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ASTHMA MANAGEMENT: A REVIEW OF GINA RECOMMENDATIONS FROM 2019
Jason K Lee, MD

BRADYKININ MEDIATED ANGIOEDEMA
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FOOD REINTRODUCTION IN FPIES
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EDITOR'S WELCOME



Dear Canadian Allergy and Immunology Community,

It is with great pleasure that we welcome and introduce you to the inaugural issue of *Canadian Allergy & Immunology Today*. As disease management becomes more complex and as we have more therapies in our arsenal, it is becoming even more important to communicate best practices and techniques across the clinical community. With this said, *Canadian Allergy & Immunology Today* will be published three times per year in English and French and will be available both as an online and print journal.

This peer-to-peer initiative, written by Canadian clinicians, is meant to serve as an educational and informational resource for all allergists and immunologists across the country. We do sincerely hope you enjoy this first issue, and we look forward to your readership and your ideas for future articles as we grow and expand the reach of this new journal!

Best wishes,

Vipul Jain, MD Nikhil Joshi, MD Jason Ohayon, MD Susan Waserman, MD

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ASTHMA MANAGEMENT: A REVIEW OF GINA RECOMMENDATIONS FROM 2019

Asthma is a chronic condition that affects more than 3.8 million people in Canada.[1] It is a condition that if not controlled may result in significant morbidity and mortality. Asthma is the leading cause of absenteeism from school and one of the leading causes of work loss through both absenteeism and presenteeism.[2] The direct costs of asthma, including hospitalization, healthcare professional services and medication and indirect costs, including decreased productivity, are estimated at $2.1 billion annually.[3] The cost of asthma to the Canadian economy is expected to climb to $4.2 billion annually by 2030.[4]

While many detrimental consequences of asthma stem from the condition itself, a significant proportion of the morbidity associated with asthma is also a result of systemic corticosteroids used to treat asthma exacerbations. There are many factors that lead to uncontrolled asthma, such as inappropriate and/or inadequate treatment of the condition. Access to appropriate treatment for realistic and achievable disease management, is critical in reducing the likelihood of experiencing an asthma exacerbation.

The Global Initiative for Asthma (GINA) Scientific Committee has developed a sophisticated set of procedures to review the world's literature with regard to asthma management and to update the GINA documents to reflect this state-of-the-art information.[5] The output is a report entitled *Global Strategy for Asthma Management and Prevention* complete with teaching slides and an abridged "pocket guide" of the main report's recommendations. All of this is made freely available at ginasthma.org. and includes an update to reflect the COVID-19 pandemic. The GINA report is not a set of guidelines but, rather, an "integrated evidence-based strategy focusing on translation into clinical practice"for health care practitioners with the goal of reducing both short- and long-term asthma exacerbations and adverse events.[6]

This article will focus on the key changes to the latest iteration of GINA recommendations for asthma management **(Figure 1)**.

NO MORE SHORT-ACTING BRONCHODILATORS ALONE

The largest fundamental change in asthma management occurred with the GINA 2019 recommendations. As of 2019, GINA no longer recommends treating adults or adolescents with asthma with short acting bronchodilators or short-acting ß Agonists (SABAs) alone. Instead, patients should receive intermittent symptom – driven (in mild asthma) or daily inhaled corticosteroids to reduce the risk of asthma exacerbations.

Many patients are referred with a diagnosis of 'mild' asthma, and a prescription for salbutamol PRN. It turns out there are significant downsides to this approach. Even mild asthmatics are at risk

of severe exacerbations and adverse events. For example, 30-37% of adults with acute asthma, 16% of patients with near fatal asthma, and 15-20% of adults dying of asthma had symptoms less-than-weekly in the previous three months.[7]

This may be a common misconception about asthma among health care professionals. It is in fact quite possible to have entirely normal lung function when someone is well, not having many symptoms of asthma and then suddenly deteriorate with severe symptoms, which may be triggered by a virus, allergen, or pollution exposure.

In the 1960s and 70s, asthma was essentially thought to be a disease of bronchospasm. As such, patients and some health care professionals felt that reliever medications, like SABAs, were sufficient for controlling asthma. Patients tended to receive rapid symptom relief with SABA treatment due to its quick onset of action. Although inhaled SABAs have been a first line treatment strategy for the management of asthma for more than fifty years, we may be required to update our disease management approach in 2021 in light of the evidence available to us.[8]

We now know that regular or frequent use of SABAs is associated with:

1. Beta receptor downregulation which causes decreased broncho-protection, rebound hyper-responsiveness, and ultimately decreased bronchodilator response[9]
2. Increased allergic responses, and increased eosinophilic airway inflammation[10]
3. Using more than or equal to three canisters of SABAs per year (average of 1.7 puffs/day) is associated with higher risk of emergency department visits[11]
4. Dispensing of twelve or more canisters per year is

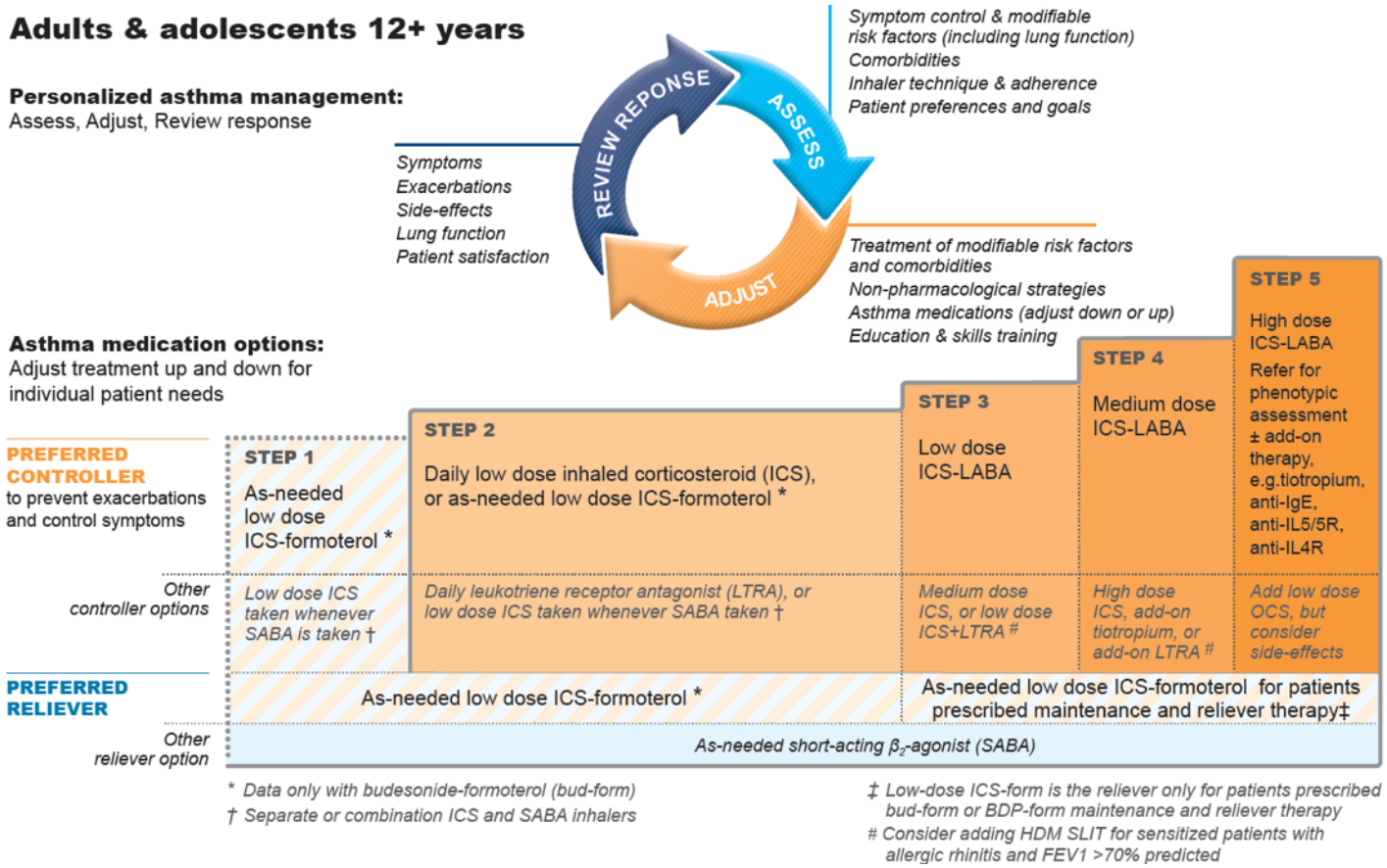


Figure 1. The 2019 Global Initiative for Asthma (GINA) treatment strategy figure for adults and adolescents, annotated to highlight key features.
ICS: inhaled corticosteroids; SABA: short-acting ß2-agonists; LTRA: leukotriene receptor antagonists; LABA: long-acting ß2-agonists; OCS: oral corticosteroids; BDP: beclometasone dipropionate; HDM: house dust mite; SLIT: sublingual immunotherapy; FEV1: forced expiratory volume in 1 s; IL: interleukin. Modified with permission of the Global Initiative for Asthma (www.ginasthma.org).

associated with higher risk of death[12]

Despite our knowledge of these issues, changes to disease management have not gained traction.

Looking at individual risk and extrapolating to a population level, one can imagine a tremendous benefit in risk reduction for asthma patients. This would be akin to the risk reduction observed when population-level algorithms model the impact of widespread use of statins and blood pressure medications to reduce the risk of coronary artery and cardiovascular disease.

INHALED STEROIDS (ICS) WITH FORMOTEROL [(A FAST-ACTING AND LONG-ACTING ß AGONIST (LABA)] IS THE BETTER APPROACH AT MANAGING MILD ASTHMA FOR ADULTS AND TEENS

Two breakthrough studies (SYGMA 1 and 2) both published in 2018 in the New England Journal of Medicine provide evidence for this approach of managing mild asthma for adults and teens. In SYGMA 1, a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma, patients were randomly assigned to one of three regimens: terbutaline (0.5 mg) used as needed (terbutaline group), budesonide–formoterol (200 µg of budesonide and 6 µg of formoterol) used as needed (budesonide–formoterol group), or twice-daily budesonide (200 µg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide–formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.

A total of 4215 patients underwent randomization, and 4176 (2089 in the budesonide–formoterol group and 2087 in the budesonide maintenance group) were included in the full analysis set. Budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy for severe exacerbations; the annualized rate of severe exacerbations was 0.11 (95% confidence interval [CI], 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16). The median daily metered dose of inhaled glucocorticoid was lower in the budesonide–formoterol group (66 µg) than in the budesonide maintenance group (267 µg). The time to the first exacerbation was similar in the two groups (hazard ratio, 0.96; 95% CI, 0.78 to 1.17). The change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy.[14]

Based on the conclusions of these studies and others, as needed inhaled corticosteroids (ICS) with fast-acting LABAs are nearly as good as using a regular ICS and as needed SABAs. However, the reality is that asthma patients are well known to have poor adherence to their medications for a variety of reasons, including but not limited to the fact that asthma symptoms routinely wax and wane as a hallmark of the condition, thereby lulling patients into a false sense of security around disease management and control. As such taking the ICS + LABA combination used as needed is a realistic approach which demonstrates good rates of reduction in asthma exacerbations and which is on par with taking daily ICS inhalers. Additionally, an ICS + LABA combination may also help to reduce the total dose of ICS.

SHARED DECISION MAKING AND PERSONALIZED ASTHMA MANAGEMENT IS KEY

Every patient and their response to their disease and medications is different. It is important to remember that a tailored approach to disease management is required. In particular, while teens and adults have a set of GINA recommendations, GINA has separate recommendations for children 6-11 years of age and for children 5 years of age and younger.

It is important that the physician have a good therapeutic rapport with patients where open and honest discussion about treatment goals are expressed. For example, patients may have steroid phobias or other misconceptions related to adverse effects of medications

that impair their ability to achieve optimal outcomes. If someone is forgetful or their lifestyle is not suited for daily therapy for mild asthma, they should be upfront about this so that modalities including the use of ICS + fast-acting LABAs can be discussed. Similarly, if a patient is more disciplined and can follow an asthma action plan or step-by-step instructions, this can be discussed in partnership with the physician in order to ensure optimal success of the treatment plan.

The goal of improved asthma outcomes is grounded in mutual trust and respect. Offering choice to patients is the correct approach. The goal is to make sure that there is mutual trust and respect so that in a real life situation, they can find a solution that is doable while still appropriate. Working toward lifestyle changes in particular such as weight loss, smoking cessation, or increasing physical activity can be better optimized with a trusted relationship.

SEVERE UNCONTROLLED ASTHMA

The definition of severe asthma for patients aged ≥ 6 years is asthma which requires treatment with guideline-suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/ theophylline) for the previous year or systemic CS for ≥ 50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.[15]

Uncontrolled asthma is defined as at least one of the following:

1) Poor symptom control: ACQ consistently ≥ 1.5, ACT < 20 (or not well controlled by NAEPP/ GINA guidelines)

2) Frequent severe exacerbations: two or more bursts of systemic CS (3 days each) in the previous year

3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in one second (FEV1) <80% of personal best (or < the lower limit of normal (LLN), in the face of reduced FEV1/ forced vital capacity (FVC) defined as less than the LLN)

There is not a consistently reliable and predictable way to choose an optimal biologic therapy for severe asthma patients since all current approved therapies for severe asthma involve type 2 inflammation. Type 2 immune responses can be induced by parasitic helminths and are associated with atopic diseases, such as allergy and asthma. Airway type 2 immune responses are mainly mediated by eosinophils, mast cells, basophils, TH2 cells, group 2 innate lymphoid cells (ILC2s) and IgE-producing B cells. Type 2 immune responses are characteristic of allergic rhinitis in the upper airways and asthma in the lower airways.[16] Unchecked activation of this repair mechanism of inflammation has many long term deleterious effects at the tissue site.

Currently, blood tests referred to as biomarkers to determine the type of severe asthma, all overlap and fluctuate for the same patient depending on the point in time at which the test was taken. In fact, the same patient can express different levels of biomarkers from morning to night owing to diurnal variation of the immune system.

Patients with severe asthma have typically maximized inhaler therapies and some oral therapies, yet still remain uncontrolled, experience symptoms and frequent exacerbations. The early use of biologic therapy for these patients is both correct and necessary. It should be guided by the atopic comorbidities of each patient. Treating a host of related conditions such as rhinitis, atopic dermatitis, urticaria, chronic sinusitis, depression, and anxiety is paramount to the optimal management of asthma.

THE IMMUNE SYSTEM IS COMPLEX, BUT OUR KNOWLEDGE IS IMPROVING

In summary, we are learning more about the shared immune basis for many conditions that involve the lung and that may also involve other body systems. The discovery of the existence of a newly-identified white blood cell called innate lymphoid cells (ILCs) suggests that several types of these cells exist in the lungs, brain, skin, and virtually every organ system. Vivier et al note that "the

discovery and investigation of ILCs over the past decade have changed our perception of immune regulation and how the immune system contributes to the maintenance of tissue homeostasis. We now know that cytokine-producing ILCs contribute to multiple immune pathways by, for example, sustaining appropriate immune responses to commensals and pathogens at mucosal barriers, potentiating adaptive immunity, and regulating tissue inflammation. Critically, the biology of ILCs also extends beyond classical immunology to metabolic homeostasis, tissue remodeling, and dialog with the nervous system."[17] This incredible scientific advance in our understanding of the immune system has allowed us to study new pathways to develop new treatments to help patients.

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Chrystyna Kalicinsky, MD



Dr Kalicinsky received her medical degree, as well as specialty training in internal medicine and clinical immunology and allergy from the University of Manitoba. From 2000-2005 she was in community practice. From 2005 onwards, she has been in academic practice at the University of Manitoba where she was the Program Director of the Clinical Immunology and Allergy Training Program at the University of Manitoba from 2009 until 2020. Dr Kalicinsky enjoys teaching medical students and residents, as well as patient education and her clinical interests include immunodeficiency, angioedema, chronic urticaria and mast cell disorders.

BRADYKININ MEDIATED ANGIOEDEMA

A 36-YEAR-OLD FEMALE IS REFERRED WITH RECURRENT ANGIOEDEMA WITHOUT URTICARIA, UNRESPONSIVE TO ANTIHISTAMINES, CORTICOSTEROIDS, AND EPINEPHRINE. HER EPISODES CAN LAST FOR MORE THAN 3 DAYS.

Bradykinin angioedema can affect mucous membranes of the oropharynx, as well as the larynx, subcutaneous tissue, bowel mucosa, and the abdominal wall.

Angioedema without urticaria, which is unresponsive to antihistamines, corticosteroids and epinephrine, is presumed to be caused by episodic buildup of bradykinin.

This article will examine the medications known to be associated with bradykinin angioedema and provide an overview on hereditary angioedema (HAE), acquired angioedema (AAE) and idiopathic bradykinin mediated angioedema.

MEDICATIONS

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI) AND ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)

The incidence of Angiotensin Converting Enzyme Inhibitor (ACEi) induced angioedema is reported to be between 0.1-0.7%. Although it occurs during the first week of exposure in over half of cases, it can occur any time during the course of therapy. A large retrospective study found that two-thirds of ACEi-associated angioedema episodes occur within the first three months of therapy while case reports have documented angioedema episodes that began after years of stable therapy.[1] ACEi angioedema tends to occur more commonly in ACEi users who are female, smokers, or of African-American descent.[2] In both ACEi and angiotensin II receptor blocker (ARB) - related angioedema, the angioedema most commonly affects the head and neck area (tongue>lips>pharynx/larynx).[3] Fatal laryngeal angioedema has been well documented. Therefore, ACE inhibitors should be discontinued in all individuals with angioedema and are absolutely contraindicated in patients with either HAE or AAE. Episodes of angioedema may occur up to 1 month (or sometimes more) after discontinuing the ACE inhibitor.[2] If an episode of angioedema occurs greater than 4 weeks after discontinuation of the ACEi, clinicians may consider a workup for HAE with C4, C1 esterase inhibitor level and function, and follow up for the possibility of HAE (including with normal C-INH level and function), as well as idiopathic bradykinin mediated idiopathic angioedema. The unmasking of these conditions may have occurred due to use of the ACEi.

Two randomized controlled trials (RCTs) and one meta-analysis evaluated ARB use in patients who were intolerant to ACEi. When the trials are analyzed together, there is a 10% or less incidence of cross-reactivity of angioedema in patients who receive an ARB after experiencing

ACEi-associated angioedema.[4] In a meta-analysis of randomised controlled trials of >12 months duration comparing ARBs with placebo or active antihypertensive treatment, the incidence of angioedema with ARBs in patients not previously on ACEi was 0.5%[5]

Other than airway management with acute attacks, there is no approved treatment to hasten recovery. There are conflicting outcomes reported in studies with the use of icatibant in ACEi- induced angioedema. In a phase II RCT of 27 patients, the time to complete resolution of edema was significantly shorter (P=0.002) with icatibant (14 patients; median time to resolution of 8 hours) than with combination therapy of a glucocorticoid and an antihistamine (13 patients; median time to resolution of 27.1 hours).[6] However, in a subsequent study and meta-analysis, icatibant did not seem to shorten the time for complete resolution of ACEi-induced angioedema symptoms compared to placebo or conventional treatment strategies.[7,8]

There are also conflicting results from published case series reports involving the use of C1-esterase-inhibitor concentrate (pdC1-INH) in ACEi- induced angioedema and RCTs with these agents have yet to be undertaken[9,10]

DIPEPTIDYL PEPTIDASE – 4 INHIBITORS (GLIPTINS)

Dipeptidyl peptidase-4 inhibitors are a class of oral diabetic agents that affect bradykinin and substance P degradation and therefore can lead to angioedema. Beginning in 2005, angioedema was specified as a safety event in clinical trials of vildagliptin. Angioedema has also been reported in post marketing surveillance of sitagliptin.[10] Treatment with dipeptidyl peptidase-4 inhibitors must be carefully considered and patients closely monitored especially during concurrent treatment with ACEi or when treating patients with a known predisposition to angioedema.[11]

NEPRILYSIN INHIBITORS

Neprilysin inhibitors are a separate class of cardiac medications, which include sacubitril, and can lead to drug-induced angioedema especially when used in combination with ARBs and ACEi.[13] If the ACEi was chosen purely as an antihypertensive agent, clinicians should consult with the referring physician and may consider substituting with amlodipine. If the ACEi was used for cardio- or nephro-protective reasons, an individual risk assessment should be undertaken with the patient regarding the use of ARBs, given its low risk of cross-reactivity. With respect to neprilysin, clinicians may consider deferring to the patient's cardiologist or seeking a cardiology consult in the event that the patient is not actively followed by a cardiologist.

TISSUE PLASMINOGEN ACTIVATOR (TPA)

Approximately 5% of patients treated with tPA for acute ischemic stroke can develop orolingual angioedema. It is typically mild, transient and contralateral to the ischemic hemisphere.[14]

HEREDITARY AND ACQUIRED ANGIOEDEMA (HAE AND AAE)

HAE

HAE is a rare, autosomal dominant disorder that results in random and often unpredictable attacks of angioedema. Attacks are associated with significant functional impairment, decreased health-related quality of life, and mortality in the case of laryngeal attacks.[15,16]

Function	C4	C1-INH antigen	C1-INH
HAE-1	↓	↓	↓
HAE-2	↓	normal or ↑	↓
HAE-nC1INH variants coagulation factor XII angiopoietin-1 plasminogen unknown	normal	normal	normal

Table 1. Laboratory findings in hereditary angioedema[17]

Table 2. Therapies for HAE supported by high level of evidence[18]

Therapies for HAE supported by high level evidence

HAE-specific treatment	Product name and company	Mechanism of action	Approved indications	Dose and route of administration	County licensed and age indications
pdC1-INH	Berinert®[a] (CSL)	Replaces C1-INH	Acute treatment	20 U/kg intravenous	Australia, Canada, EU, USA (adult and pediatric)
			Pre-procedural	Adults: 1000 U Pediatrics: 15 to 30 U/kg body weight	EU (adult and pediatric)
	Cinryze® (Shire—now part of Takeda)	Replaces C1-INH	Acute treatment	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Pre-procedural	≥ 12 years: 1000 U intravenous 2–11 years: 1000 U (> 25 kg body weight) 500 U (< 25 kg body weight)	Australia (≥ 12 years) EU (≥ 2 years)
			Long-term prophylaxis	1000 U intravenous q 3–4 days (6–11 years 500 U q 3–4 days)[b]	Australia, Canada (≥ 12 years) EU, USA (≥ 6 years)
	Haegarda® (CSL)	Replaces C1-INH	Long-term prophylaxis	60 U/kg body weight twice weekly (every 3–4 days)	Australia[c], Canada, EU[d], USA (≥ 12 years)
rhC1-INH	Ruconest® (Ruconest)	Replaces C1-INH	Acute treatment	50 U/kg intravenous (< 84 kg); 4200 U intravenous (≥ 84 kg)	EU (adults), USA (adults and adolescents)
Ecallantide	Kalbitor® (Shire—now part of Takeda)	Selective, reversible inhibitor of plasma kallikrein	Acute treatment	30 mg (3 × 10 mg/1 ml) subcutaneous injections	USA (≥ 12 years)
Icatibant	Firazyr® (Shire—now part of Takeda)	Synthetic selective and specific antagonist of bradykinin 2 receptor	Acute treatment	30 mg subcutaneous injection; dose-adjusted for adolescents < 65 kg and children ≥ 2 years[e]	USA (≥ 18 years) Australia, Canada, EU (≥ 2 years)
Lanadelumab	Takhzyro® (Shire—now part of Takeda)	Fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity	Long-term prophylaxis	300 mg subcutaneous injection every 2 weeks a dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months	Australia, Canada, EU, USA (≥ 12 years)

Please refer to current country-specific monographs for further details regarding specific indications and listings of adverse events

[a] Berinert 1500 in EU

[b] Dose-adjustment up to 2500 U q3–4 days for ages 12 and above, and up to 1000 U q3–4 days for ages 6-11, based on patient response

[c] Berinert SC in Australia

[d] Berinert 2000/3000 in EU

[e] 12 kg to 25 kg: 10 mg (1.0 ml); 26 kg to 40 kg: 15 mg (1.5 ml); 41 kg to 50 kg: 20 mg (2.0 ml); 51 kg to 65 kg: 25 mg (2.5 ml); > 65 kg: 30 mg (3.0 ml)

Table 1 differentiates the three forms of HAE, based on deficiency C1 esterase inhibitor antigen (Type 1), C1 esterase inhibitor function (Type 2), and hereditary angioedema with normal C1 esterase inhibitor level and function (HAE nC1-INH). The latter is more prevalent in females but has been reported in males. Three genes have been identified in HAE nC1-INH families (FXII, ANGPT1, PLG) but in the majority of families the pathogenesis is unknown. Type 1 HAE accounts for the majority of HAE cases, with 25% arising from spontaneous mutation and with no family history.

MANAGEMENT OF HAE

ACUTE TREATMENT OF HAE WITH NORMAL C1-INHIBITOR

As per the 2019 International/ Canadian Hereditary Angioedema Guidelines, non-randomized, retrospective studies and small case series have shown that intravenous pdC1-INH may reduce the duration and intensity of attacks of angioedema in these patients, despite the fact that the pathogenesis of the angioedema, by definition, is not caused by a deficiency in C1-INH.[19-22]

LONG TERM PROPHYLAXIS (LTP) OF HAE WITH NORMAL C1-INHIBITOR

Although treatments used for LTP for HAE-1 and HAE-2 may potentially be beneficial for patients with HAE nC1-INH, published and peer-reviewed data is lacking and therefore the authors of the International/Canadian Hereditary Angioedema Guidelines could not make a recommendation regarding their use.

PREGNANCY

By unanimous consensus, the authors of the guidelines from 2019 agreed on the use of pdC1-INH during pregnancy to treat acute attacks. Short term prophylaxis is not routinely required prior to vaginal delivery but is recommended with C-section and intra-partum instrumentation.[23]

PEDIATRICS

When children with HAE-1 and HAE-2 are treated with pdC1-INH for HAE attacks, responses are consistent with those seen in adults.[24] Dosing for pdC1-INH is 20 units (U)/kg IV Berinert®(CSL), 500 U IV Cinryze® (Takeda) for children 10–25 kg, or 1000 U IV Cinryze® for children > 25 kg.[18] Icatibant has been approved to treat patients ≥ 2 years of age according to the manufacturer's product monograph.

ACQUIRED ANGIOEDEMA

Acquired angioedema is a very rare condition and can be associated with lymphoproliferative disorders and systemic lupus erythematosus. It usually presents after the fourth decade. As with HAE, deficiency in C1 esterase inhibitor antigen or function can occur. Laboratory differentiation between AAE and HAE is by means of C1q, which is normal in HAE and decreased in 70% of those with AAE. Acute attacks can be effectively treated using pdC1-INH, but some patients become progressively non-responsive, due to autoantibody-mediated rapid catabolism. In these patients icatibant can be effective.[25]

IDIOPATHIC BRADYKININ MEDIATED ANGIOEDEMA

Patients with idiopathic bradykinin mediated angioedema present similar to HAE, with cutaneous, pharyngeal, laryngeal, and abdominal attacks, but without a family history and with normal C1 esterase inhibitor antigen and function. Treatment with tranexamic acid at 1 g p.o. t.i.d. for 3 months, tapered according to its effectiveness has shown benefit in some published case series.[26,27] There are also case reports of icatibant and pdC1-INH use providing benefit.[28]

CONCLUSION

Bradykinin-mediated angioedema results from either overproduction of bradykinin or inhibition of its degradation. Its etiology can be hereditary or acquired and it is a rare disease, which affects the abdomen and/or upper airways. It is known to differ clinically from histamine-mediated angioedema by the absence of urticaria or skin rash and the use of antihistamines and corticosteroids have not been shown to be effective.[29]

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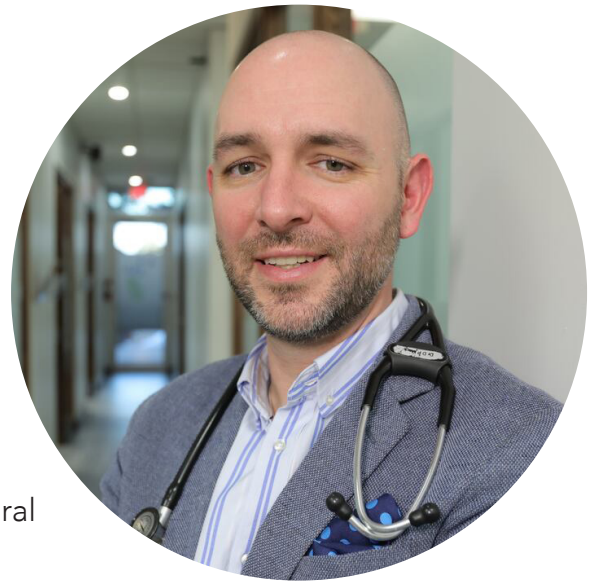
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ORAL IMMUNOTHERAPY: AN OVERVIEW OF KEY STUDIES

Food allergy affects approximately 7% of the Canadian population and is a lifelong diagnosis for many patients.[1,2] While fatal anaphylaxis is rare, accidental exposures are common, with many accidental reactions being moderate-to-severe.[3] The fear of severe or fatal anaphylaxis is of major concern and food allergy represents a significant burden on the life of food-allergic families.[4,5] Until recently, the standard of care for food allergy management in North America included avoidance of the allergenic food and epinephrine autoinjector carriage.[9] However, additional proactive therapeutic options are becoming increasingly more commonplace.

Oral immunotherapy (OIT) has been investigated through real world evidence and in phase II and III clinical trials. Canadian experience with OIT is increasing with the publication of guidelines to support this clinical activity.[7-11] OIT is an elective, non-curative procedure which carries a risk of allergic reaction. Comprehensive and effective education for families to ensure informed consent is essential as part of the shared decision making (SDM) process and is key to successful OIT implementation.

OIT BACKGROUND

OIT involves administering the allergenic food starting with a sub-threshold dose and gradually increasing the dose during the "buildup phase" to improve tolerance.[14] Patients then remain on the final target dose during the "maintenance phase". The maintenance phase is likely indefinite, but patients may have the option of reducing dosing frequency depending on the protocol. Some patients may eventually demonstrate "sustained unresponsiveness" where they are able to stop daily dosing for a predetermined period of time, often 2-6 weeks, and then restart safely. Some have referred to this state as food allergy "remission".

While OIT was first described over 100 years ago, over the past few decades this approach has been increasingly performed both in academic research and clinical trials as well as in private practice.[15-17] Although debate has been ongoing about the readiness of OIT for clinical practice, a recent survey suggests that a high percentage of Canadian allergists are currently offering OIT.[9] Furthermore, the acceptance of OIT as a reasonable clinical option has been reinforced by European and Canadian guidelines and the FDA approval of a peanut-OIT product.[8,10,11]

KEY STUDIES

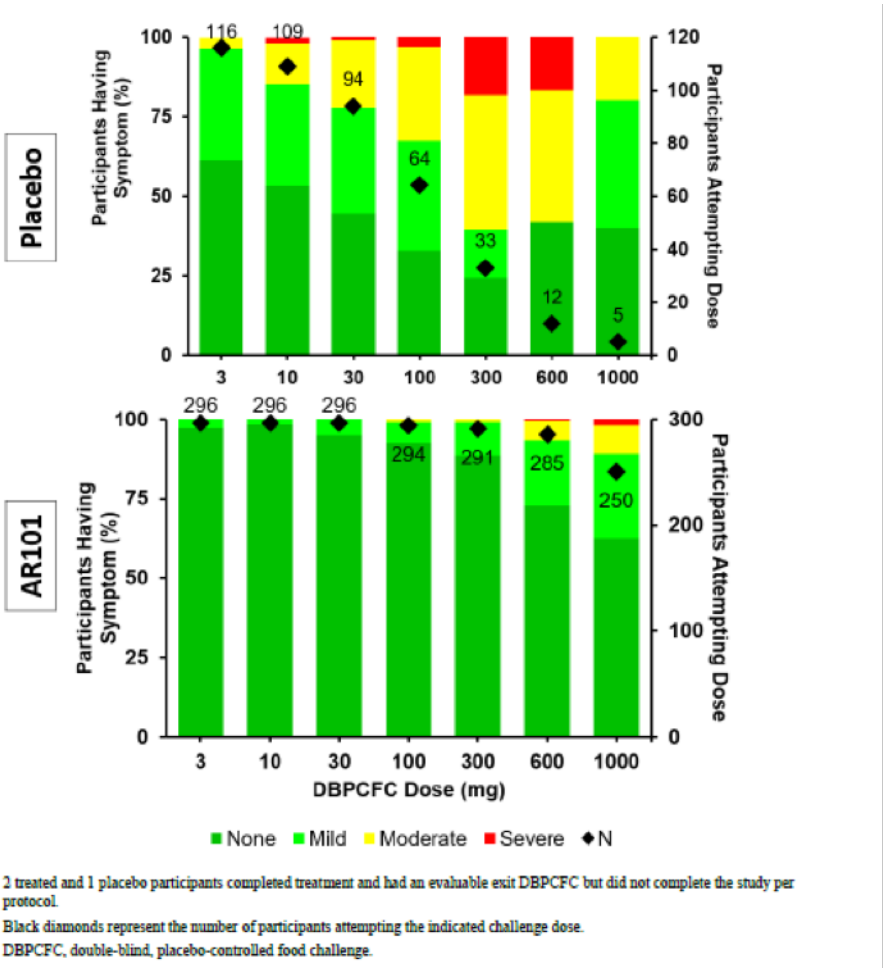
The first phase 3 trial, to evaluate OIT for peanut (PALISADE) was published in 2018 with the proprietary OIT-product AR101.[8] AR101 is a 12% light roast, defatted peanut flour, not dissimilar to peanut flours that are readily available for consumer purchase. Briefly, 551 patients with a median age of 11.3 were randomized in a 3:1 manner to receive either the peanut flour or placebo. Doses were increased incrementally in-office every 2 weeks as tolerated to a final dose

of 300 mg peanut protein (the equivalent of approximately 1.5 peanuts). After 6 months of maintaining their daily dose, patients that were able to tolerate the buildup and maintenance protocols completed an oral food challenge (OFC) to determine how much peanut they could now tolerate.

The results demonstrated that approximately 67.2 % of the per-protocol patients could tolerate at least 600 mg peanut protein (cumulative dose 1043 mg) in a graded oral challenge compared to 4% of placebo. Of those that completed the protocol, 84.5% could tolerate the 600 mg oral challenge dose and 63.2% could tolerate the 1000 mg challenge dose - a cumulative dose of 2043 mg or approximately 10 peanuts. Importantly, further analysis demonstrated that OIT-treated patients had significantly increased thresholds of peanut tolerance, had less severe reactions and required less epinephrine during the OFC than patients who had been given the placebo **(Figure 1)**.[8]

However, 95% of active participants experienced adverse events during the buildup and the 6 month maintenance (with 4.3% severe) and 0.8% of placebo subjects reporting severe reactions. Only one case of eosinophilic esophagitis (EoE) was confirmed in the treatment group.[8]

The effectiveness of a lower dose OIT has been recently demonstrated in a set of RDBPC studies from



2 treated and 1 placebo participants completed treatment and had an evaluable exit DBPCFC but did not complete the study per protocol.

Black diamonds represent the number of participants attempting the indicated challenge dose.

DBPCFC, double-blind, placebo-controlled food challenge.

Figure 1. Maximum severity of symptoms occurring during each dose of the exit DBPCFC among completers, Ages 4-17

Germany.[18,19] In these studies, a low dose of peanut and a slow rate of build up over 14 months was evaluated. The active group received either 125 mg of peanut protein or 250 mg per day - lower doses than were used in PALISADE. There was clear evidence of efficacy with 74.2% of the active group tolerating 300 mg of protein versus 16.1% of the placebo group. Most importantly, treatment-related side effects were only mild-to-moderate and there was no epinephrine use at all.

Impressively, no patients developed EoE or similar GI symptoms. Effectiveness was evaluated in a follow-up study which demonstrated a significant reduction in the number of accidental reactions and reduction in accidental reaction severity in the active group.[19] This promising study suggests that protection from accidental reaction can even occur safely with a "low-and-slow" approach. Other ongoing studies are evaluating whether even lower doses may be effective.

While much of the focus of OIT research and practice has been in older patients, Vickery et al implemented a pilot project to modify the early responses to peanut OIT in preschoolers.[20] They evaluated 37 preschool patients ages 9 – 36 months with peanut allergy confirmed by OFC. The patients were randomized to either low or

high dose OIT (300 or 3000 mg protein) and the primary endpoint was the ability to demonstrate sustained unresponsiveness after four weeks of discontinuation. After a median treatment time of only 29 months, 78% of patients were able to tolerate 5000 mg of peanut protein after stopping for four weeks. Impressively, there were no severe reactions noted and only one patient required epinephrine. Side effects appeared to decrease after the build-up phase. Five-year follow-up, consisted of a 21-item telephone survey to gather information about "real world" domains as they related to peanut consumption such as, quantity, frequency, safety, tolerability, and lifestyle impact. Questions also targeted information about other ongoing atopic conditions.The results of this long-term follow-up demonstrated consistent safety with no severe reactions and 90% of parents reported an overall improved quality of life.[21]

Some Canadian allergists employ a similar approach with peanut OIT treatment in primarily preschool patients. A multi-centre real-world study suggested that while the overall successful buildup rate was similar to other studies, the safety and effectiveness was preferential in the younger age group.[22] In their first article, the authors reported a 0.4% severe reaction rate and a 4% epinephrine rate during the buildup phase. In their follow-up study they demonstrated a similarly low rate of side effects and high adherence.[23] This study demonstrated a high rate of tolerance (78%) of 4000 mg peanut protein after only one year on OIT and all patients that had a follow-up OFC were able to tolerate 1000 mg. As a reference, the ability to tolerate over 1000 mg has been suggested to reduce the risk of accidental reaction by 99%. While this study did not require entry food challenges, this real-world approach was consistent with the current clinical approach used by many Canadian allergists and demonstrated greater safety than other real-world studies of older patients.[9,17]

A number of large multi-centre studies in private practice have reported their experiences with OIT, primarily for peanut.[15,17, 24] These real-wold studies have demonstrated relatively similar safety and effectiveness data to clinical trials despite very different buildup schedules and target doses.

While the primary food studied for OIT is peanut, many studies have been performed using other foods including milk and egg and typically demonstrate similar results to peanut.[11] More well-designed trials will ideally demonstrate optimal doses and regimens for these foods. In the meantime, many allergists are incorporating these foods into their OIT approaches.[9,25]

SAFETY

Patient safety has been an ongoing criticism of OIT. While the efficacy and effectiveness of OIT in both clinical studies in real-world settings have been demonstrated, all protocols result in some form of adverse event of varying severity in most patients.[17] While the frequency of reactions may be similar to subcutaneous immunotherapy reactions, a critical distinction is that many of the OIT reactions occur at home, necessitating a focus on patient preparation and risk-mitigation. A recent well-publicized meta-analysis reviewed 12 randomized controlled peanut trials with 1041 participants.[26] This study suggested an increased risk of anaphylaxis in the first year of OIT, with increased frequency of anaphylaxis and epinephrine use, despite demonstrating increased tolerance of peanut protein in an OFC. While there has been criticism of the conclusions of this review, patients and clinicians must be fully aware of the potential for allergic reaction during immunotherapy.[27-30] Interestingly, while allergic reactions are expected during OIT a recent RCT reframing the occurrence of mild reactions as expected signals of desensitization demonstrated improved outcomes and compliance with OIT regimens. Specifically, patients and their families all received symptom management training. In a 1:1 approach, 24 patients and their families were informed that non-life-threatening symptoms during OIT were unfortunate side effects of treatment, and 26 patients and their families were informed that non-life-threatening symptoms could signal desensitization. Families participated in

activities to reinforce these symptom mindsets. Compared to families informed that symptoms are side effects, families informed that symptoms could signal desensitization were less anxious, less likely to contact staff about symptoms, experienced fewer non-life-threatening symptoms as doses increased, less likely to skip/reduce doses, and showed greater increase in patient peanut-specific blood IgG4 levels.[31]

Gastrointestinal side effects ranging from abdominal discomfort to confirmed EoE are a common cause of OIT-discontinuation.[8,32] While the true incidence of EoE is unknown, estimates of approximately 1% are quoted, however no cases were reported in the recent European phase 3 trial using AR101.[33]

To prevent reactions, many cofactors such as exercise, illness and asthma status must be monitored and controlled during this process and extensive patient/family counseling is required to fully educate and communicate these limitations.[13,14] Some studies have demonstrated that older age, uncontrolled or intermittently treated asthma, and high food-specific IgE are associated with reaction.[15,17,24,34]

QUALITY OF LIFE

OIT is not curative, yet many families consider OIT to improve their quality of life. Limited high-quality data exist and the Peanut Allergen immunotherapy, Clarifying the Evidence (PACE) review did not demonstrate improved quality of life, albeit with very limited data to evaluate.[26] Tang et al evaluated 51 participants taking a combined probiotic/peanut OIT and demonstrated a significant improvement in the Food Allergy Quality of Life Questionnaire (FAQLQ-PF) and Food Allergy Independent Measure (FAIM) in the active group that acheieve sustained unresponsiveness, with no improvement in the placebo.[35] Israeli data also demonstrated a significant improvement in FAQLQ-PF in the maintenance phase of OIT **(Figure 2)**.[36]

Blumchen et al similarly demonstrated improvement in some, but not all of the domains of health related QOL, such as emotional impact and risk of accidental reaction.[18] Further study is necessary to draw broader conclusions.

GUIDELINES

Over the past few years, evidence-based clinical guidelines have been developed supporting the use of OIT in clinical practice. The European Academy of Allergy and Clinical Immunology first published evidence-based guidelines strongly supporting the use of OIT to increase tolerance to peanut, milk and egg, with grade 1A recommendations for the former two foods.[11] More recently, the Canadian Society of Allergy and Clinical Immunology published their own guidelines strongly supporting the use of OIT in clinical practice.[10] The Canadian guidelines stressed a patient-centred approach that is adaptable to needs, abilities and expectations of individual patients and families.

SHARED DECISION MAKING

OIT is an elective, non-curative and potentially risky procedure. Unlike SCIT, families shoulder the burden of risk with daily doses of immunotherapy at home with no immediate access to physician aid or resuscitative equipment. As such, the

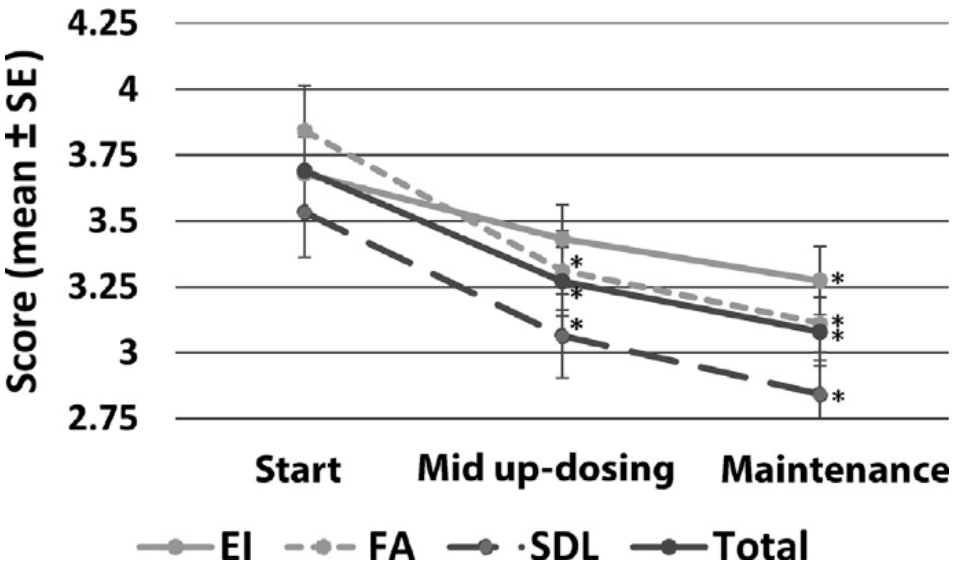


*Figure 2. Changes in the FAQLQ-PF scores in OIT-treated patients from start to mid up-dosing and then to maintenance in the EI, FA, SDL, and total score. *Represents a significant difference from the start of OIT.*

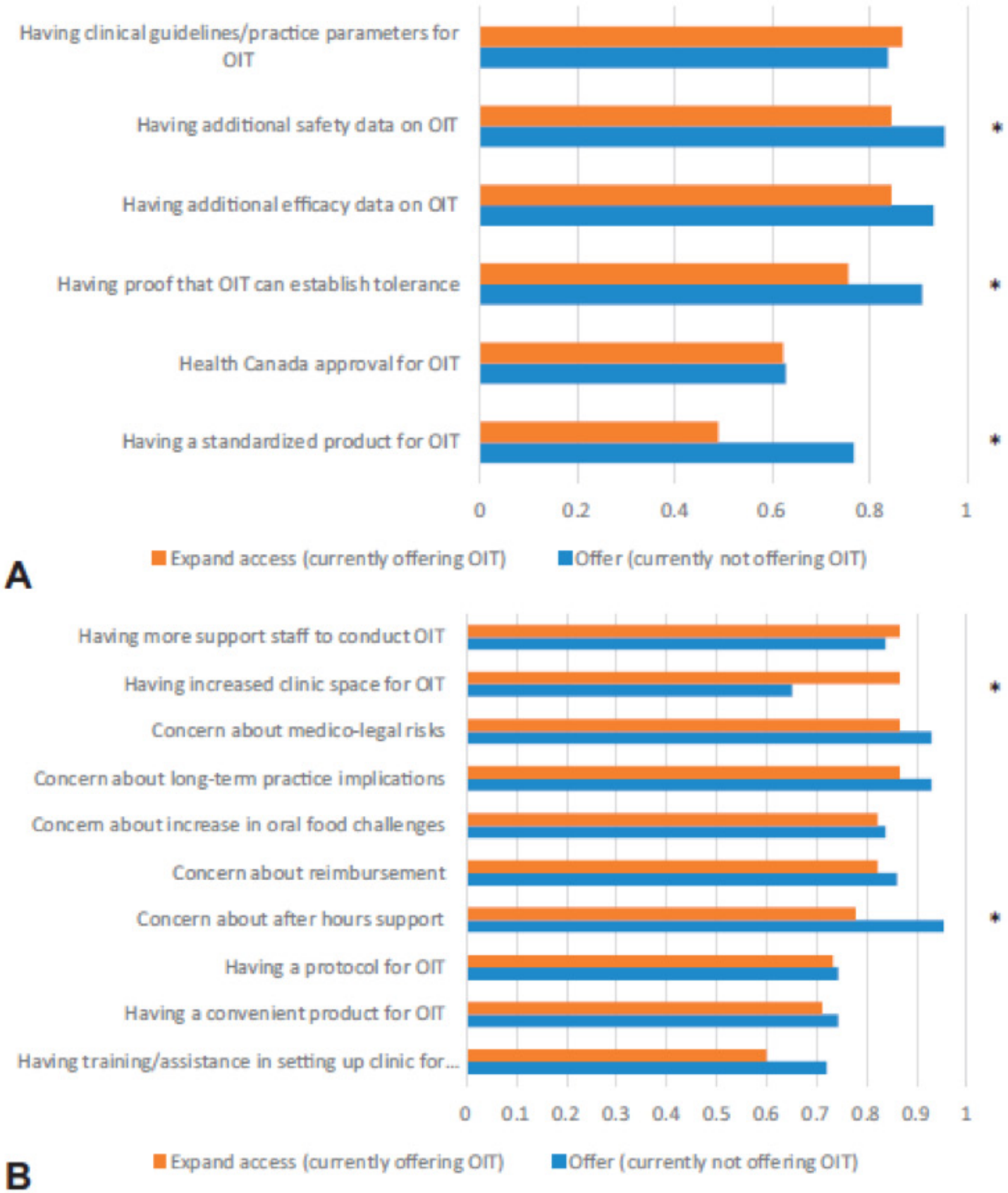


*FIGURE 3. A, Clinical factors identified as "moderately to extremely important" in influencing allergists' ability to expand access to or offer OIT. B, Logistical factors identified as "moderately to extremely important" in influencing allergists' ability to expand access to or offer OIT. * Indicates P <.05 between those allergists offering and not offering OIT. OIT, Oral immunotherapy.*

clinician is obligated to ensure that families are well informed and prepared. Many families may have misconceptions or unrealistic expectations about OIT and the clinician needs to ensure that all major risks and benefits of OIT are clarified. A structured discussion with careful documentation is essential and a checklist-based consent may be of benefit.[13] The SDM process can take a substantial amount of time with two studies demonstrating approximately one hour discussions in order to educate families about the risks and benefits of OIT.[13,29]

The use of adjunctive aids such as a counselling video has been demonstrated to significantly improve both patient and parent knowledge about OIT.[13] Importantly, mothers demonstrate higher levels of knowledge about OIT than fathers, supporting the inclusion of all parents in the consent discussion. Once enrolled in OIT, ongoing support and education is important to ensure continued safety and compliance.

CURRENT CANADIAN PRACTICE OF OIT

A recent survey of Canadian allergists demonstrated that a high proportion are beginning to offer OIT.[9] The most common food allergy treated was peanut and sublingual immunotherapy was practiced by some allergists as well. Other key findings from this study demonstrated that while there was significant interest in performing OIT for food, there were a number of barriers to either implementing or expanding their OIT practice. Many of these barriers were logistical in nature but also included clinical issues **(Figure 3)**. For example, over 80% of allergists offering OIT felt that remuneration, clinical space, support staff, and concern about after-hours coverage were barriers to the expansion of their OIT practice. Allergists not offering OIT reported that clinical factors such as inadequate research and inadequate safety data represented significant barriers to implementing or expanding their practice. These valid objections suggest that further high-quality data will be necessary before many Canadian allergists consider performing OIT.

CONCLUSION

While OIT can raise the threshold of reaction in the majority of patients, it is not curative and carries a risk of reaction. Careful attention must be paid to ensure that education and safety are optimized. Despite challenges in implementation, many Canadian patients and allergists consider OIT a reasonable therapeutic option to manage this life-threatening disease.

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ANTIHISTAMINES IN CSU: PRACTICE POINTS

INTRODUCTION

Urticaria is a mast cell mediated condition characterized by transient, raised, pruritic wheals on an erythematous background, with each individual lesion resolving within 24-48 hours without bruising or scarring. Angioedema (AE) is localized subcutaneous swelling which may occur with urticaria, or independently. Urticaria is classified as acute or chronic depending on the duration. Chronic urticaria is further subdivided into inducible or chronic spontaneous. The focus of this article will be chronic spontaneous urticaria (CSU), which is characterized by wheals and/or swelling occurring spontaneously on most days of the week for 6 weeks or more **(Figure 1)**. The prevalence of chronic urticaria has been estimated to be 0.5–5%. Chronic urticaria is more common in adults, with a peak age of onset between 20 and 40 years, affecting women more frequently than men. In CSU, an external trigger cannot usually be identified.[1]

Current global urticaria consensus guidelines recommend that first line treatment for CSU consists of regular daily use of a second-generation long-acting non-sedating antihistamine at standard dose. If no response or inadequate response is observed in 2-4 weeks or sooner, second line treatment is advised with two, three or four times the standard dose, usually divided in two daily doses. **(Figure 2)** Spontaneous remission of CSU occurs in up to 50% of patients within 6 months or less, but the average duration is 3-5 years.

While disease-modifying drugs are currently not available for CSU, the objective of treatment is to control or suppress symptoms impacting on the patient's quality of life until remission occurs. Due to the chronic nature of the disease and the requirement for continuous treatment for months or years, it is important that therapies used are well-tolerated and without significant long-term morbidity.

SECOND GENERATION (NON-SEDATING) H1 ANTIHISTAMINES

Second generation antihistamines available in Canada include cetirizine, loratadine, desloratadine, fexofenadine, bilastine and rupatadine. Although comparative studies suggest that all second-generation antihistamines may not be equally effective in CSU, there is not sufficient evidence to make strong recommendations for or against any of these antihistamines at the current time.

All the therapies mentioned have proven efficacy in CSU as evidenced by their key registration trials, which include a total of nearly 4,000 patients and all have demonstrated safety and efficacy with no significant adverse effects. Reported levels of somnolence and sedation are consistently comparable with placebo-treated patients and significant improvements in health-related quality of life, work performance and activities of daily living have also been reported. Minor adverse events have been noted in a minority of patients, including headache, drowsiness, constipation, and abdominal pain.[2-25]

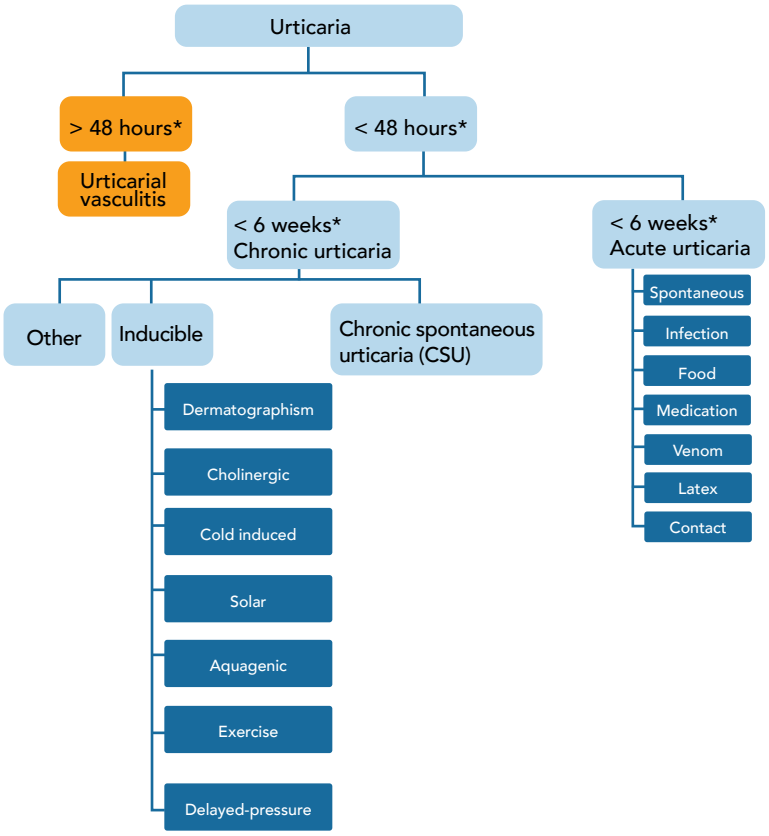


*Figure 1. Classification of urticaria: overview. *The 48-h cut-off refers to individual lesions, while the 6-week cut-off refers to the condition as a whole; adapted from Kanani et al, 2018*

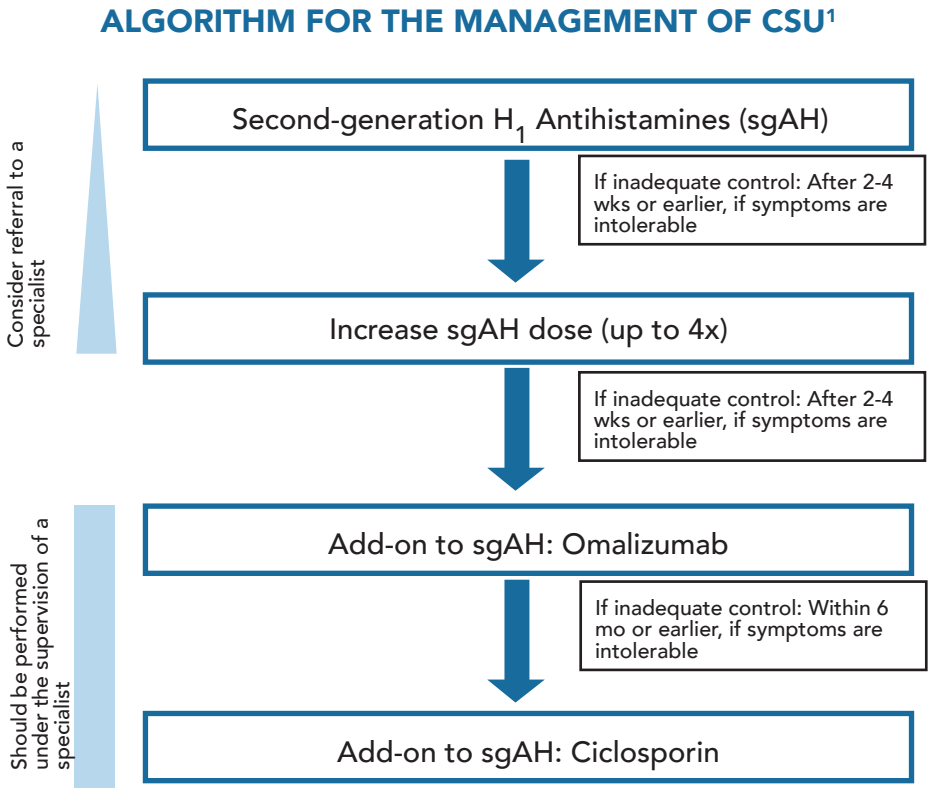


Figure 2. Recommended treatment algorithm for urticaria; adapted from Zuberbeir et al, 2018

Second-generation H1 antihistamines are generally well tolerated by most patients, even at high doses. A recent retrospective analysis examined data from one centre in which antihistamines were up-dosed at doses greater than four times the standard dose. The objective of this study was to investigate the frequency of ineffectiveness of treatment with antihistamines up to fourfold the standard dose in patients with CSU, and to determine the effectiveness and safety of antihistamine treatment above fourfold the standard dose. The investigators reported that of 200 screened patients, 178 were included in the final analysis and that treatment started with a once-daily dose of antihistamines. Persisting symptoms meant that up-dosing up to fourfold occurred in 138 (78%) of patients, yielding sufficient response in 41 (23%). Up-dosing antihistamines was necessary in 110 (80%) patients with weals alone or weals with AE and 28 (64%) with AE only ($p = 0.039$) and side effects after up-dosing higher than fourfold were reported in 10% of patients (6/59).[26] However, given this is a single study, a recommendation to increase to greater than 4 times the current dose cannot be made at this time.

TREATMENT OF CSU IN PEDIATRIC POPULATIONS

Evidence to date suggest that the prevalence and causes of CSU in the pediatric population are similar to that in adults[35,36] and second-generation long-

	Bilastine[27]	Cetirizine[28]	Desloratadine[29]	Fexofenadine[30]	Loratadine[31]	Rupatadine[32]
Onset of action	1 hour	0.7 hours to suppression of skin wheal and flare[33]	Within 1 hour	1-2 hours[34]	1-3 hours	1-2 hours
Duration of action	24-26 hours	≥24 hours suppression of skin wheal and flare[33]	24 hours	24 hours[34]	≥24 hours	24 hours
Absorption	Rapid	Rapid	Rapid	Rapid	Rapid (Food increases total bioavailability by 48%)	Rapid
Protein binding	84-90%	93%	82-87%	69.4%	97-99% loratadine, 73-76% metabolite	98.5-99%
Metabolism	Minimal (~5% of dose) No induction or inhibition of CYP450	Limited hepatic	Desloratadine is extensively metabolized. The enzyme responsible for the metabolism of desloratadine has not been identified yet.	Metabolism of fexofenadine is negligible. The methyl ester of fexofenadine and MDL 4829 were the only potential metabolites of fexofenadine detected.	Extensively; hepatic via CYP2D6 and 3A4 to active metabolite	Mainly by CYP3A4, to lesser extent by CYP2C9, CYP2C19 and CYP2D6.
Bioavailability	~61%	n/a	n/a	Estimated at ~33%	n/a	n/a
Half-life	~14.5 hours	Children 6.2 hrs, Adults 8 hrs	~27 hours	13-14 hours	7.8-11.0 hours for loratadine; 28 hours for metabolite	Children 2-5 years 15.9 hours; Children 6-11 years 12.3 hours; Adults 4-6 hours; Elderly 8.7 hours
Time to peak	1.3 hours	1.1 hours	~3 hours	~1.5 hours	1.3 hours loratadine, 2.3 hours metabolite	0.75 - 1 hour
% somnolence	4.0%	9.6%	1.9%	1.3%	8.0%	2.0%
Pregnancy Category	N/A	B	C	C	B	B
Excretion	Feces 67% as unchanged bilastine, Urine 28% as unchanged bilastine	Urine 70% (50% as unchanged drug), feces 10%	87% (equally distributed in urine and feces as metabolic products)	~11% urine; 80% feces	Urine 40% and feces 40% as metabolites	Urine 34.6%, Feces 60.9%
Pediatric (<12 y.o.)	Safety not established	Not recommended	Safety not established	Safety not established	Not to be administered to children between 2 and 12 for longer than 14 days	Tablets not recommended > 2 and < 12 y.o.; suspension should be used instead
Geriatric (> 65 y.o.)	No dosage adjustment warranted	Dosage adjustments required	No dosage adjustment warranted	Dosage adjustments required	No dosage adjustment warranted	Limited information on use in 65 y.o. and older

acting antihistamines remain the mainstay of treatment. First-generation antihistamines should be avoided due to the higher incidence of adverse events

TREATMENT OF CSU IN PREGNANCY AND LACTATION

During pregnancy therapeutic agents used to achieve control of symptoms, particularly pruritus should be used sparingly. The majority of patients can be treated during pregnancy and lactation with second-generation H1 antihistamines. There is no data available on the advisability of escalating the currently recommended doses of antihistamines in pregnancy, and careful discussion regarding benefits and risks of available treatment options is advised.

PRACTICE POINTS

- ✓ Second-generation long-acting (non-sedating) antihistamines are used in standard prescribed doses as first-line treatment in patients with CSU
- ✓ Second-generation long-acting (non-sedating) antihistamines are used in two, three or four times the standard dose as second-line treatment in patients with CSU with inadequate response to first-line treatment, often given as a double dose twice daily
- ✓ First-generation sedating antihistamines should not be used for treatment in patients with CSU, due to significant side effects and safety concerns
- ✓ The choice of second-generation H1 antihistamine depends largely on physician preference, taking into account patient preference, previous antihistamine therapy, patient age and underlying conditions such as renal impairment, hepatic impairment, cardiac conditions, and financial considerations
- ✓ Optimal adherence to medications will result in optimal symptom control. There is no evidence that adherence to medications (for example, regular compared with on-demand antihistamines) has any influence on the natural history of CSU but it has been shown to result in improved quality of life.[37]
- ✓ Patients with CSU who do not respond to second line treatment within 2 weeks, should be referred for evaluation by an allergist or dermatologist

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FOOD REINTRODUCTION IN FPIES

INTRODUCTION

Food Protein Induced Enterocolitis Syndrome (FPIES) lies within the spectrum of non-IgE-mediated food allergies. It is a clinical diagnosis based on a suggestive and reproducible history. T-cells are the likely mediators for FPIES; a neuro-endocrine mechanism is also suspected, but there is still considerable need for further understanding of the pathophysiology of FPIES. Classic FPIES is a delayed onset gastrointestinal reaction, usually 1-4 hours post ingestion and can vary in duration and symptom severity. Symptoms can include anyone, or a combination of, projectile emesis, diarrhoea, abdominal pain, lethargy, ashen appearance, hypotension, and even hypothermia. Urticarial and respiratory complaints are not characteristic. Any food can be a trigger and any age can be affected though it is more common in children. Clinicians should suspect FPIES in any patient with a consistent reproducible history to a specific food. Due to lack of provider familiarity with the condition, it may go misdiagnosed especially in the adult population; misdiagnosing FPIES for food poisoning with seafood for instance. Unlike IgE-mediated allergies, in the paediatric population, FPIES usually resolves sooner with an average age of about three. Excellent resources exist differentiating the spectrum of food allergies—in particular the non-IgE spectrum.[1-4]

The majority of patients with FPIES (65-80%) will be fairly clear when there is a single trigger. It is more difficult in polysensitized individuals or when the food allergen is consumed on a regular basis leading to chronic FPIES. Foods that are empirically most likely to trigger a patient vary based on geography and age, but FPIES often involves foods that are often overlooked as common allergens. Milk is by far the most common and best documented within the literature. There is no objective diagnostic tool to confirm FPIES except for a food challenge in the clinical setting. Acute events may show serological evidence of neutrophilia, thrombocytosis, methemoglobinemia, or acidemia and IgE may be present through serum specific or skin prick testing. It is important to note that though IgE may be present, FPIES is not IgE-mediated. None of these are useful tools to confirm or predict FPIES. The only treatment for FPIES is avoidance, there is no other established therapeutic algorithm.

Chronic FPIES can be more insidious and often overlooked. It may present with changes to stool consistency; frequency of bowel movements and constipation can be present especially after a diarrhoeal event; reflux potentially requiring medication for its management; gastrointestinal pain which can lead to frequent nocturnal awakenings. There is also the potential concern that enteropathies may impact a child's growth; if a child was to show growth curves falling significantly, it may be due to malnourishment secondary to a cellular food allergy. FPIES can have a very

low threshold required for a reaction. Though not common, a maternal diet involving the consumption of the culprit food in an exclusively breastfed infant can be enough to lead to reactions in the most sensitive infants.[6] Advanced cases of chronic FPIES can lead to more significant symptoms and laboratory changes such as leukocytosis, eosinophilia, and even failure to thrive. These situations pose difficulty in distinguishing FPIES from eosinophilic enteropathies and food protein induced enteropathies. These other conditions will not be addressed but they may in fact lie along a continuum or spectrum of non-IgE-mediated food allergies.

The aim of this article is to inform practitioners on a safe and reliable strategy for introduction of the food in the context of FPIES. This approach can be utilised to confirm the diagnosis in a suspected patient or to confirm the persistence of FPIES. A confirmational challenge is recommended to establish a diagnosis and avoid the unnecessary burden of avoiding a food that is not responsible.[2] Ultimately, it is a shared decision between the patient/family and clinician to perform a challenge especially if the original reaction was severe. Unlike IgE-mediated allergies, a challenge in FPIES should never be converted to a therapeutic protocol; oral immunotherapy is not applicable to FPIES. IgE-mediated allergies can be treated with oral immunotherapy (OIT). If a food challenge were to induce a reaction, clinicians might consider switching over to OIT to treat the allergy. FPIES can present with or without symptoms. If a challenge or reintroduction fails in FPIES, clinicians can discontinue and attempt it again later.

FOOD REINTRODUCTION

It may be preferable to use the term 'reintroduction' rather than 'challenge' in the setting of FPIES as it should be a slower process. Below, four important elements involved with food reintroduction are introduced. Baseline quiescence of symptoms for a patient should be clearly established prior to any reintroduction. If chronic FPIES is suspected it is recommended to postpone reintroduction; the best treatment for FPIES remains avoidance and/or elimination of the culprit food(s) from the diet. Clinicians should consider that chronic FPIES may lead to further problems if the chronic inflammation acts a nidus for further sensitisations or can act to delay spontaneous resolution.

1) LOCATION: Physician-supervised challenges are typical, and the severity of the original reaction may certainly warrant such an approach in a supervised setting. However, recent changes in how to deliver healthcare in a pandemic setting have made virtual challenges more common and permissible. These can be performed safely if families/patients are properly informed of the risks and benefits and if the initial reaction is not severe.[5]

For FPIES, a home-based reintroduction may be more appropriate given that:

a) Time constraints make dosing intervals in the office impractical as symptoms may take hours to develop between doses. There is no consensus as to how long patients should wait between doses, as this varies based on patient history.

b) Patients may feel most comfortable at home if a reaction were to occur. Protracted emesis or diarrhoea may last hours. A busy office with an unfamiliar washroom is not the ideal setting for a patient to weather these symptoms.

c) Reactions can be disconcerting to other patients and staff. Contact with bodily fluids also may pose a risk to others, including cleaning staff.

d) To date, there has never been a documented case of death in the literature from FPIES.

e) The majority of reactions will have occurred in the home setting. As there is no standardised treatment for FPIES, and the original reactions used for the clinical diagnosis will invariably have resolved spontaneously on their own, it should be reasonably safe to assume home reintroduction is safe.

2) TIMING: After clear avoidance of the suspect food, a reintroduction can be attempted usually every 6-18 months. As the timing of spontaneous resolution varies, there is no steadfast rule to predict when this will occur.

a) The risk of accidental ingestion may preclude the need for a scheduled reintroduction. Accidental ingestions for peanut average 12.4% per annum based on a large Canadian cohort.[7] Peanut ingestion is a good benchmark due to the awareness surrounding this allergen. Common foods like soy or milk may be even more common to ingest accidentally and can be used as an advantage to ensure follow-ups are booked every 6-12 months in the paediatric population knowing that many will have had an exposure.

b) Temper a reintroduction with the need for a particular food within a diet. Shrimp is not a necessary requirement in any diet and an adult may not wish to schedule any exposure. Nutritional and fiscal constraints on a family should be considered for the timing of reintroduction since avoidance can be onerous on a family, with alternatives being expensive.

c) Reintroductions should be timed around daycare, school, or work schedules in the event of symptoms.

3) PRODUCT CHOICE:

a) Some proteins are denaturable especially those within the liquid FPIES spectrum. The UK Milk Ladder and Egg Ladder are very useful and easily accessed resources based on denaturable proteins. Each step along the ladder would be one reintroduction.

b) If the patients has more than one trigger, start with the least reactive food based on the patient's history. A successful reintroduction of a milder allergen may also act as a predictor of gradual tolerance.

c) A successful reintroduction of a food into the diet allows the patient/family to expand the diet but also provides a sense of achievement and positive reinforcement. It is important to avoid starting with a food reintroduction failure.

d) If possible, a single product should be used for reintroduction such as cheese instead of pizza or soy milk rather than chicken nuggets.

e) It is also important to use a product that is typical in a diet (i.e. peanut butter rather than peanut protein). While the reaction will be due to the protein, isolating the protein is not critical for reintroduction. The modification of proteins can change reactivity as indicated by the dairy ladder.

f) In rare cases if the allergen can trigger symptoms through lactation, it is fully permissible to conduct the reintroduction first through the maternal diet. This situation may be the exception in terms of scheduling a reintroduction much earlier to avoid cessation of breast feeding and/or restricting the maternal diet.

4) PROTOCOL: There is a paucity of literature demonstrating the optimal method to challenge or reintroduce non-IgE-mediated food allergy. One protocol for FPIES recommends a target weight-based dose of 0.06–0.6 g/kg of body weight.[3,5] The target dose is divided into three equal measures with consumption over 30-45 minutes, generally not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid). It should be noted that lower challenge doses are used for patients with a history of severe reactions. In addition, this protocol recommends having IV access and a baseline CBC prior to challenge.

a) Start with sub-threshold levels (lowest dose at which no observed reaction). This minimizes the severity of reactions but also indicates to the patient/family what levels are permissible in the diet.

b) The actual starting dose should be as small as possible and may depend on the concentration of protein. Tofu compared to soy milk will be different. For tofu even a touch to the tongue could be enough to elicit symptoms. Generally, 2mg of protein is a good starting point.

c) Doses can be doubled or quintupled each interval. This can be done by weight or volume depending on the product. A pre-printed hand out to give to patients/families can be useful for home reintroductions.

d) Trials can be done over days simply with a single dose each day. The history may dictate onset of symptoms

after perhaps an hour; milder symptoms may manifest and result in onset later at lower doses.

e) If a quicker protocol is desired, the dosing interval should be double that of the historical timing for the patient. In other words, if on history the onset was 1 hour post ingestion, dose every 2 hours.

f) Home reintroductions require open lines of communication with the physician. Families and patients need to be instructed to contact the physician's office if and when symptoms develop. Milder symptoms may be overlooked that are otherwise identifiable to the physician. The patient's lowest observed eliciting level may not be as overt as the previous reaction(s). A specific list of symptoms to monitor for can be provided to the patient/family prior to the reintroduction.

SUMMARY

FPIES is a fascinating entity within the spectrum of food allergies. It generally has a very clear history and reproducibility. The reintroduction of suspect foods can be done to confirm the diagnosis or persistence of FPIES, but a pragmatic and cautious approach is recommended. The decision to proceed with a reintroduction should be mutually agreed to by the physician and the patient/family and there should be a clear rationale for the utility of a food reintroduction. The risks associated with reintroduction can be mitigated with careful consideration of the timing, location, and pace of the reintroduction.

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