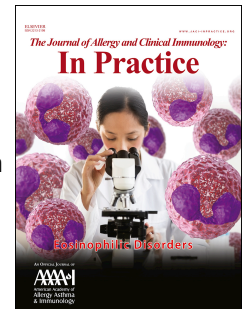


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A high proportion of Canadian allergists offer oral immunotherapy but barriers remain

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Title: A high proportion of Canadian allergists offer oral immunotherapy but barriers remain

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Abbreviations: OFC, oral food challenge; OIT, oral immunotherapy; SD, standard deviation; CSACI, Canadian Society of Allergy and Clinical Immunology; EPIT, epicutaneous immunotherapy; FDA, Food and Drug Administration; IQR, Interquartile Ratio.

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Abstract**Background**

Limited data on clinical implementation of oral immunotherapy (OIT) has been reported with incomplete evaluation of barriers.

Objective

To survey Canadian allergists on their current practice of OIT and barriers to implementation and expansion of OIT.

Methods

A survey investigating current practice and logistical and clinical barriers to offering or expanding OIT was distributed to all CSACI allergists.

Results

Of 90 responding allergists, 52.2% reported offering OIT, most commonly to peanut. Food sublingual immunotherapy was offered by 7% of allergists. Having received training for OIT was associated with currently performing OIT ($p=0.008$); 44.7% of allergists offering OIT had received training on OIT, and 81.4% not offering OIT had no training. 87% of allergists performing OIT reported lack of efficacy data, lack of support staff and clinic space, and concerns about increased oral challenges (84 %) were “moderately” to “extremely” important barriers to expanding OIT. For clinicians not offering OIT, concerns about safety (95%) after-hours support (95%), efficacy (93%), medicolegal risk (93%) and long-term practice

implications (93%) were prioritized as significant barriers. Qualitative assessment suggested concerns about the practical challenges associated with OIT, the need for increased safety and efficacy data and a desire for OIT guidelines and training.

Conclusion

The implementation of OIT faces many barriers, both clinical and logistical. Increasing high-quality safety and efficacy data may support those hesitant to offer OIT, and improving funding may address the practical infrastructure challenges. Additionally, training will help expand access for allergists interested in performing OIT.

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117 **Highlights**118 **1. What is already known about this topic?**

119 Discussion of OIT has historically centered around its readiness for clinical practice.
120 Previous North American surveys have suggested a relatively low allergist uptake for
121 OIT with a desire for a standardized product and guidelines.

122 **2. What does this article add to our knowledge?**

123 Using survey data we identified a relatively high proportion of Canadian allergists
124 performing OIT with multiple food products. Logistical and clinical barriers were
125 identified related to the practice and evidence base of OIT.

126 **3. How does this study impact current management guidelines?**

127 The implementation of OIT faces many barriers. Increasing high quality data may
128 encourage those hesitant to offer OIT. Improving funding and training will help to
129 expand access for allergists performing OIT.

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137 **Introduction**

138 Food allergy affects approximately 6% of the Canadian population.¹ For many of these patients,
139 food allergy is a lifelong diagnosis. Accidental exposures are common, with many accidental
140 reactions being moderate to severe.^{2,3} While fatal anaphylaxis is uncommon, this potential
141 outcome is often a major concern for families.^{4,5} As a result, food allergy remains a significant
142 burden for families affected by food allergy.^{5,6} The current standard of care in much of North
143 America is avoidance of the offending food with reactive treatment including the use of
144 epinephrine and other adjunctive medications.⁷

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146 Oral immunotherapy (OIT) for the treatment of food allergy has been practiced for decades by a
147 relatively small number of private practice allergists.^{8,9} The use of OIT has increased in the past
148 decade as clinical trials and real world studies have increased.¹⁰ More recently, immunotherapy
149 approaches such as OIT and epicutaneous immunotherapy (EPIT) have been evaluated in phase
150 2 and 3 clinical trials.^{11,12} Recent FDA approval of a proprietary OIT product (PalforziaTM) for
151 the treatment of peanut allergy has shifted the landscape in the United States.¹² Previous surveys
152 of allergists in the United States have demonstrated that there has been a strong desire for an
153 approved proprietary OIT product, as well as a desire for guidelines supporting the use of OIT in
154 clinical practice.¹³ While some of the first major OIT guidelines originated in Europe, American
155 allergy societies have been more reluctant to endorse the use of OIT outside of the research
156 setting.¹⁴ Recently, Canadian guidelines have been developed supporting the use of oral
157 immunotherapy in clinical practice.¹⁵

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Barriers to the implementation of allergy-specific procedures such as oral food challenges have recently been published in Canada and the US.^{16,17} These studies have identified barriers such as lack of ancillary staff, reimbursement, risk, and physician training. While research has been lacking regarding the barriers to more widespread use of OIT, two American surveys have been published describing some of the potential issues; however, one was limited in scope and largely qualitative and the other is older and may not be representative of the current practice of OIT.^{13,18} Neither survey dealt specifically with barriers to OIT implementation of expansion.

To our knowledge, there is no published data on the current practice of OIT amongst Canadian physicians. As well, there is limited data on the current barriers to OIT implementation. We surveyed Canadian allergists to determine their food immunotherapy practice patterns, barriers to expansion of OIT and barriers to offering OIT.

Methods

An online survey was sent using REDCap to all 237 allergist members of the Canadian Society of Allergy and Clinical Immunology (CSACI) on January 1, 2020. Two reminder emails were sent and the survey was closed on January 31, 2020. This study received an ethics waiver as a Quality Improvement project from the Research Ethics Board at The University of British Columbia/British Columbia Children's Hospital.

Survey questions included: information about the allergist's practice, if they offered OIT, what factors (logistical and clinical) prevented them from offering OIT, and barriers in expanding OIT.

A 7-point Likert scale was used to capture possible answers for each barrier: "Not at all influential," "A little bit influential," "Slightly influential," "Moderately influential," "Quite influential," "Very influential," and "Extremely influential." These were later recoded to "Not at all to slightly influential" versus "Moderately to extremely influential" for the purposes of data analysis.

Qualitative data analysis was performed using the allergists' written description of the barriers to OIT implementation. These descriptions were organized and common themes were identified.

Statistical analysis

Descriptive statistics were compiled for all variables; frequency and proportion for categorical variables, and median and interquartile range for continuous variables. A two-sample t-test was used to compare characteristics of allergists who did, and who did not, offer OIT. A two-sample t-test was also used to compare characteristics of allergists offering OIT in academic practice with those offering OIT in non-academic practice. A p-value <0.05 was considered statistically significant. Univariate logistic regression was used to determine whether clinical or logistical factors predicted offering or considering offering OIT, compared with those not offering and not considering OIT. StataSE 15.1 was used for all data analyses.

Results

Quantitative results

Allergist practice of OIT

Of the 237 surveys distributed, a total of 90 participants completed the survey (38.0% response). Of these, 52.2% of Canadian allergists reported performing OIT. Table 1 lists a comparison of those that were performing OIT versus those that were not. Working primarily in an academic setting ($p=0.04$), focusing primarily on pediatrics ($p=0.002$) and having previous OIT training were significantly associated with a greater likelihood of performing OIT ($p=0.008$). Amongst allergists not offering OIT, 47.7% report not wanting to perform OIT at all.

Of those allergists who reported that they were offering OIT, the most commonly offered food was peanut, followed by tree nuts, milk and egg as shown in Table 2, with 55.6% of physicians offering OIT to multiple foods. When comparing the practices of physicians who worked in a primarily academic or non-academic setting, academic physicians were more likely to use an ethics-approved protocol and perform OIT to tree nuts, milk, egg, wheat and mustard ($p<0.05$). (Table 2)

Canadian allergists tended to perform OIT in younger children (<6 years old), although approximately 20% of allergists offered OIT to adult patients (Table 3). During their careers, allergists reported performing OIT for a median of 2 years (IQR: 2, 4). The median total number of patients treated was 27.5 (IQR: 15, 96.5).

Allergists (n, %) reported primarily using whole peanuts (28, 60%) for peanut OIT, followed by peanut puffs (22, 47%) and peanut butter (21, 45%). (Figure 1a) Egg OIT was primarily performed using cooked egg (17, 35%). (Figure 1b)

Sublingual immunotherapy for food was performed by 6 (7%) clinicians (including one physician that does not perform OIT), primarily to peanut (5, 6%), but also to tree nuts (3, 3%) and milk (1, 1%).

Consent discussions were performed by 95.6% of those offering OIT. 51.1% of physicians require a minimum of one parent at the discussion and median length of consent discussion was 40 (IQR: 15, 60) minutes (Table 4)

Barriers to OIT implementation and expansion using Likert scale

Using a Likert scale, allergists that were currently performing OIT reported clinical factors such as more efficacy data (87%), proof that OIT could establish tolerance (84%), and more safety data (84%) as “moderately to extremely important” prior to expanding their OIT practice (Figure 2a). Logistical barriers reported as “moderately to extremely important” were: having more support staff (87%), having increased clinic space (87%) and concern about an increase in oral challenges (87%) (Figure 2b). For those clinicians not currently offering OIT, clinical concerns about insufficient safety data was reported as being “moderately to extremely important” on a Likert scale by the highest percentage of respondents (95%), followed by a need for efficacy data (93%) and need to demonstrate long-term tolerance (91%). Logistically,

concern about after hours support (95%) long-term practice implications (93%), and concern about medico-legal risk (93%) were most likely to be reported as “moderately to extremely important”.

Compared to allergists offering OIT, the “moderately important” to “extremely important” clinical factors chosen more often by allergists not performing OIT were “Having a standardized product” ($p < 0.01$), “Having additional safety data” ($p = 0.04$) and “Having proof that OIT can establish tolerance” ($p = 0.03$) (Figure 2a). The logistical factor that was ranked significantly higher amongst allergists offering OIT was “Having increased clinic space for OIT” ($p < 0.01$), whereas allergists not offering OIT expressed significantly different “Concern about after hours support” ($p < 0.01$) (Figure 2b).

Barriers to OIT implementation and expansion using allergist’s individual ranking

When individually asked to rank the top 3 reasons (with both logistical and clinical factors combined), those performing OIT reported logistical factors such as having more support staff, and more clinical space, followed by concerns about efficacy. Amongst those not performing OIT, concerns about after hours support, and having more support staff were followed by concerns about efficacy. If the top 3 barriers to offering OIT were addressed, 34 (79.1%) of the allergists not performing OIT said they would implement OIT into their practice. If the top 3 barriers to expanding OIT specific to the individual allergist were addressed, 45 (100%) of the allergists offering OIT reported that they would expand their OIT practice.

Qualitative Results

35 respondents documented further comments and concerns in the free text. These comments were grouped into 3 main themes. No respondents reported desire to have a standardized product or Health Canada approval. The following themes emerged during the data analysis.

1. *Practical challenges related to OIT.* This was the most commonly reported theme with 17 of the respondents reporting concern about after-hours coverage, already overloaded practices, need for more staffing and lack or inadequacy of funding to offer OIT. Adequate reimbursement was the most commonly reported concern by free-text. “If there was more support financially, many more allergists would be willing to take on the extra risk and train staff. No incentive at all right now to offer [OIT].”
2. *Need for more safety and efficacy data.* 9 respondents reported concerns about inadequate safety or efficacy data. One respondent wrote “Are we really confident that [OIT] does more good than harm” and similar concerns were raised by a number of these 9 respondents that suggested the need for more high quality (randomized controlled trial) data.
3. *Desire for guidance with guidelines or training.* 6 respondents reported a desire for guidelines or training opportunities with a need for “adequate training materials” and that “standardized guidelines are most important”.

Discussion

We report the first survey of OIT use in Canada. More than half of the respondents reported offering OIT of some kind, which appears to be higher than older American estimates.¹³ Interestingly, while concerns with safety and efficacy data were still mentioned, organizational and training aspects were the dominant themes in both the quantitative and qualitative analysis. The apparent shift from conceptual concerns to more practical concerns may reflect a progression in allergists' disposition toward OIT over the last few years. This said, still nearly a quarter of respondents reported no desire to offer OIT in future. This subgroup was more likely to identify the lack of safety and efficacy data as a potential impediment to the widespread adoption of OIT, consistent with past and ongoing debates about the suitability of OIT for clinical practice.^{13,19} A legitimate concern raised is that the reduction in reactions from accidental exposures with OIT²⁰ may not justify a potentially greater increase in reactions as side effects of OIT dosing.^{13,19} A recent systematic review reinforced the need for cautious adoption of immunotherapy, and while quality of life data is continuing to evolve, this review highlights some of the current concerns raised by survey respondents.¹⁹ Therefore, while there is a general progression in allergists' disposition towards OIT, it is important to recognize that there is still not a unanimous consensus amongst allergists as to whether and in which context it should be offered. Our survey was conducted before the publication of the Canadian guidelines on OIT, which recognized the various perspectives on OIT and stressed the need to consider patient individual context and personal preferences when determining treatment options.¹⁵ The guidelines specifically recommend high-quality research on patient-oriented outcomes to help

address such barriers relating to clinical relevance and indications. The results of this survey are consistent with this recommendation. The majority of allergists, regardless of whether they practice OIT, support improving the efficacy, effectiveness and safety data of this procedure.

The practical barriers of adequate support staff, clinic space, medico-legal concerns and reimbursement deficiencies are similar to the barriers to OFCs reported by Hsu et al.¹⁷ These challenges are reflective of a lack of financial priority given to food allergy in general as highlighted in recent Canadian OIT guidelines.¹⁵ Cost-effectiveness analyses in the US have demonstrated potential savings in cost and quality-adjusted life years with peanut OIT, especially in models using non-proprietary food products.^{21,22} However, current Canadian infrastructure and qualified personnel are insufficient to support this new clinical offer and at this time no province has a dedicated OIT billing code. A similar lack of coverage in the US was cited as a deterrent for OIT-naïve allergists in the Blaiss survey.¹⁸ American insurers are in the process of implementing OIT-specific billing codes, and it will be important to evaluate the subsequent changes in practice after increased coverage. Coordinating after-hours coverage appeared to be a major concern amongst those not-performing OIT, and this after-hours commitment may represent a novel clinical responsibility for a primarily out-patient specialty. The ability to support adequate staffing, after-hours commitment, clinic space and time is fundamental to the successful and meaningful long-term uptake of OIT amongst already overloaded allergists.

There appears to be a strong desire amongst Canadian allergists to have guidance for performing OIT. Similarly, Greenhawt and Vickery's and Blaiss et al's surveys also suggested that American allergists place a high priority on clinical guidelines.^{13,18} Future evaluation of the

uptake of OIT following the publication of Canadian and other international guidelines will be instructive. However, the guidelines so far have focused mainly on establishing the limits of the indications and drawing the path through which OIT should be developed.¹⁵ Specific training material addressing pragmatic and logistical questions still needs to be produced. The guidelines also recognize that the promotion of a personalized, patient-centered approach to OIT (as opposed to a rigid, fully standardized approach) creates a specific challenge with regards to training. The importance of adequate training of clinicians was highlighted with a significantly increased probability of offering OIT amongst those that received training in OIT. Training on OIT in allergy fellowship programs is presently variable across the country and more widespread practical guidance should be made available to trainees and the practicing allergist. Future surveys of fellows-in-training and training program directors may be beneficial.

Unlike American allergists, Canadian allergists reported a relative low priority to having a standardized product for OIT or having Health Canada (equivalent to FDA) approval, and no respondents reported these concerns as being a priority during the qualitative discussion. Blaiss' survey suggested that the majority of American allergists, especially OIT-naïve practitioners, placed a high priority on an FDA-approved product.¹⁸ The 2014 survey by Greenhawt and Vickery also suggested a strong desire for official approval of a standardized product and suggested this as a major barrier to OIT uptake in the US.¹³ However, this earlier survey documented that those that were currently performing OIT placed less importance on an FDA-approved proprietary product. Similarly, in our survey, the desire for a standardized proprietary product was significantly higher amongst those allergists not performing OIT. It should be noted that at the time, a smaller proportion of American allergists were performing OIT. The time

since those two surveys, an increase in published efficacy and safety data and a higher proportion already performing OIT in Canada, especially in toddlers and in patients with high reactivity threshold may be responsible for the shift in this overall thinking.²³ Our survey closed hours before the FDA approval of PalforziaTM, although Health Canada has not yet approved this product. A repeat survey after the Canadian approval of PalforziaTM should be considered in the future. A standardized product may offer increased comfort for OIT-naïve allergists and patients seeking this level of consistency. Thus, while allergists that are already comfortable using non-proprietary products may not switch to standardized products, the availability of a Health Canada-approved product will likely change OIT utilization by physicians and select patients.

Canadian allergists have used various types of food to support their OIT practice. The foods offered by Canadian allergists are similar to those reported by American surveys, with peanut being the most common food. Using actual peanuts was the most common approach, with peanut puffs being the second most common approach, likely influenced by the Canadian approach of targeting preschool patients.²³ Our data demonstrated a clear preference for treating younger children amongst Canadian allergists, potentially because of the perception of a lower side effect profile. This preferred age group would fall outside of the approved age group for proprietary immunotherapy products.

To our knowledge, this is the first North American report to address availability of SLIT for food. Approximately 7 % of respondents reported offering SLIT, including one respondent not offering OIT, similar to the practice in Italy.²⁴ This immunotherapy approach may represent an

option for those patients and clinicians not ready to perform OIT and recent long-term outcomes have been encouraging.²⁵

Consent for OIT was obtained by nearly all physicians as compared to the findings in the US survey demonstrating approximately two-thirds.¹³ The length of discussion was extensive, consistent with the need for a robust shared-decision making process when discussing OIT.^{26,27} Nearly half of respondents require both parents to be present at this discussion. Because a recent study suggested that fathers have a significantly lower knowledge base regarding this elective procedure, allergists may want to consider involving both parents in the consent discussion.²⁷

Limitations of this study include a relatively small respondent size, even though there was a relatively high response rate reflective of the small number of Canadian allergists. This resulted in underpowering of a number of comparisons. The incomplete response rate could also lead to a potential overestimation of the proportion of allergists offering OIT and SLIT. It is possible that those allergists not responding to the survey at all may represent allergists who do not perform or do not want to perform OIT and as such this selection bias would overestimate the number of those performing OIT. If there was indeed a non-response bias in favor of OIT-inclined allergists the actual rates could potentially be as low as 19.8 and 2.5 % for OIT and SLIT respectively. However, the response rate and respondent characteristics of this survey were very similar to other Canadian surveys for unrelated allergy topics, which suggests that non-response was more likely determined by respondent's dispositions toward online surveys in general.^{17,28,29} Response rates were also higher than Greenhawt and Vickery's 2014 survey.¹³ A

further limitation is that not all allergists chose to use the free text option to provide qualitative data, which can inform on recurrent themes but not on their weight or importance.

In conclusion, while practice patterns are changing, barriers still remain to the widespread adoption of OIT in Canada. The nature of the barriers appears to be shifting from questions on legitimacy to more pragmatic concerns. These results indicate that the next step should be to address the need for consistent and adequate reimbursement and training. A sizeable proportion of allergists are still reluctant to introduce OIT in their practice and their reservations should continue to drive further high-quality patient-oriented research. This high-quality research should also evaluate the real-world utility and effectiveness of food immunotherapy to ensure that adequate infrastructure is developed to support the safe practice of OIT. This is a critical time to shape the future of this therapeutic procedure. Ensuring that these identified barriers are addressed now is essential to ensure long-term access to this new therapeutic option.

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Figure Legend

Figure 1a: Products being offered for peanut OIT

Figure 1b: Products being offered for egg OIT

Figure 2a: Clinical Factors identified as 'moderately to extremely important' in influencing allergists' ability to expand access to or offer OIT

Figure 2b: Logistical Factors identified as 'moderately to extremely important' in influencing allergists' ability to expand access to or offer OIT

Table 1: Comparison of characteristics of physicians offering oral immunotherapy with those not offering oral immunotherapy

	Offering OIT N=47	Not offering OIT N=43	P-value
Practice type, n (%)			
Primarily Academic	23 (48.9)	12 (27.9)	0.04
Primarily Non-academic	24 (51.1)	31 (72.1)	
Office/waiting room space, n (%)			
≤2500 square feet	30 (63.8)	34 (79.1)	0.11
>2500 square feet	17 (36.2)	9 (20.9)	
# of allergists in the office, median (IQR)	3 (2, 5)	2 (1, 5)	0.71
Practice population*, n (%)			
Primarily pediatric	24 (51.1)	10 (23.3)	0.002
Primarily adult	1 (2.10)	7 (16.3)	
# of years in practice, median (IQR)	10 (4, 21)	12 (5, 29)	0.35
# of patients/month, median (IQR)	220 (150, 300)	200 (135, 300)	0.86
Received OIT training, n (%)			
Yes	21 (44.7)	8 (18.6)	0.008
No	26 (55.3)	35 (81.4)	
Region of practice, n (%)			
Eastern (ON and east)	33 (70.2)	37 (86.0)	0.07
Western (MB and west)	14 (29.8)	6 (14.0)	
Ever had one of your patients go to another physician for OIT, n (%)			
Yes	27 (57.4)	34 (79.1)	0.03
No	20 (42.6)	9 (20.9)	

Table 2: Trends related to the administration of OIT based on practice type

	Academic practice, n (%)	Non-academic practice, n (%)	P-value
Total offering OIT (N=47)	N=23	N=24	
OIT protocol IRB approved (n=13)	9 (39.1)	4 (16.7)	0.04
Informed consent obtained (n=43)	21 (91.3)	22 (91.7)	0.52
Always challenge before entry (n=9)	4 (17.4)	5 (20.8)	0.62
Offer OIT to peanut (n=45)	22 (95.7)	23 (95.8)	0.51
Offer OIT to tree nuts (n=29)	18 (78.3)	11 (45.8)	0.01
Offer OIT to milk (n=23)	16 (69.6)	7 (29.2)	<0.01
Offer OIT to egg (n=20)	15 (65.2)	5 (20.8)	<0.01
Offer OIT to wheat (n=13)	9 (39.1)	4 (16.7)	0.04
Offer OIT to mustard (n=10)	8 (34.8)	2 (8.30)	0.01
Offer OIT to Legumes (n=14)	9 (39.1)	5 (20.8)	0.09

Table 3: Age groups treated with OIT

In what age groups do you perform OIT?	n (%)
3 years old and under	40 (85.1)
4 to <6 years old	40 (85.1)
6-17 years old	31 (66.0)
18 years old and older	10 (21.3)

Table 4: Consent discussion characteristics for OIT

	n (%)
Do you obtain detailed informed consent for OIT?	43 (95.6)
Who do you require to be at the consent discussion?	
Both parents (if applicable)	18 (38.3)
One parent	24 (51.1)
Child	25 (53.2)
Other	1 (2.13)
Who performs the consent discussion?	
Physician	39 (83.0)
Resident	4 (8.51)
Physician assistant	2 (4.26)
Nurse Practitioner	0
Nurse	4 (8.51)
Other	1 (2.31)
How long do you estimate you spend obtaining informed consent (minutes)? Median (IQR)	40 (15, 60)

