Home-based program of maintaining unresponsiveness in children with allergic reactions to larger amounts of peanuts

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Suggested Reviewers:

Opposed Reviewers:

Response to Reviewers: Thank you to you the Editors and Reviewers for
assessing our revised manuscript.

Point by point response:

Reviewer #2:

1. Reference 1 and 2 have now been reordered in the first two
sentences of the text and in the reference list.

Reviewer #4:

1. Line 7, the sentence has been changed as suggested to . . . "that
desensitization and to some extent sustained unresponsiveness can be
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Home-based programme of maintaining unresponsiveness in children with allergic reactions to larger amounts of peanuts

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Allergists currently advise the majority of patients with peanut allergy to observe life-long avoidance. This is in contrast to milk and egg allergy, where many children are partly tolerant to the food and tolerance induction with food ladders is now routine.^{1,2} Twenty one percent of children with proven peanut allergy on challenges appear to outgrow their clinical reactivity.^{2,4} Furthermore, clinical trials using oral, subcutaneous and epicutaneous peanut immunotherapy have demonstrated that patients vary in the amount of peanut needed to trigger a reaction and that desensitization and to some extent sustained unresponsiveness can be achieved in children and adolescents.²⁻⁴ There are currently no reliable biomarkers identifying which children will outgrow their peanut allergy, or only react to larger amounts of the food.

At our tertiary pediatric allergy referral center in the United Kingdom, 41 (32%) of 130 children undergoing supervised open oral peanut challenges between 2012 - 2016 developed objective signs of an allergic reaction. Of these 41 patients, 31 (76%) reacted after eating more than one peanut (200mg total weight).⁵ We hypothesized that in this group of children with a higher threshold of reactivity and non-anaphylactic reactions, it should be possible to maintain and increase the threshold amount of peanut required to induce an allergic reaction by regular exposure, irrespective of allergy test results. As proof of principle, Garvey *et al* from Cork, Ireland recently published the results of their home-based oral peanut immunotherapy (OIT) programme. It was not a formal research study but a case series based on clinical observations performed with motivated families in a university based clinical practice. They described 10 children who previously experienced non-anaphylactic reactions to 4g or more of peanut during supervised hospital oral challenge.⁶ After six months on their programme, all children were able to tolerate more peanut than the eliciting threshold at the initial oral challenge: a minimum cumulative dose of 4g and up to 16g of peanut. There were no significant adverse events and no need for additional clinical reviews.

From September 2015, our center supported a small group of children through a similar home-based peanut OIT programme. The aim of this case series review is to describe our center's experience in maintaining partial non-responsiveness to peanut. After formal oral peanut challenge, six children who had tolerated the equivalent of one or more (≥ 200 mg by weight) peanuts in their oral challenge were invited to start consuming sub-threshold amounts of peanut as determined by their oral challenge. Joining the programme was a collaborative decision made after discussions initiated by the pediatric allergist. The most common reason for patients being excluded was that the child had no interest in eating, or did not like the taste of peanuts.

Although the aim was to start patients on a quarter of the threshold amount of either peanut butter or shelled peanuts that caused the allergic reaction in open challenge, the starting amount was individualized depending on how much peanut the patient felt comfortable eating. Patients were asked to consume the peanuts or peanut butter at least three times a week, doubling the amount, up to a maximum of 15 peanuts three times a week. Progress up the food ladder depended on their confidence and that of their parents and was formally reviewed in clinic every 2 to 3 months. If patients suffered from an allergic reaction, they were instructed to stop eating the peanuts and contact their clinician. Patients who did not eat the peanut-containing food for more than four weeks were asked to contact their physician before recommencing the food. During the programme, no patients informed the clinical team that they had missed more than four weeks. Allergy management plans, including use of epinephrine auto-injectors were provided and regularly reviewed. As with the Cork programme, ethics approval was not sought as children started with a quantity of food they already tolerated. Procedural details were clearly documented in the clinical records and clinic letters to the primary physician were copied to the family.

Data from the six children in the programme aged between 1 to 16 years who reacted to 200mg or more of peanut on formal open challenge with urticaria, superficial angioedema and/or vomiting, but no breathing problems are described in Table I. Four to 24 months into their programme all children tolerate one to six peanuts three times a week. None of the children have had significant allergic reactions during up dosing or the maintenance phase, nor have they required additional visits to the allergy center outside routine review. Furthermore, none of the patients contacted the physician between appointments because of allergic reactions.

This case series, albeit of a small number of children, independently supports that of Garvey *et al.*⁶ By selecting children with well-controlled asthma and non-anaphylactic reactions to the equivalent of one or more peanuts, we suggest that it is possible to safely maintain and increase peanut non-responsiveness through a home OIT programme. Patients will continue to be encouraged to eat the equivalent of up to 15 peanuts (tablespoon of peanut butter) 3 times a week, although some will only feel comfortable with smaller amounts. As with any immunotherapy programme, the main concern is anaphylaxis either during up dosing, intercurrent infection or because of prolonged periods of noncompliance. Allergy management plans need to be reviewed regularly, including competence and availability of epinephrine auto-injectors. Patients should be carefully monitored for adverse events such as allergic reactions and eosinophilic esophagitis.⁷

In summary, published studies indicate that complete avoidance of foods to which children were previously partly tolerant can lead to more severe allergic reactions, while continuing to consume the food in an amount and form that is tolerated maintains non-responsiveness.⁸⁻⁹ We suggest that regular ingestion of tolerated amounts of peanut-containing food, as with cow's milk and egg, may reduce rather than increase the risk of

future serious allergic reactions. Formal studies are required to determine if this is indeed the case.

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References

- ~~[12]~~ Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:113-1147.
- [24] Ho MK, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol*. 2008;121:731-6.
- ~~[2]~~ Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:113-1147.
- [3] Jones SM, Sicherer SH, Burks AW, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. 2017;139:1242-1252.
- [4] Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173-181.
- [5] Rajput S, Sharma V, Hughes SM, Ewing CI, Arkwright PD. Reply to van Erp *et al*: allergy testing in predicting outcome of open food challenge to peanut. *J Allergy Clin Immunol* 2017, Jun 14.
- [6] Garvey AA, O'Sullivan D, Hourihane JOB. Home-based induction of sustained unresponsiveness in children with mild reactions to high doses of peanut. *J Allergy Clin Immunol Pract* 2017; Apr 28.
- [7] Semancik E, Sayej WN. Oral immunotherapy for peanut allergy induces eosinophilic esophagitis: three pediatric case reports. *Pediatr Allergy Immunol*. 2016;27:539-41.
- [8] Young MC. Elimination Diets in Eczema. A Cautionary Tale. *J Allergy Clin Immunol Pract*. 2016;4:237-8.

- 24 [9] Chang A, Robison R, Cai M, Singh AM. Natural History of Food-Triggered Atopic
25 Dermatitis and Development of Immediate Reactions in Children. *J Allergy Clin Immunol*
26 *Pract.* 2016;4:229-36.e1.

Table I Characteristics of patients undergoing home peanut OIT

Patient number	Age (years)	Gender	Clinical history of reactions to peanut	SPT (mm)	total IgE / peanut IgE/ Ara h2 (kAU/L)	Doctor supervised peanut oral food challenge	Home peanut OIT programme
1	17	Female	At 4 years ate peanuts, within 5 minutes urticaria, facial swelling, husky voice, cold & clingy. Mild asthma: no steroid inhaler Grass-induced rhinitis: on grass SLIT	10	1000 12.8 -	At 14 years failed stage 5: 5g peanut: urticaria, angioedema, vomiting. Given antihistamine only.	24 months into home peanut OIT programme. No acute allergic reactions. Started with 1, now tolerating 6 peanuts, 3/week
2	15	Female	At 2 years ate roasted peanut, within 5 minutes itchy mouth, cough listless, agitated. No asthma	18	340 8.1 5.1	At 12 years failed stage 4: 1g peanut, lip swelling. Given antihistamine only.	20 months into home peanut OIT programme. No acute allergic reactions. Started with 1/4, now tolerating 4 shelled peanuts, 3/week
3	7	Male	At 1 year ate peanut butter, within 5 minutes facial angioedema only. Mild asthma: no steroid inhaler	7	910 3.4 0.7	At 6 years, failed stage 5: 5g peanut: large vomit.	13 months into home peanut OIT programme. No acute allergic reactions. Started with 2, now tolerating 9 peanuts, 3/week

4	8	Male	At 6 years, ate a peanut-containing chocolate bar, within 30 minutes developed generalized urticaria only. Mild asthma: no steroid inhaler Mild allergic rhinitis	10	903 1.1 1.3	At 7 years, failed stage 5: 5g peanut: localized urticaria on torso	6 months into home peanut OIT programme. No acute allergic reactions. Started with 1, now tolerating 4 peanuts, 3/week
5	2	Female	At 1y, given peanut butter, within 5min developed facial urticaria and angioedema only. No asthma.	3	25 0 0	At 1 year, failed stage 3: 200mg peanut butter: localized urticaria.	9 months into home peanut OIT programme. No acute allergic reactions. Started with 100mg peanut butter, now tolerating 2.5g peanut butter, 3/week
6	13	Male	No history of peanut consumption prior to challenge	3	100 0 0	At 11 years failed stage 3: 200mg of peanut: abdominal pain, vomiting, anxiety, itch, conjunctivitis	14 months into home peanut OIT. No acute allergic reactions. Describes stinging in his mouth when taking peanut after missed doses. Started with ½, now tolerating one peanut 4 – 7 times a week.

Why have I been given this information sheet?

A hospital oral challenge has confirmed that your child has a peanut allergy. Although your child reacted to the food, small amounts of peanut in the early stages of the challenge were tolerated without any allergy symptoms. By giving your child these small amounts of peanut at least 3 times a week and then slowly increasing the amount in your child's diet, we aim is to make your child more tolerant to peanut and less likely to have an allergic reaction if they accidentally come across peanuts.

What's the evidence that desensitisation works?

Clinical trials in the UK and the USA have shown that in children with proven peanut allergy, slowly increasing the amount of peanut protein in their diet improves their tolerance to the food.¹⁻³ Quality of life for both the child and the family also improves.⁴ Although peanut desensitisation is currently largely performed in research and private allergy practice settings, for cow's milk, egg and wheat this is now routine practice in our clinic, other clinics in the UK and other parts of the world.^{5,6}

What's involved for your child?

- **Inclusion/Exclusion criteria** Your child was selected for this program as they did not suffer from any breathing problems during their oral peanut challenge and their asthma is under control.
- **Starting dose** Based on the result of your child's peanut food challenge, we know the amount of peanut-containing food that triggered an allergic reaction. Your child will start eating one quarter of the amount of peanut-containing food that caused the reaction at least 3 times a week. For instance, if you child reacted to a teaspoon of peanut-butter he/she will start with a ¼ of a teaspoon.
- **Dose escalation** Every 3 weeks the amount of peanut-containing food your child eats will be doubled until they reach the equivalent of 6 - 8 peanuts 3 times a week. For example, if your child started on ¼ of a teaspoon of peanut butter 3 times a week, after 3 weeks of eating the peanut-containing food regularly, the amount should be doubled to ½ teaspoon, after 6 weeks to 1 teaspoon (5g) and finally after 9 weeks 2 teaspoons.
- **Dose maintenance** Once your child reaches the equivalent of 15 peanuts (one tablespoon), he/she needs to continue eating this amount of peanut at least 3 times a week. Stopping the peanut diet for more than 4 weeks may lead to your child losing their tolerance and becoming allergic to peanut again.
- **Follow-up** Your child will be followed up by your specialist every 2 - 3 months or more frequently if required. **If your child does not attend his appointments, then they will be withdrawn from the programme.**

What are the potential benefits?

The aim is to allow your child to be more tolerant to peanuts so that he/she can eat peanut-containing foods and will not react to the food after accidental exposure. It should also help to lift restrictions in diet and life-style such as eating out and going on group activities.⁷

References 1. Varshney P, *et al.* A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol.* 2011. 2. Anagnostou K, *et al.* Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy.* 2011. 3. Anagnostou K, *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet.* 2014. 4. Nurmatov U *et al.* Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy.* 2017. 5. Burks AW *et al.* Oral immunotherapy for treatment of egg allergy in children. *New Engl J Med.* 2012. 6. Pajno GB *et al.* Safety profile of oral immunotherapy with cow's milk and hen egg: A 10-year experience in controlled trials. *Allergy Asthma Proc.* 2016. 7. Vickery BP *et al.* Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol,* 2017.

What are the potential risks?

- Potential risks of the peanut desensitisation program need to be weighed up with the benefits.
- It is likely that your child will experience some allergic symptoms during the program. These symptoms are likely to be minor e.g. hives, lip swelling, vomiting, particularly in preschool children.⁶ More severe reactions (anaphylaxis) including wheeze and difficulty breathing may occur are uncommon. An allergy management plan will be provided so you know what to do if your child suffers an allergic reaction.⁴
- If your child is unwell with colds, coughs or vomiting bugs, he/she may be more prone to allergic symptoms. Your child should continue with the amount, but if s/he does get symptoms then the dose should be reduced by half for one week before going back up again.
- We do not know how long children remain tolerant to peanuts if they stop eating the food. We presently assume that children need to continue to eat peanut-containing food indefinitely/without stopping at least 3 times a week to maintain their tolerance.
- **If your child does not eat the peanut-containing food for more than 4 weeks, or suffers from an asthma attack requiring oral steroids (prednisolone), then you should contact your specialist before restarting the peanut diet.**

What support can I expect for my child during the program?

You and your child will be counselled throughout the program and will be seen at regular intervals in a consultant-led clinic. If you have queries about your child's peanut allergy between their appointments, you can leave a message on 0161 701 5422 during working. Your doctor will return your call. If your child has a severe allergic reaction you should follow your allergy management plan and come to the ED, just as you would do if your child was not on the programme

If you have any concerns about giving your child peanut-containing foods, you can withdraw from the program at any time and we will revert to standard follow-up for children with peanut allergy.

Program discussed and agreed:		
Patient		
Name	Signature	Date
Parent		
Name	Signature	Date
Specialist		
Name	Signature	Date

References 1. Varshney P, *et al.* A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol.* 2011. 2. Anagnostou K, *et al.* Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy.* 2011. 3. Anagnostou K, *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet.* 2014. 4. Nurmatov U *et al.* Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy.* 2017. 5. Burks AW *et al.* Oral immunotherapy for treatment of egg allergy in children. *New Engl J Med.* 2012. 6. Pajno GB *et al.* Safety profile of oral immunotherapy with cow's milk and hen egg: A 10-year experience in controlled trials. *Allergy Asthma Proc.* 2016. 7. Vickery BP *et al.* Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol,* 2017.

YOUR CHILD'S PERSONALIZED PEANUT DESENSITISATION PROGRAM

Patient details	
Name	
Hospital Number	
Date of birth	
Your specialist is	
Oral peanut challenge result	
Date	
Stage at which reaction occurred	
Details of reaction	
Starting dose of peanut	
Amount to be given 3 times a week	
Date	
UPDOSING PHASE: food to be given at least 3 times a week	
Updosing stage 1 (usually 1/4 of the dose that caused the reaction in peanut oral challenge)	
Date	
Updosing stage 2	
Date	
Updosing stage 3	
Date	
Updosing stage 4	
Date	
Updosing stage 5	
Date	
Updosing stage 6	
Date	
Additional notes	
MAINTENANCE PHASE to be given 3 times a week long-term	
Amount	
Date	

References 1. Varshney P, *et al.* A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol.* 2011. 2. Anagnostou K, *et al.* Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy.* 2011. 3. Anagnostou K, *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet.* 2014. 4. Nurmatov U *et al.* Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy.* 2017. 5. Burks AW *et al.* Oral immunotherapy for treatment of egg allergy in children. *New Engl J Med.* 2012. 6. Pajno GB *et al.* Safety profile of oral immunotherapy with cow's milk and hen egg: A 10-year experience in controlled trials. *Allergy Asthma Proc.* 2016. 7. Vickery BP *et al.* Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol,* 2017.