

DR RONGBO ZHU (Orcid ID : 0000-0002-3184-0139)

DR JENNIFER PROTUDJER (Orcid ID : 0000-0002-3888-8688)

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Impact of age on adherence and efficacy of peanut oral-immunotherapy using a standardized protocol

Rongbo Zhu, MD FRCPC^{1,2}, Kara Robertson, MD FRCPC^{1,2}, Jennifer LP Protudjer, PhD³⁻⁷, Andrea Macikunas HBSc², Rebecca Kim⁸, Samira Jeimy, MD PhD FRCPC^{1,2}, Harold Kim, MD FRCPC^{1,2,9}

¹Division of Clinical Immunology and Allergy, Department of Medicine, Western University

²Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

³Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Canada

⁴George and Fay Yee Centre for Healthcare Innovation, Winnipeg, Canada

⁵Children's Hospital Research Institute of Manitoba, Winnipeg, Canada

⁶Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, Canada

⁷Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

⁸Queen's University Faculty of Arts and Science, Kingston, Ontario, Canada

⁹Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Corresponding author

Harold Kim

B3-110, 268 Grosvenor St, London, ON N6A 4V2

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Phone: (519) 685 8167

Email: Harold.Kim@lhsc.on.ca

Author emails

RZ- Rongbo.Zhu@lhsc.on.ca

KR – Kara.Robertson@lhsc.on.ca

JP – Jennifer.Protudjer@umanitoba.ca

AM – Amacikunas2021@meds.uwo.ca

RK – Rkimkw@gmail.com

SJ – Samira.Jeimy@lhsc.on.ca

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RZ has no competing interests to declare.

KR has no competing interests to declare.

JP sits on the steering committee of Canada's National Food Allergy Action Plan; is the Section Head of Allied Health, of the Canadian Society of Allergy and Clinical Immunology; and, does research with DBV Technologies.

AM has no competing interests to declare.

RK has no competing interests to declare.

SJ has been on speaker's bureaus for Aralez, Astra Zeneca, Sanofi, Medexus, Stallergenes Grier, and Novartis, and on the advisory board for Sanofi.

HK has been on the speakers' bureau and/or advisory boards for ALK, Aralez, Astra Zeneca, Bausch Health, GSK, Kaleo, Mylan, Pediapharm, Pfizer, Stallergenes Greer.

Keywords

Peanut allergy, peanut oral immunotherapy, children, pediatrics, efficacy, safety, age

Abbreviations

IgE Immunoglobulin E

OR Odds ratio

POIT Peanut oral immunotherapy

SPT

Skin prick test

95%CI

95 percent confidence interval

Word Count: 980

To the Editor:

Peanut oral immunotherapy (POIT) has been shown to be an effective therapy in peanut allergic children, as it improves food allergy-related quality of life [1-2]. Randomized controlled trials and observational, real world studies have shown that POIT may be effective and safe in children of all ages, although starting POIT at a younger age may be more efficacious and safer [3,5,8]. Furthermore, initiation of POIT at a younger age may have higher rates of sustained unresponsiveness [3]. However, there has not been formal evaluation of this concept, using a standardized protocol [6]. The aim of our study was to examine associations between the age at initiation of POIT, and the safety of POIT, using a standardized protocol for all patients.

A multi-centered retrospective study of pediatric patients (ages 1-17 years) was conducted between June 2016 and October 2020. Research ethics approval was obtained through the Lawson Health Research Institute Research Ethics Board at Western University (project number: 114291). All patients referred for peanut allergy underwent assessment. POIT was offered to all patients with a positive oral challenge to peanuts or to patients who declined oral challenge due to high risk of reaction based on initial exposure, peanut skin prick wheal diameter and peanut-specific serum Immunoglobulin E (IgE) [7]. All patients received the same standardized POIT protocol (Table 1). Patients underwent monthly clinic visits over 14 months. Peanut dosing was incrementally increased to 250 mg of peanut protein, using formulary capsules containing peanut flour. Efficacy was defined as completion of our POIT protocol and successfully passing a challenge to at least 250 mg of peanut protein in the form of a peanut kernel, peanut butter, and/or peanut M&Ms. Following the challenge, the patients are maintained on at least 250 mg of peanut protein daily. Peanut M&Ms were chosen as maintenance therapy for most patients as the M&Ms are a chocolate-covered candy containing a single peanut (equivalent to 225-275 mg of peanut protein based on a weight of 900 – 1100 mg), are easier to administer, and are consistent in size. Safety was assessed by the frequency of epinephrine administration requirement during up-dosing of POIT. Data were analyzed using n/N, %, mean $\pm$ standard deviation, and binary logistic regression analysis (Odds Ratio and 95 percent confidence interval [OR, 95%CI, respectively]), using Stata® 15.1 (StataCorp. 2017, College Station, TX).

A summary of baseline patient demographics and results of POIT is presented in Table 2a. Overall, 160 patients ages 1-17 years (61.9% male; mean age 8.33 ± 4.37 years) were included. Mean baseline skin prick test (SPT) wheal size for peanut was 8.45 ± 3.91 mm. Mean baseline peanut-specific IgE was 49.84 ± 41.40 kU/L. In addition to peanut allergy, 41.3% (66/160) had at least one other food allergy and 80.6% (129/160) had comorbid allergic disease. In total, 80.6% (129/160) of patients ages 1-17 years completed POIT per protocol (Figure 1a), and 3.1% (5/160) required epinephrine during up dosing of POIT. Patient

characteristics surrounding epinephrine use are shown in Table 2b. Overall, three children (60%) had anaphylaxis related to a cofactor and only one child under age 6 years required epinephrine. Despite having anaphylaxis during POIT up dosing, 2 (40%) of the children still finished the POIT protocol. Older age at start of POIT was inversely associated with the odds of completion (OR 0.88; 95% CI 0.80 - 0.98, $p=0.018$; Figure 1b). A corresponding analysis for the outcome of epinephrine use during POIT buildup was not possible due to the low number of patients who required epinephrine.

Reasons for discontinuation of POIT are also presented in Table 2b. Most children stopped POIT as a result of side effects of the therapy (58.1%) with gastrointestinal symptoms being the most common (72.2%). No patients in our study developed eosinophilic esophagitis as a result of POIT.

Our study is the first to demonstrate a statistically significant trend that younger children are more likely to complete POIT using our standardized protocol (Figure 1) after adjusting for variables including sex, IgE at start, and atopic comorbidities. This finding corroborates that of Wasserman *et al* who performed POIT in children aged 4-18 years, using a protocol that was modified based on patient experience through POIT [8].

The efficacy and adherence rate of POIT in our protocol was 80.6%. This is similar to published literature on POIT in both controlled and uncontrolled settings [4,8]. The rate of epinephrine administration during POIT up dosing in our protocol was 3.1%. This is comparable to the rate of 4.1% reported by Soller *et al* in a real-world, observational study [4]. Only one child under age 6 years required epinephrine, similar to the findings of Vickery *et al* [3]. Overall, this finding supports the safety of our standardized protocol in all pediatric age groups.

There are some limitations associated with our study. Although an oral challenge was offered to all participants, not all of them underwent one before undergoing POIT. This is reflective of real-world practice and shared decision making. We believe this approach may be safer, especially in this high-risk population [7], as fatal anaphylaxis has been reported with oral food challenge prior to OIT initiation [9]. There are inherent biases in real-world retrospective studies such as a lack of randomization and comparison to placebo [10]. However, all patients that underwent POIT were included in the analysis. Furthermore, all patients followed a standardized protocol to ensure treatment was uniform across different age groups.

In conclusion, this is the first study to demonstrate a statistically significant trend that younger children are more likely to successfully complete POIT using a standardized protocol. Furthermore, we showed that our standardized POIT protocol is safe with similar completion rate and epinephrine usage during build up dosing compared to other real-world data for POIT [4,5,8]. This study supports starting POIT early in peanut allergic

children. Future prospective randomized controlled trials are needed to re-affirm the findings presented in our study.

Rongbo Zhu, MD FRCPC

Division of Clinical Immunology and Allergy, Department of Medicine, Western University
Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

Kara Robertson, MD FRCPC

Division of Clinical Immunology and Allergy, Department of Medicine, Western University
Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

Jennifer LP Protudjer, PhD

Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Canada
George and Fay Yee Centre for Healthcare Innovation, Winnipeg, Canada
Children's Hospital Research Institute of Manitoba, Winnipeg, Canada
Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, Canada
Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

Andrea Macikunas HBSc

Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

Rebecca Kim

Queen's University Faculty of Arts and Science, Kingston, Ontario, Canada

Samira Jeimy, MD PhD FRCPC

Division of Clinical Immunology and Allergy, Department of Medicine, Western University
Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

Harold Kim, MD FRCPC

Division of Clinical Immunology and Allergy, Department of Medicine, Western University
Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada
Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Table 1. Standardized peanut oral immunotherapy up-dosing protocol with maintenance therapy

Clinic visit	Peanut	Peanut
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(every 4 weeks)	capsule (mg)	protein (mg)
1	1	0.5
2	2	1
3	4	2
4	6	3
5	12	6
6	25	12.5
7	50	25
8	75	37.5
9	100	50
10	150	75
11	200	100
12	300	150
13	400	200
14	500	250

Maintenance therapy	Peanut protein (mg)
1 peanut M&M	250
¼ teaspoon of peanut butter	
1 peanut kernel	

Table 2a Baseline demographics and completion rates for patients aged 1 to 17 years who underwent POIT using a standardized protocol (N=160)

Variable	n	%
Sex		
Male	99	61.9
Female	61	38.4
Food allergies in addition to peanut	66	41.3
Comorbid allergic conditions	129	80.6
Asthma	82	51.3
Allergic Rhinitis	64	40.0
Atopic Dermatitis	74	46.3
Number of patients completing POIT	129	80.6
Number of patients requiring epinephrine during POIT up dosing	5	3.1
	Mean ± SD	
Mean Age (in years) at start of POIT	8.33 ± 4.37	
Mean Baseline Peanut Skin-Prick Wheal Size (mm)	8.45 ± 3.91	
Mean Baseline Peanut-specific IgE (N=154; kU/L)	49.84± 41.40	
Mean Baseline Peanut Ara h2 IgE (N=61; kU/L)	45.30 ± 41.02	

Table 2b Reasons for POIT discontinuation and patient demographics requiring epinephrine usage during POIT buildup

Reason for POIT discontinuation (N=31)											
Side effects											18
Cutaneous (hives, pruritus)											5
Respiratory (dyspnea, cough)											0
GI symptoms (abdominal pain, nausea)											13
Non-adherence											2
Psychosocial factors (e.g. patient/caregiver anxiety)											7
Lost to follow up											4
Children requiring epinephrine during POIT up dosing											
Age at POIT start	Sex	SPT wheal size(mm)	Peanut IgE (KU/L)	Asthma	AR	Eczema	Reaction Dose	Symptoms	Cofactor	Completed POIT?	
5	M	10	>100	Y	N	N	1 mg	Wheezing, throat pruritus	None	Y	
12	F	11	>100	Y	Y	N	150 mg	Chest tightness, emesis, angioedema	Exercise	N	
12	M	11	83.9	N	N	N	75 mg	Cough, angioedema	None	N	
14	F	12	>100	N	N	N	150 mg	dyspnea, throat pruritus, abdominal	NSAID use	N	

								pain		
14	M	13	>100	Y	Y	N	500 mg	dyspnea, urticaria	Exercise	Y

Abbreviations: AR – allergic rhinitis; IgE - Immunoglobulin E; N=No; POIT - Peanut Oral Immunotherapy;
SD - Standard Deviation; SPT – skin prick testing; Y=Yes

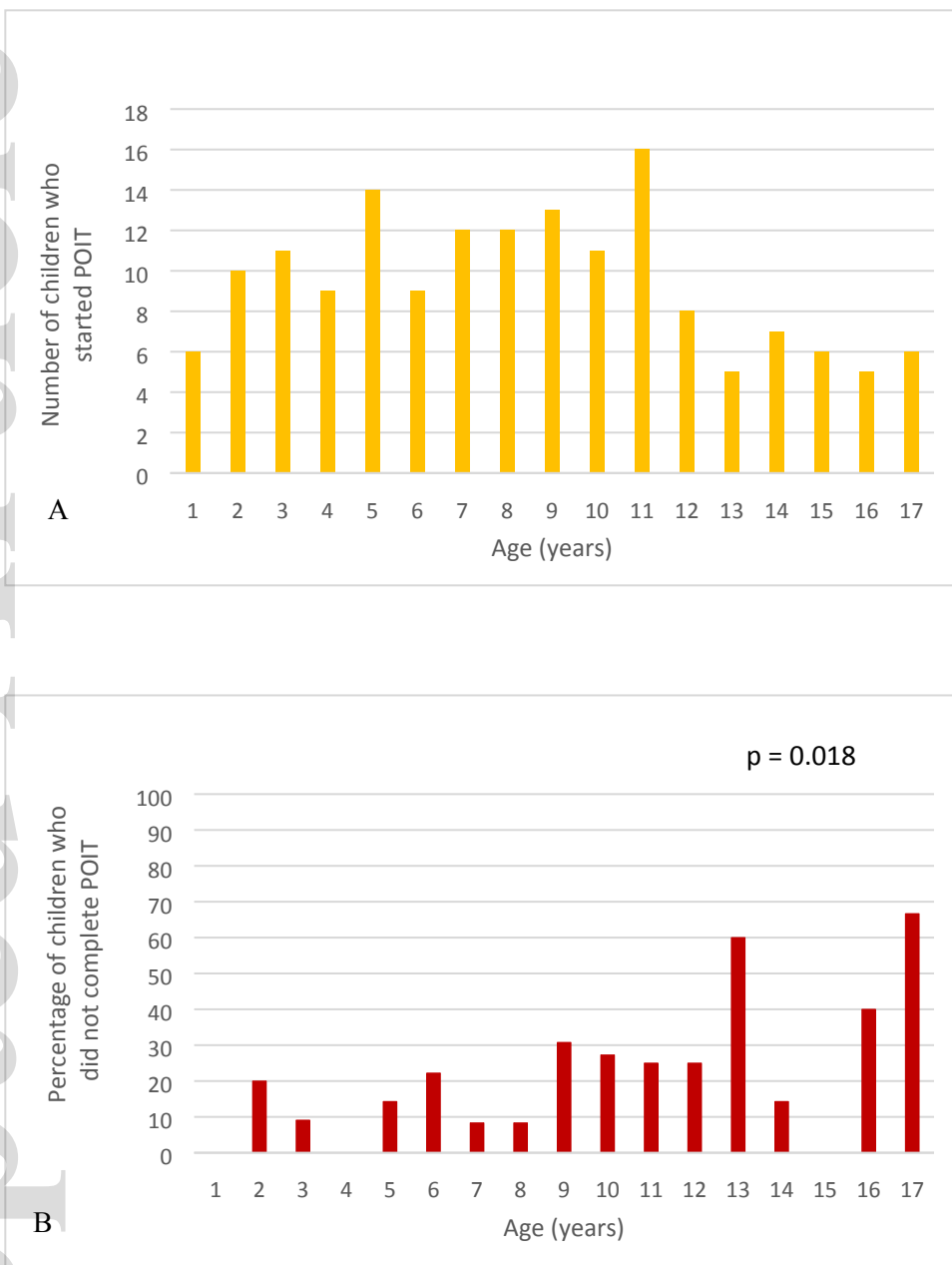


Figure 1. (A) Absolute number of patients who started POIT, by age in years, and (B) percentage of children who did not complete POIT, by age in years.

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