ABOUT THE AUTHOR

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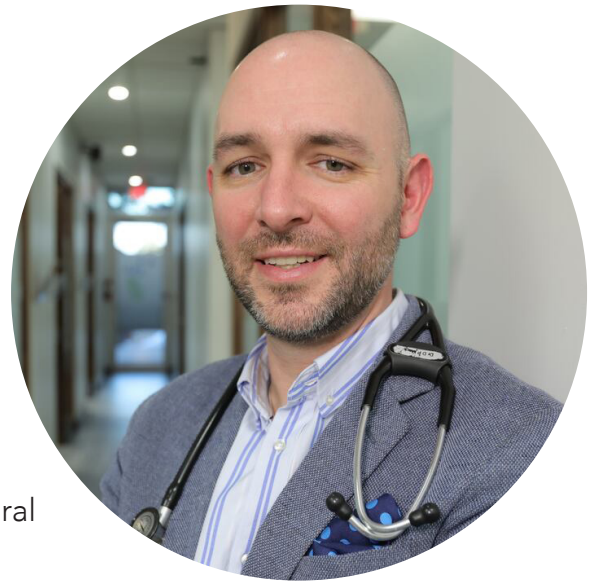


Dr. Mack is a pediatric allergy, asthma and immunology specialist. He is an Assistant Clinical Professor in the Department of Pediatrics at McMaster. He sits on the Board of Directors of the Canadian Society of Allergy and Clinical Immunology. He is co-author of guidelines on the prevention of allergy, epinephrine use and anaphylaxis. Dr. Mack is co-founder of Halton Pediatric Allergy Clinic and Ontario Pediatric Allergy Research Corporation where his focus is on asthma, allergic rhinitis and oral immunotherapy for food.

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]

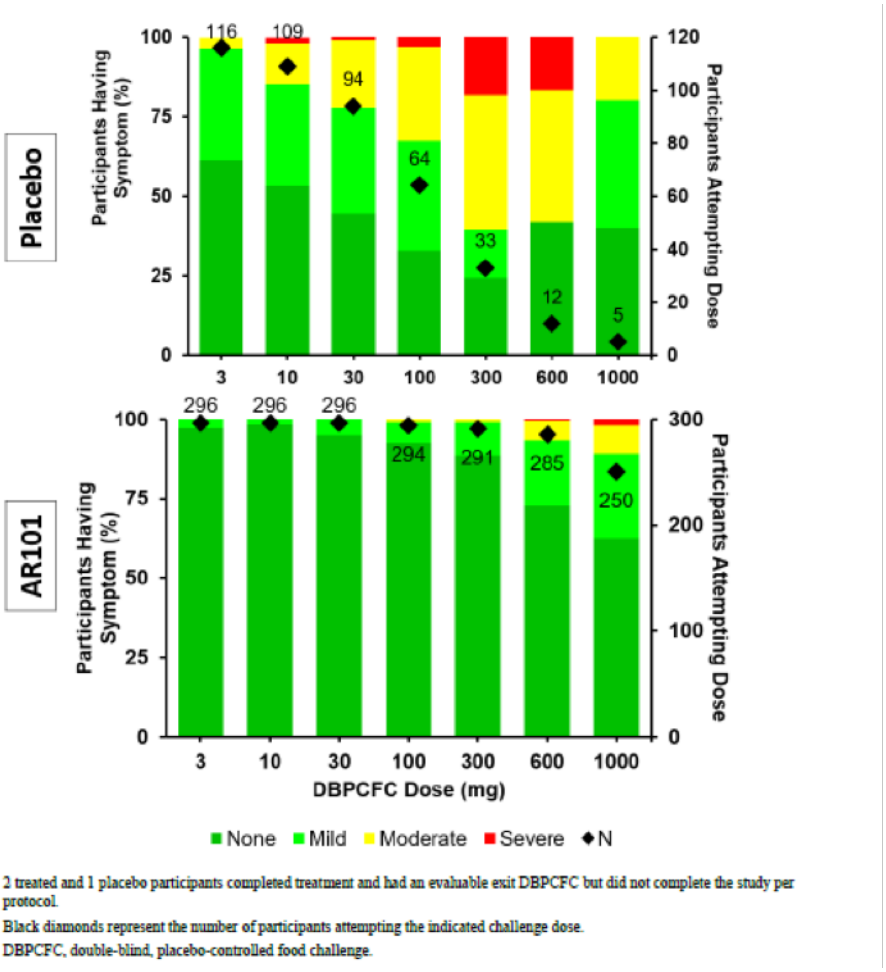
KEY STUDIES

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]



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

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

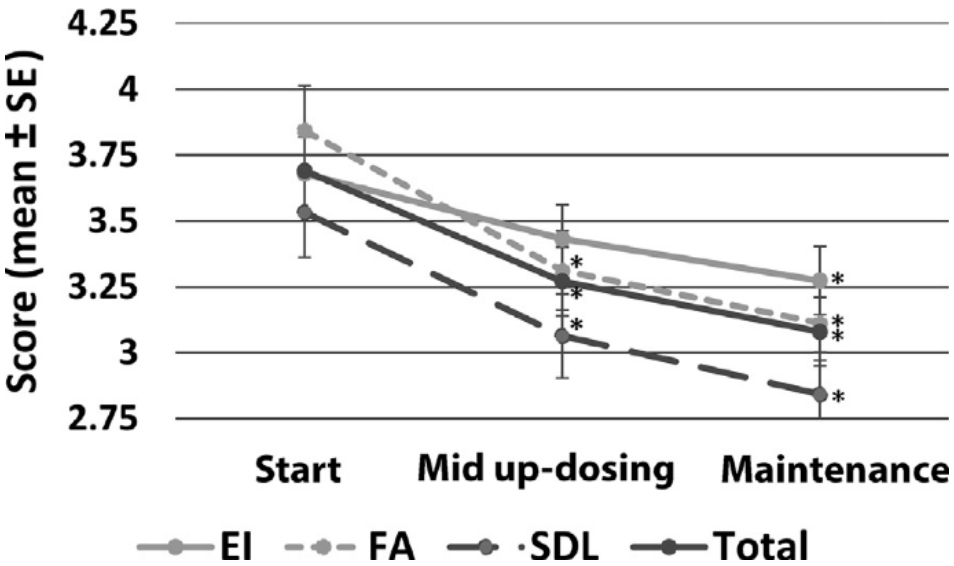


*Figure 2. Changes in the FAQLQ-PF scores in OIT-treated patients from start to mid up-dosing and then to maintenance in the EI, FA, SDL, and total score. *Represents a significant difference from the start of OIT.*

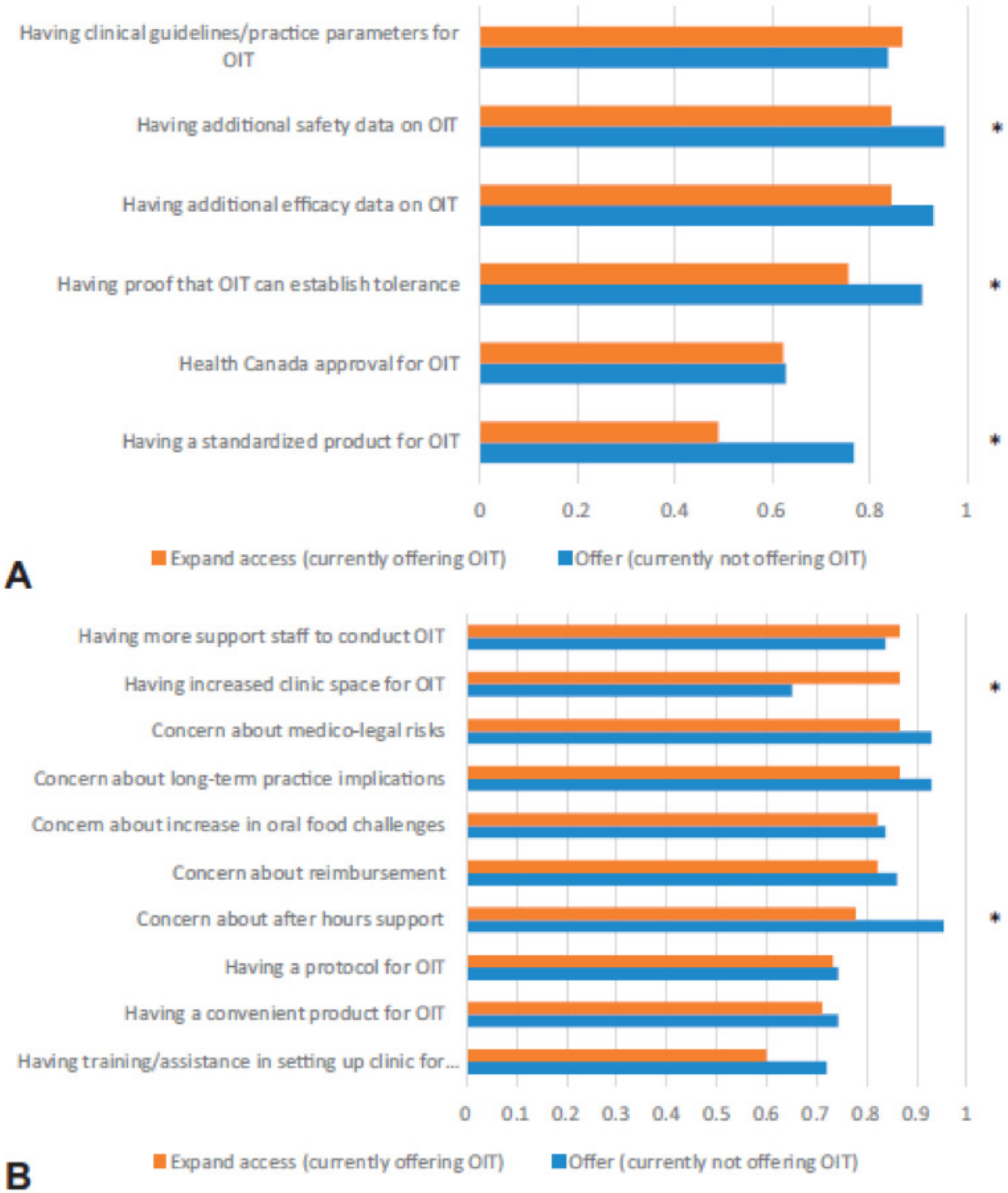


*FIGURE 3. A, Clinical factors identified as "moderately to extremely important" in influencing allergists' ability to expand access to or offer OIT. B, Logistical factors identified as "moderately to extremely important" in influencing allergists' ability to expand access to or offer OIT. * Indicates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

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 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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