or intrapartum instrumentation. Dosing may need to be repeated based on the timing of delivery, and two doses of on-demand therapy should be readily available during and post-delivery including for patients who receive STP.

**Summary**

The management of patients with HAE is a multifaceted process that requires a thorough understanding of the underlying genetic causes and the various treatment options available.

In addition, dose monitoring and regular follow-up with a healthcare provider are essential for ensuring proper management of HAE and to minimize the risk of complications. With appropriate care, patients with HAE can lead fulfilling lives, despite the challenges that accompany this rare, unpredictable disorder.

### *Clinical pearls*

1. Patient education about HAE is necessary. Patients must understand potential triggers for angioedema attacks.
2. Multiple agents are available for acute attack management, including intravenous pdC1-INH (Berinert®, off-label Cinryze®) and subcutaneous icatibant (bradykinin 2 receptor antagonist). It is recommended that a care plan is formulated information on the patient's local hospital Emergency Department or urgent care centre to ensure that therapies are readily available when needed.
3. Intravenous pdC1-INH products (Berinert®, Cinryze®) are recommended for STP prior to anticipated triggers (e.g., medical procedures). A second of dose of on-demand therapy should be available post-procedure.
4. LTP should be considered in patients with significant disease burden and access to acute care. Agents currently available for LTP include subcutaneous or intravenous pdC1-INH (Haegarda®, Cinyrze®, off-label Berinert®); the subcutaneous plasma kallikrein inhibitor lanadelumab; and the oral plasma kallikrein inhibitor berotralstat. Danazol may be an option for some patients.
5. All immediate and extended family members of HAE-1 and HAE-2 patients should have genetic screening performed as it is an autosomal dominant disease. Referral to a genetic counsellor should be considered.
6. Pregnant patients do not routinely require STP for uncomplicated vaginal delivery, although STP may be considered based on attack frequency, and should be used if a C-section or intrapartum instrumentation occurs.

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Dr. Nair graduated in 1989 from the University of Kerala Medical College in Trivandrum in India. He trained in Internal Medicine and in Respiratory Medicine at the University of Kerala, Royal Sussex County and Royal Sunderland Hospitals in the UK, and at McMaster University in Canada, where he did his doctoral thesis on leukotriene biology in asthma. He is currently the Frederick E. Hargreave Teva Innovation Chair in Airway Diseases & Professor of Medicine in the Division of Respirology at McMaster University, an Adjunct Professor of Medicine at McGill University, and a Staff Respirologist at the Firestone Institute for Respiratory Health at St. Joseph's Healthcare Hamilton. At the Firestone Institute, through inter-disciplinary clinics, he looks after patients with severe asthma and other complex airway and eosinophilic disorders, and provides access to them for biologics, molecular microbiology, novel pulmonary imaging, and bronchial thermoplasty, and opportunities to participate in research programs. His laboratory, funded by federal and provincial agencies, the Canada Research Chair program, AllerGen National Centre of Excellence, and industry partners, characterizes the types of bronchitis in airway diseases using biomarkers in sputum, identifies mechanisms of persistent bronchitis and airway hyperresponsiveness, and explores targeted therapies using small molecules and biologics. The patient-centred translational research program has been recognized by the Fellowships of the Canadian Academy of Health Sciences, the European Respiratory Society and the American College of Chest Physicians, the ATS Ann Woolcock Award, and the Asthma Society of Canada Bastable-Potts award, and has contributed to over 300 peer-reviewed publications (H-index 67, >21,000 citations) in major respiratory, allergy, and general medical journals. These observations, including 6 publications in the New England Journal of Medicine, paved the way for the development and approval of biologics that are currently available to treat patients with severe asthma.

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# SEVERE ASTHMA PHENOTYPES: CHALLENGES AND OPTIONS FOR CONTROL

## Introduction

The practice of medicine has evolved from "arm-chair medicine" through "evidence-based medicine" to "precision medicine". Medical literature has seen a proliferation of the use of the phrases "precision medicine" and "personalized medicine," with little distinction made between the two. While both strategies promote individualizing patient care, precision medicine is guided by information based on the genes, proteins, metabolites, and other biomarkers in the human body. In addition to these biological markers, personalized medicine would consider various social, economic, behavioural, and environmental factors that might be specific to a particular individual in planning a treatment strategy unique to that individual. The term P4 Medicine (Predictive, Preventive, Personalized and Participatory) has also been proposed to reflect the increased understanding and implications of the pathobiology of disease on management strategies.[1] The use of biologics and cell-based therapies, particularly in cancer therapeutics, has demonstrated the power of these strategies.[2] This brief review will focus on how this strategy is currently being applied in the management of severe asthma.

## Definition of Phenotypes and Endotypes

A precise understanding of the pathobiology of disease and definitions is paramount to the practice of personalized medicine. The concept of "nominalism" as opposed to "essentialism" of asthma definitions is helpful to understand the mechanisms of disease and to identify the "treatable traits" that contribute to asthma symptoms and severity in individual patients.[3] This involves identifying obvious clinical and physiological features (generally referred to as phenotypes),[4] and specific biological characteristics that provide unique mechanistic insights (generally referred to as endotypes).[5] These characteristics are generally identified based on unbiased hierarchical cluster analysis from data collected from large numbers of well-characterized patients in various cohort studies and cross-sectional studies.

Therefore, phenotypes include features such as: "early-onset or late-onset asthma"; "atopic or non-atopic asthma"; "obese or non-obese asthma"; "aspirin-sensitive or non-aspirin-sensitive asthma"; "smoker or non-smoker"; "nasal polyposis-associated asthma or non-nasal polyposis-associated asthma"; and "asthma with fixed airflow obstruction or asthma with significant bronchodilator reversibility". Triggers of bronchoconstriction, including occupational vs non-occupational; virus vs non-virus; exercise; cold air; and thunderstorm-related have also been employed to define phenotypes.[6] While these clinical features are very helpful in predicting the clinical course of disease and, to some extent, responses to treatment, they do not provide precise information about the pathobiology of these features. A good example of this is so-called "exacerbation-prone asthma". The reason for exacerbation might well be inappropriate therapy afforded to the patient rather than a patient characteristic.

Conversely endotyping endeavours to provide significant biological insights into specific disease or symptom manifestations. This requires the development and validation of simple clinically relevant and useful biomarkers that might reflect the underlying biology. The most widely employed marker is the eosinophil number in circulation or in the airway secretions (sputum). The term "eosinophilic" asthma is increasingly being used to classify patients with asthma whose symptoms and severity are believed to be mediated by the eosinophil, although this may not always be the case as a raised eosinophil number alone may not indicate that the key effector cell in the pathobiology of disease in that patient is the eosinophil. Thus, the presence or absence of eosinophils or their numbers is not an endotype. The mechanisms or cytokine pathways that lead to eosinophil recruitment are what truly constitute an endotype. The use of omics platforms has enabled the identification of genes (transcriptome); proteins (proteome); metabolites (metabolome); lipids (lipidome); and environmental factors interacting with biological factors (exposome), among other factors, to further endotype asthma.[7]

## Identification of Phenotypes and Endotypes in Clinical Practice

A summary of the measurements or observations that are currently being used in our clinic at the Firestone Institute for Respiratory Health is shown in **Table 1**. Some of the examples of phenotyping guiding therapy include: "allergic asthma" responding well to allergen immunotherapy or to omalizumab; late-onset eosinophilic asthma responding well to anti-IL5

biologics; "aspirin-exacerbated asthma" responding to aspirin avoidance or aspirin desensitization; "obesity-related asthma" being associated with airway hyperresponsiveness and bronchomalacia; and "neutrophilic or non-eosinophilic asthma" characterized by susceptibility to recurrent airway infections.

Currently, there are only three biomarkers widely available for clinical use with which to gain insights into endotypes (although these markers are not precise indicators of the biology of the disease). These are total (or specific) IgE, eosinophil numbers in blood or in sputum, and the fraction of exhaled nitric oxide (FeNO). The relative merits and disadvantages of these three biomarkers have been extensively reviewed.[8-10] While raised total IgE indicates allergy, it has very limited value in predicting response to a particular biologic. A combination of clinical features such as measuring airway hyperresponsiveness, FeNO, and blood (and preferably sputum) eosinophils can reasonably guide our choice of biologics for severe asthma. There are currently seven biologics approved for use in Canada.

**Application of biomarkers and phenotyping/ endotyping to manage severe asthma**

**A. Current clinical practice**

Current clinical practice, which employs the above biomarkers, are endorsed by most National[11] and International[12] asthma guidelines including the Canadian Severe Asthma guidelines.[13] The general principles are as follows:

a) Confirm diagnosis of asthma with objective demonstration of variable airflow obstruction (peak flow, bronchodilator response or bronchoconstrictor response)

b) Commence treatment with inhaled corticosteroids and bronchodilators (long-acting anti-cholinergics and long-acting beta-agonists), after checking inhaler technique and advising on allergen-avoidance measures, and regularly encouraging adherence to prescribed therapy. Allergen immunotherapy by adequately trained physicians is also effective in patients whose asthma is driven by one or two proven allergen sensitizations.[14]

c) Most clinical trials have suggested that additional biomarkers are unlikely to make a significant difference to asthma outcomes compared to good clinical assessment and a spirometry.[15,16]

d) Increase the dose of inhaled corticosteroids and consider oral corticosteroid in patients with persistent raised blood eosinophil count (typically >300/μL). A persistently raised FeNO (typically >35 ppb), particularly when it is suppressed following a witnessed administration of corticosteroid, would indicate poor adherence.[17]

e) With ongoing symptoms indicating poor control, additional endotyping/phenotyping is recommended. Early-onset asthma, young age and history of clinical allergies, along with raised blood eosinophil or total or specific IgE, would indicate omalizumab as the next step in the therapeutic algorithm. Conversely, late-onset asthma (whether associated with IgE or not); raised blood eosinophils, particularly associated with older age; nasal polyposis; and prednisone dependence (or frequent, 3-4 or more/year) might suggest an anti-IL5 biologic as the first choice.[18] Currently available biomarkers do not help to differentiate between the three anti-IL5 biologics. A persistently raised FeNO (often >35-50 ppb) despite normalizing or modest blood eosinophil count in patients with ongoing nasal polyposis or atopic dermatitis would suggest dupilumab as the next choice of biologic. Currently, there are no unique biomarkers that would help predict response to tezepelumab. It is claimed that biologics might be effective in all asthmatics including those with normal or low blood eosinophils or low FeNO. While this might be true for patients on high doses of inhaled corticosteroids, the efficacy of tezepelumab in the truly prednisone-dependent patients is still unproven.[19]

**B. What can additionally be achieved in a research-supported environment?**

The key to managing severe asthma and practicing precision medicine is to see patients at the time they are experiencing exacerbations,[20] (rather than adhering to the standard action plan of doubling inhaled steroids, or using prednisone or antibiotics); to assess if the symptoms (and reduction in airflow, FEV1) are due to luminal obstruction by eosinophils, neutrophils, other cell types, mucus, smooth muscle constriction, or airway wall thickness (or a combination of the above); and to target the dominant process that is contributing to the pathobiology (**Figure 1a**).[21]

A baseline blood eosinophil count, while a predictor of response to ALL biologics, does not help to discriminate between the biologics, and particularly is not helpful in monitoring the response to biologics or in assessing exacerbations while on biologics.[22] Additional biomarkers that are (and can be) measured include: airway mucus (assessed by a CT mucus score);[23] sputum eosinophils and sputum neutrophils, sputum autoantibodies; sputum cytokines; and immunophenotyping. This includes assessment of primary and secondary immunodeficiencies (including whole exome sequencing), NK cell and macrophage functions, and the consequence of luminal obstruction by functional $Xe^{129}$ ventilation MRI. The application of these technologies to initiate and switch between biologics is summarized in (**Figure 1b**).

This strategy[24] provides direction for deciding between the three anti-IL5 biologics considering the intensity of sputum eosinophilia, the presence of endogenous IgG autoantibodies in sputum, NK cell dysfunction, and anti-drug antibodies. For example, intense eosinophilia in sputum (often >20%) requiring >15 mg daily prednisone and in the presence of endogenous autoantibodies, would be associated with suboptimal response to the approved 100 mg subcutaneous dose of mepolizumab in almost 50% of prednisone-dependent patients.[25] Patients with NK cell dysfunction or anti-drug antibodies might demonstrate sub-optimal response to benralizumab.[26] Patients with severe airway hyper-responsiveness without demonstrable airway inflammation are likely to best respond to bronchial thermoplasty.[27] Persistent airway neutrophilia, unless otherwise proven, indicates an airway infection and should prompt investigations for susceptibility to such infections.[28]

## C. Future Diagnostic and Treatment Modalities

Airway measurements are critical in the management of severe asthma. Point of care assessments of airway eosinophilic[29] and neutrophilic activities[30] are likely to be available for clinical use. Comprehensive assessments, using large scale omics platforms, computational analytics andtopological data analyses would precisely characterize the specific inflammatory pathways (Th2 high or Th2 low) and the airway microbiome; and develop "handprints" for individual patients (as envisaged by the U-BIOPRED program),[31,32] in order to truly individualize therapies for patients with severe asthma (**Figure 2**).

## Summary

In recent years tremendous advances in biotechnology have resulted in the development of effective medications, biologicals and technologies for bio-imaging and bio-intervention to treat patients with asthma. Currently, they are being more widely studied in adult asthmatics than in children with severe asthma. However, the same principles apply to the pediatric population.[33] What is required is to truly practice endotyping and precision medicine rather than giving perfunctory attention to this strategy. It is not possible to practice true precision medicine and to achieve optimal asthma control in every patient by solely monitoring a blood eosinophil count that is simply an overall marker of the burden of a Th2 disease. True personalized medicine requires: careful clinical examination; identifying phenotypes based on clinical characteristics; endotyping based on airway inflammatory responses and the pathways that modulate them; biomarkers and bio-imaging that reflect these processes; and selecting the appropriate therapy for the individual with consideration of their behavioural, social, economic, and environmental factors.

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| Phenotype | Investigations |
|---|---|
| **CLINICAL** | **BLOOD** |
| Atopy | CBC |
| Rhinosinusitis | Vasculitis workup |
| Obesity | Autoantibodies (blood/sputum) |
| Late-onset | B12, tryptase |
| ASA sensitivity | AAT |
| Infective bronchitis | Routine chemistry |
| **PHYSIOLOGICAL** | **IMAGING/PULMONARY** |
| Reversibility | CT/fMRI thorax |
| COPD | CT sinus |
| AHR | Echocardiogram |
| Tachyphylaxis | Full PFT |
| **INFLAMMATORY** | **HAEMATOLOGY (when indicated)** |
| Sputum eosinophilia | Bone marrow |
| Sputum neutrophilia | Cytogenetics |
| Blood eosinophilia | T-cell and receptors |
| Vasculitis | Cytokines |
| HES | |
| **CURRENT TREATMENT** | **OTHER (as indicated)** |
| Prednisone | GI (endoscopy) |
| High dose ICS | Stool |
| LABA | Skin prick test |
| LTRA | Bone density/Optometry |
| LAMA | EMG/NCV |
| Biologics | Sputum microbiome |
| Cytotoxics | FeNO |
| Antibiotics | |
| Nasal CS | **CONSULTS** |
| Sinus surgery | GI |
| Immunotherapy | Psychiatry |
| | ENT |
| **ASTHMA EDUCATION** | Allergy |
| Inhaler technique | Rheumatology |
| Compliance | Endocrinology |
| | Sleep medicine |

***Table 1*** *A checklist of biomarkers and endotyping to assess patients with severe asthma in an outpatient severe asthma clinic; courtesy of Parameswaran Nair, MD, PhD, FRCP, FRCPC*

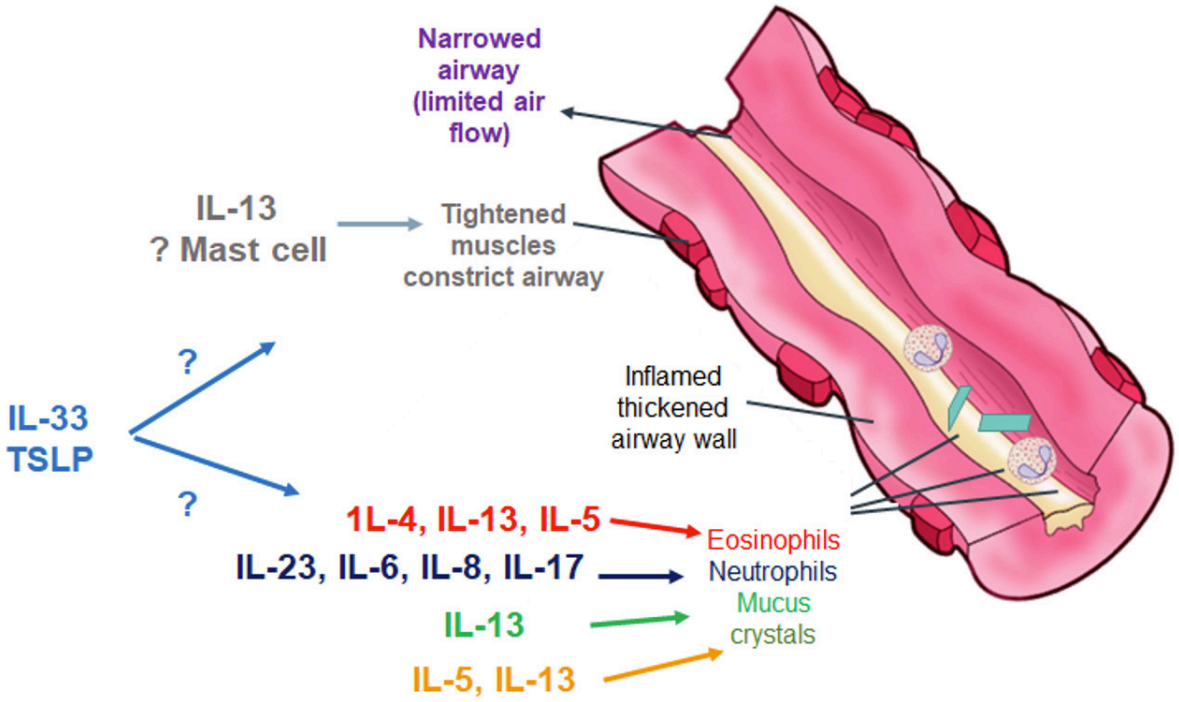



***Figure 1a*** *Contributors to severity and symptoms in asthma; reproduced with permission from Nair et al, 2021.*

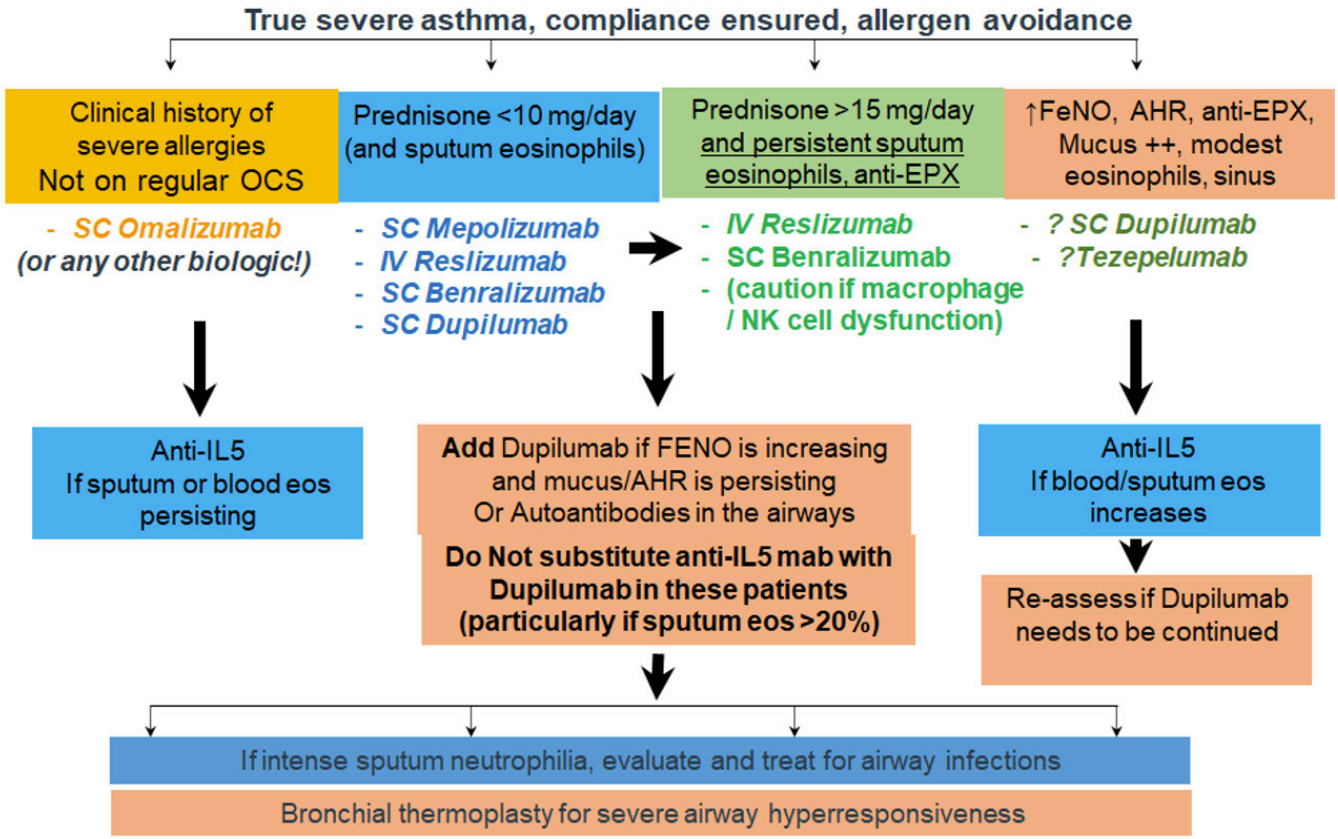



***Figure 1b*** *A strategy to initiate and switch biologics; reproduced with permission from Venegas Garrido C, et al, 2022*

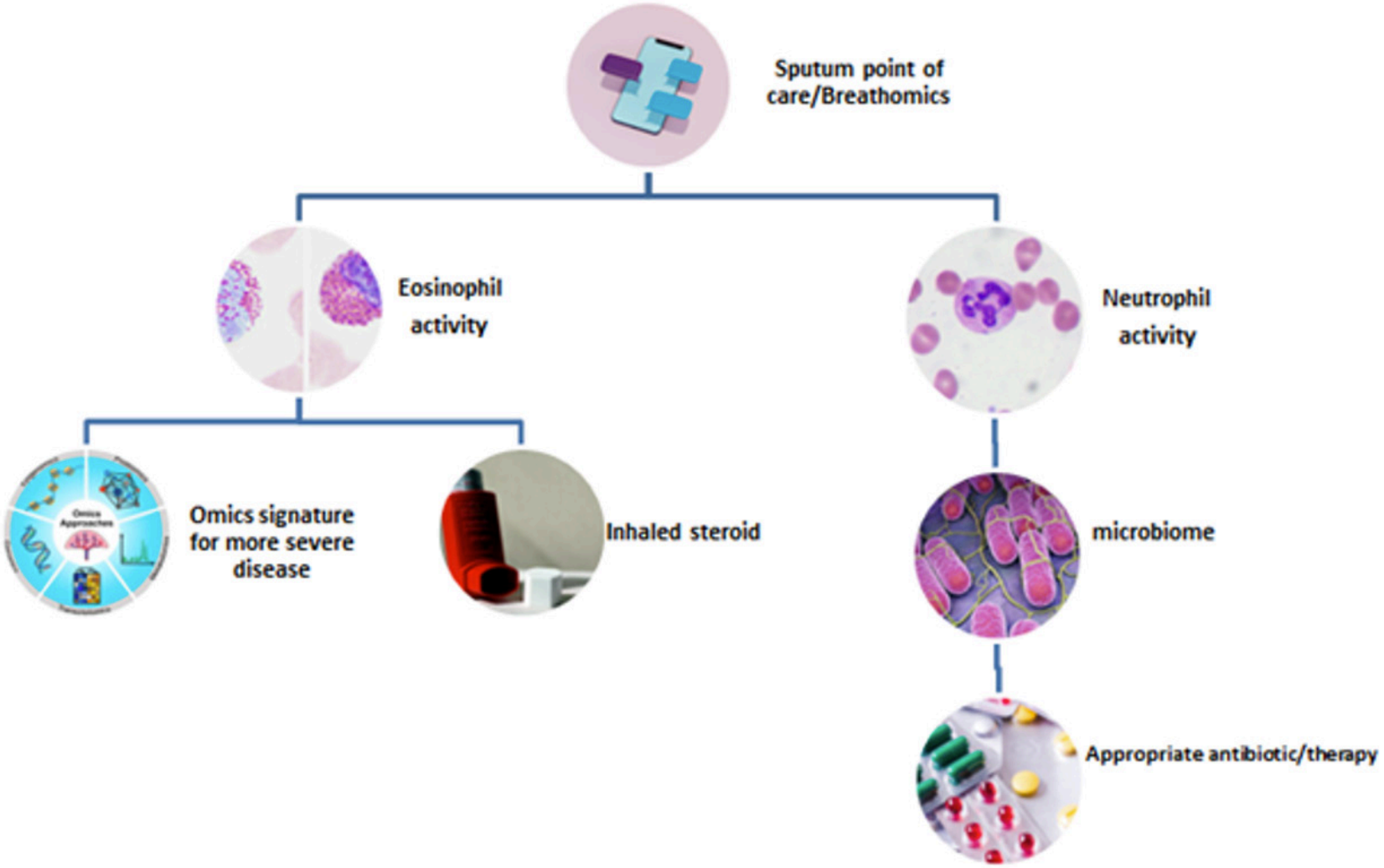



***Figure 2.*** *The concept for the future. Point of care tests would detect eosinophilic or neutrophilic activity in sputum that would then lead to the application of "omics" platforms to precisely identify the Th2 pathways or the microbial dysbiosis that leads to the cellular patterns, to guide therapy; courtesy of Parameswaran Nair, MD, PhD, FRCP, FRCPC*

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## Rachel Freeman, MSc, RD



Rachel Freeman is a registered dietitian currently working in pediatric outpatient clinics at McMaster Children's Hospital, and she also runs her own small virtual pediatric private practice nutrition clinic. She has special interests in working with children (and their families) with food allergies (both IgE- and non IgE- mediated), as well as in pediatric cystic fibrosis. She graduated from the University of Guelph in 1998 with an Honours degree in Biological Sciences and a Masters degree in Human Biology and Nutritional Sciences and Immunology, and she completed her Practical Training Program in Clinical Nutrition (Internship) at Hamilton Health Sciences in 2001. She is a member of the College of Dietitians of Ontario, and of Dietitians of Canada.

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# FOOD ALLERGY AND PEDIATRIC NUTRITION: UNDERSTANDING REPLACEMENT NEEDS FOR THE COMMUNITY ALLERGIST

**Introduction**

Food allergies are reported to affect between 7% and 10% of children in the developed world.[1,2] Most children develop food allergies within the first 2 years of life, which is a crucial period of growth and development.[3] Currently, no cure exists for food allergies; traditionally they are managed by avoiding the ingestion of the allergen to which a child is allergic. Additional emerging therapies include desensitization and/or inducing tolerance to the allergens.[4-6] Eight foods account for more than 90% of food allergies: milk, soy, wheat, eggs, peanuts, tree nuts, fish, and shellfish.[2] The elimination of any of the nutrient-dense foods from the diet without adequate substitution may result in poor nutrient intake and impaired growth in children.[7]

**The role of macronutrients and micronutrients**

A child requires a delicate balance of macronutrients (carbohydrate, protein, fat), as well as micronutrients (vitamins, minerals, trace elements) from their diet to promote growth and weight gain, and to support a healthy immune system.[8,9]

Macronutrients provide energy and the foundational elements required for growth in children. Inadequate substitution of any food group can result in insufficient energy intake and undernutrition.[11] The term "undernutrition" as defined by the World Health Organization (WHO) includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age), and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals).[12] Several studies have reported that children with multiple food allergies were shorter than children with one food allergy, and that weight for age percentiles decreased as the number of food allergies increased.[11]

Some of the most common allergens, such as milk, egg, soy and wheat are important sources of carbohydrates, protein and fat; therefore, avoidance diets must be carefully planned to ensure that nutritional requirements are met. Children require approximately 45%-65% of their daily energy from carbohydrates, 5%-30% from protein, and 25%-40% from fats, depending on their age and stage of growth and development. (**Table 1**)[8,9]

Micronutrients are needed by the body in very small amounts, but each micronutrient has a critical impact on the body's health, and a deficiency in any of them can cause severe and even life-threatening conditions. Micronutrients perform a range of functions, including enabling the body to produce enzymes, hormones and other substances required for normal growth and development.[12] Each food contributes its particular profile of micronutrients, and deficiencies resulting in negative health outcomes can occur when foods are eliminated without adequate supplementation. For example, Vitamin D deficiency may result in rickets; iron deficiency may result in anemia; and iodine deficiency may result in goiter. Most deficiencies are preventable through nutrition education and patient counselling, as well as the consumption of a healthy diet

| | |
|---|---|
| Carbohydrate<br>(45%-65% of energy in children) | Grains, fruits, starchy vegetables, juice, certain dairy products |
| Protein<br>(5%-30% of energy in children) | Meats, poultry, fish, dairy products, tree nuts, peanuts, legumes, seeds, eggs, soy |
| Fat<br>(25%-40% of energy in children) | Milk and dairy products (not skim), butter, margarine, vegetable and seed oils, nuts, avocado, fish, poultry, meat |

*Table 1: Dietary sources of macronutrients; courtesy of Rachel Freeman, MSc, RD*

consisting of diverse foods, and food fortification and supplementation where needed.

The greater the number of foods to which a child is allergic, the more complicated it may be for the child to attain the nutrition they require for optimal growth and health, and the greater the effect of undernutrition on their growth.[11] A registered dietitian can play a significant role in aiding a family in assessing a child's current nutrient intake. They are also in a position to suggest replacement foods and/or supplements to provide all the nutrients the child needs to thrive in good health, within the context of their food allergies and preferences.[6,13]

It is especially important that food allergies are diagnosed accurately so that a child does not unnecessarily avoid foods or food groups essential to growth. Several clinical studies have demonstrated that the greater the number of foods to which a child is allergic and avoiding, the greater the impact of the resulting missing nutrients on their nutrition, growth and development, particularly if they are not replacing the missing nutrients in their diet.[14] Parental perceived food allergy (a parent is convinced that their child is allergic to foods to which they are not actually reacting) can lead to severe exclusion diets with nutritional consequences, including failure to thrive; additionally, it could potentially increase the risk of developing an IgE-mediated food allergy.[15,16]

Although elimination of dietary allergens may appear simple ("don't eat the foods to which you are allergic"), it is not without risk. Children with food allergies are at higher nutritional risk than adults, as they are more likely to need to avoid foods of greater nutritional importance for growth, such as milk and eggs. Furthermore, their nutritional needs for growth and development are substantial and unique.[6] Several of the most common food allergens (milk, eggs, wheat and soy) are foods that commonly comprise the greatest proportion of a growing child's nutritional needs.

One of the most common pitfalls seen in pediatric allergy practice occurs when an infant is diagnosed with a cow's milk allergy. A nursing mother will be instructed to eliminate cow's milk protein and soy from her own diet in order to continue nursing, and an infant on a cow's milk formula will have to discontinue and find a dairy-free (and often soy-free) alternative. Often, there are no further instructions given as to what alternate or dairy-free products may be suitable replacements for the infant at the 4-6 month milestone when solid foods are typically introduced. Many times, a parent will attempt to introduce an alternative plant-based milk (e.g., rice milk, oat milk, coconut), which do not provide the correct balance of nutrients for a growing child and are not recommended as replacements for cow's milk in children. These children will often have diets that are low in fat, protein, calcium, and vitamin D. It is important to stress that Health Canada recommends that a milk-allergic child (that is also intolerant to soy) be placed on a hypoallergenic infant formula (e.g., Neocate, Nutramigen, Puramino) until the age of 2 years when they can safely be transitioned to either a fortified soy milk or alternate plant-based milk under the supervision of a registered dietitian.[9]

Growth is an overall indicator of the adequate provision of energy and protein intake in children.[3,10] Weight is a more sensitive indicator of energy intake and is affected earlier than height, however, stunting of height has also been observed when an energy deficiency persists. Numerous clinical studies have reported that growth can be affected by elimination diets, particularly when counselling has not taken place regarding how to replace the eliminated nutrients in a safe way with foods and supplements, without allergenic risk.[3,7,14,17-19] An international multicentre survey reported that low weight for age, low height for age, and low BMI for age are common in children with food allergies, and that stunting will affect nearly 1 in 10 children with any number of food allergies.[18] A clinical study examining the effects of a cow's milk elimination diet found that the elimination of cow's milk before the age of 2 can affect nutritional habits and eating behaviours of children between the ages of 2 and 6 years old, and can cause the insufficient intake of both macro- and micronutrients, resulting in poor growth. More severe nutrient deficiencies have also been observed with elimination diets. For example, cases of vitamin D deficiency rickets and low bone mineral density have been reported as a result of unsupervised cow's milk elimination diets.[3]

In addition to nutritional deficiencies and poor growth, food allergy is associated with parental stress. The food allergic child may experience reduced opportunities to participate in typical social eating situations where food is commonly shared.[13] Children with food allergies may experience problems such as food aversion, food refusal, food neophobia, and anxiety about eating in general, which can also lead to inadequate nutrient intake.[3,10] This has been shown to be of concern in both the IgE-mediated food-allergic population, as well as the non-IgE-mediated food-allergic population, particularly those with resulting esophagitis and other types of gastrointestinal pain and discomfort. These children may learn maladaptive behaviours such as food

refusal, low volume and variety of intake, grazing, and spitting out food out to avoid discomfort. These symptoms and resulting behaviours can condition a child to avoid eating and can result in nutritional deficiencies and failure to thrive.[20]

The primary objective in the management of food allergy is to avoid reactions to the offending foods while providing an adequate, healthy, enjoyable, and nutritionally balanced diet that will allow the child to grow and develop normally. It is, therefore, particularly beneficial for the family of a child with one or more food allergies to be able to access nutritional support for their child.[6,2123] Data suggest that dietetic consultation can improve eating habits and the nutritional status and growth of children living with food allergies. They additionally indicate that avoidance of a particular food does not necessarily lead to nutritional deficiencies, provided the diet is adequately supplemented, and appropriate substitute foods are consumed (**Table 2**).[12,22,23] A dietitian practicing in the field of food allergies needs to understand the immunological mechanisms, differing clinical presentations and tolerance levels of food allergies; and to have the ability to advise patients and their caregivers appropriately.[6,13]

A registered dietitian can assist the allergist and patient's family by providing a comprehensive assessment of a child's current dietary intake, monitoring of the child's growth and nutrient intake, and providing nutritional counselling to aid with food substitutions and supplements tailored to the individual child's preferences and requirements. The dietitian would also take into consideration the family's eating habits and culturally relevant food choices.

If an allergist or family physician does not have access to referral resources for a dietitian within their practice or institution, in Canada, a physician or patient can search for a private practice-based dietitian using the "Find a Dietitian" page on the Dietitians of Canada website[24] or can access some education and services from registered dietitians through their local Public Health Department.

***Clinical Pearls and Tips***

*(for Community Allergists and Family Physicians diagnosing infants with food allergies)*

1. At the time of allergy diagnosis, it is important to inform parents of an allergic child what to avoid, but equally as important to tell them replacements may be considered to avoid nutrient deficiencies resulting in poor growth and development. (**Table 2**)
2. Breastmilk (from a mother following an appropriate elimination diet) or a hypoallergenic formula (e.g., Neocate, Nutramigen, or Puramino) is recommended for a child with a milk allergy that cannot tolerate soy until the age of 2 years. If the child does not react to soy, then a soy infant formula can be given.
3. At the time of allergy diagnosis, parents should be counselled to avoid giving alternate (plant-based) beverages (e.g., rice, oat, coconut) until after the age of 2 years, and then may include them in a varied diet in consultation with a registered dietitian.
4. None of the plant-based milks currently available in Canada are nutritionally equivalent to cow's milk. They are each missing some nutrient(s) a child requires for proper growth and development.
5. Parents wishing to use plant-based milks for their child, should only do so after age 2, only if they are fortified (with Vitamins A and $D_3$), and only in consultation with a registered dietitian who can help the parents supplement any nutrients that may be missing as a result of their substitution.
6. A food-allergic child should have their weight and growth followed regularly by their pediatrician or family doctor and consult with a registered dietitian if any concerns arise with their intake or growth.

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**Financial Disclosures:**
None

| Food Eliminated | Most critical nutrients involved in growth | Alternate dietary sources |
|---|---|---|
| **Dairy** | Macronutrients:<br>Fats, protein<br><br>Micronutrients:<br>Calcium, vitamin D, vitamin A, phosphorus, riboflavin, vitamin B12 | Breast milk, hypoallergenic infant formulas(< age 2) or enriched soy milk (> age 2), other fortified alternative beverages (under supervision).*<br><br>Healthy fats from vegetable oils, margarine, avocado, meats, fatty fish, peanuts, tree nuts, seeds.<br><br>Protein from meat, fish, poultry, eggs, soy products, peanuts, legumes, tree nuts, seeds.<br><br>May also require vitamin/mineral supplements such as calcium and vitamin D. |
| **Eggs** | Macronutrients:<br>Fats, protein<br><br>Micronutrients:<br>Riboflavin, pantothenic acid, vitamin B12, biotin, selenium, iron | Healthy fats from vegetable oils, margarine, butter, dairy products (not skim), avocado, meats, fatty fish, peanuts, tree nuts, seeds.<br><br>Protein from meat, fish, poultry, cheese, yogurt, soy products, legumes, peanuts, tree nuts, seeds.<br><br>Vitamin/mineral supplements may be required, particularly iron and B vitamins in plant-based diets.<br><br>Egg replacement products can be used in baking but do not provide equivalent nutritional value. |
| **Wheat** | Macronutrients:<br>Carbohydrates, fibre<br><br>Micronutrients:<br>Thiamine, riboflavin, niacin, iron, folate (if fortified) | Fruits, vegetables, legumes, alternative whole grains and products made with alternative grains or flours (rice, oat, corn, buckwheat, potato, tapioca, amaranth, millet, quinoa.<br><br>Vitamin/mineral supplements may be required, particularly of iron and B vitamins in plant-based diets. |
| **Soy** | Macronutrients:<br>protein<br>(A significant source of protein in plant-based diets)<br><br>Micronutrients:<br>Thiamine, riboflavin, pyridoxine, folate, calcium, phosphorus, magnesium, iron, zinc | Protein from meat, fish, poultry, cheese, yogurt, eggs, legumes, peanuts, tree nuts, seeds. |
| **Nuts and Peanuts** | Macronutrients:<br>Protein, fat<br><br>Micronutrients:<br>Vitamin E, niacin, magnesium, manganese, chromium | Other nuts and legumes that do not cause symptoms can continue to be included.<br><br>Protein from meat, fish, poultry, cheese, yogurt, eggs, legumes.<br><br>Healthy fats from vegetable oils and avocados, fatty fish, seeds. |
| **Fish/seafood** | Macronutrients:<br>Protein, fat<br><br>Micronutrients:<br>Omega-3 fats, zinc, iron, iodine | Other fish and seafood not causing symptoms can be included.<br><br>Protein from meat, soy products, poultry, cheese, yogurt, eggs, legumes, peanuts, tree nuts, seeds.<br>Healthy fats from vegetable oils, margarine, butter, dairy products (not skim), avocado, meats, fatty fish, peanuts, tree nuts, seeds.<br><br>Flax/linseeds (or supplements) can provide some Omega-3.<br><br>Seaweed, milk, eggs, and iodized salt can be sources of iodine. |

***Table 2:*** *Nutrients of concern due to food eliminations (and alternate sources); courtesy of Rachel Freeman, MSc, RD*
** Fortified soy beverages (or other plant-based alternative beverages) are not suitable as a primary milk source for children under 2 years of age. For the older infant or young child who is not being introduced to cow's milk, soy-based or hypoallergenic infant formula is recommended until 2 years of age.*[9]

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