# ABOUT THE AUTHORS

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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**

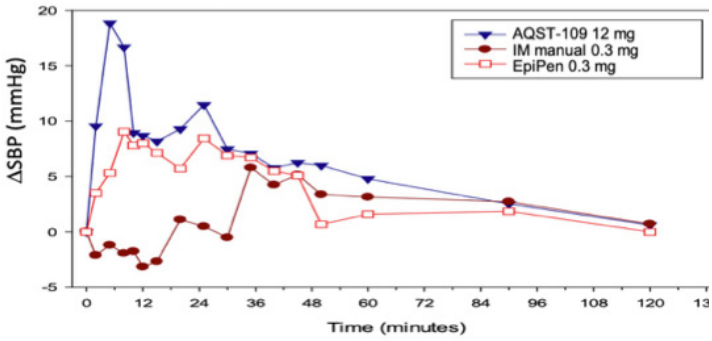



**Figure 2: Mean Change from Baseline in Diastolic Blood Pressure**

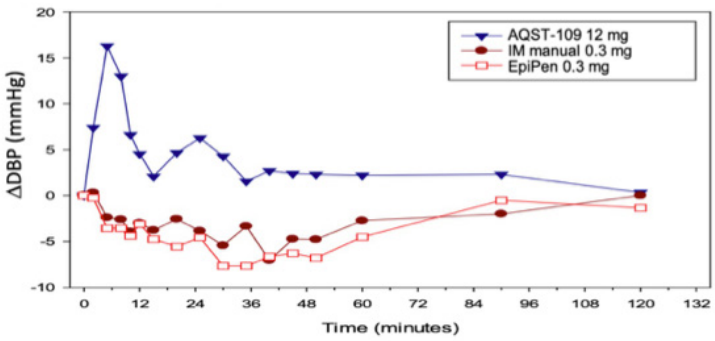
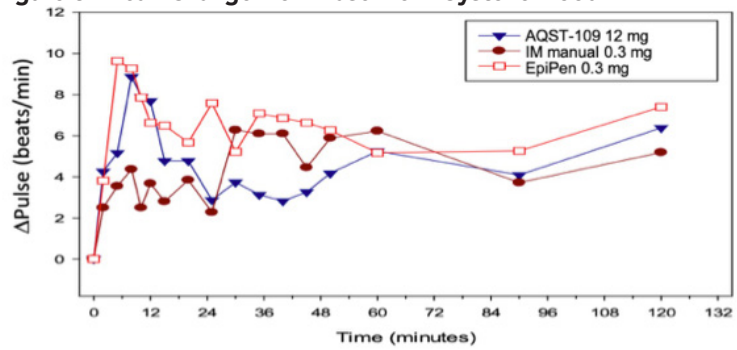



**Figure 3: Mean Change from Baseline in Systolic Blood**



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

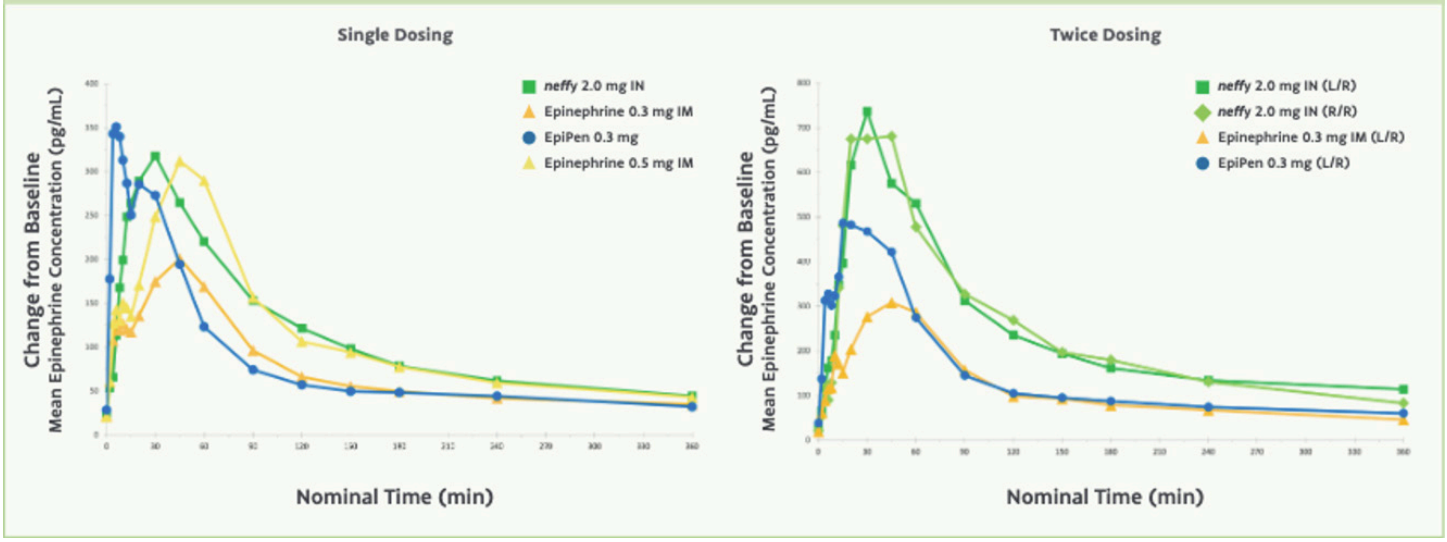
Lieberman, J. et al. ARS-1 (neffy® Nasal Spray) 2.0 mg Versus Epinephrine Injection Products: An Integrated Pharmacokinetic Analysis. *Journal of Allergy and Clinical Immunology. 151(2): AB5.*

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.

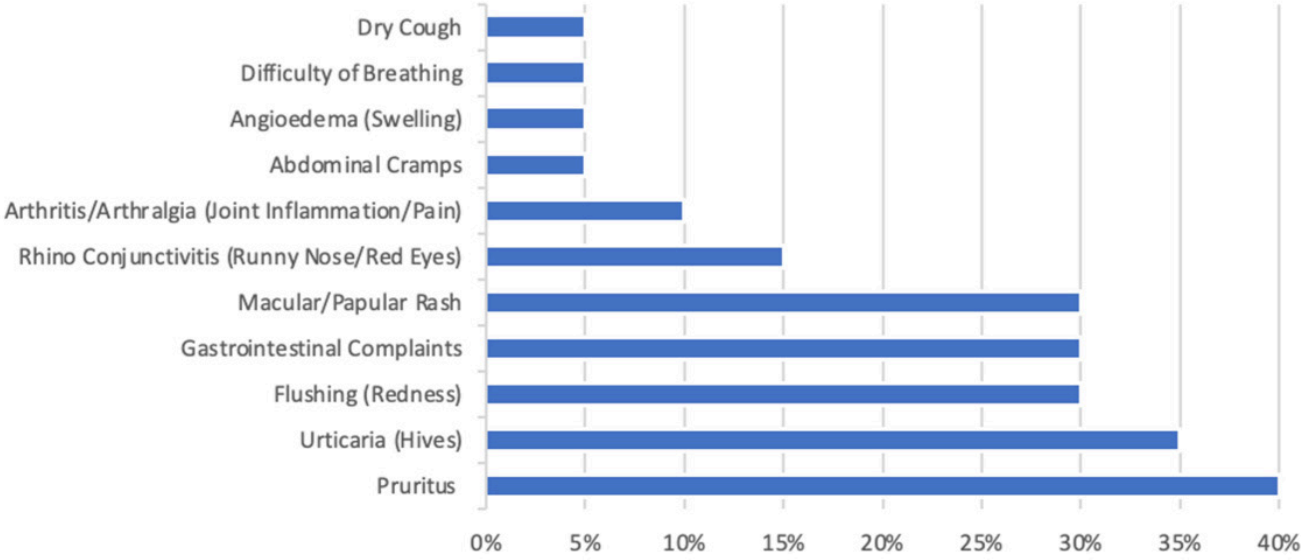
In the case of cephalosporin allergies (CA) in children, there is a need to help address the above concerns to allow their early re-introduction. Testing for cephalosporin allergy in children will likely decrease health care costs and enable children to receive both in the inpatient and outpatient setting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