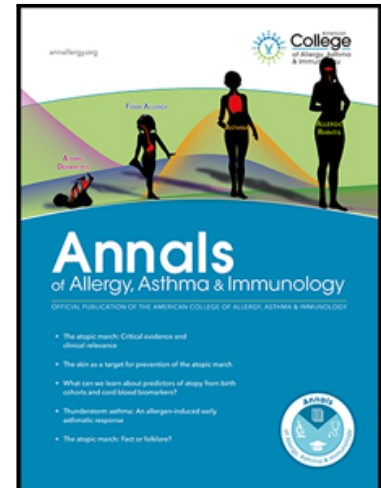


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Title:

Grass Pollen Allergy as an Anaphylaxis Co-factor during Peanut Oral Immunotherapy

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Grass pollen allergy, typically associated with non-life-threatening symptoms such as rhinoconjunctivitis is one of the most common allergies worldwide.¹ Rarely, anaphylaxis occurs after grass pollen exposure in children.² Oral immunotherapy (OIT) for the treatment of food allergy has been gaining popularity over the last decade as evidence on methodology, effectiveness and safety has progressed.^{3,4} Studies have shown that peanut-allergic patients on OIT with seasonal allergic rhinitis experience dose-related adverse events more frequently with seasonal patterns.^{5,6} However, pollen allergy as an anaphylaxis co-factor while on peanut OIT (POIT) has never been described.

We report a 7-year-old ethnic-Japanese girl from Victoria, British Columbia, Canada, with anaphylaxis at 21 months old who presented with vomiting and cough after

ingesting a small amount of peanut butter. Skin prick testing showed that she was sensitized to peanut (10mm), and her peanut sIgE was >100kU/L. She also had severe infected atopic dermatitis, and moderate allergic rhinoconjunctivitis that worsens during grass pollen seasons and was treated intermittently with desloratadine only. She was sensitized to multiple aeroallergens, including dust mite (4mm), grass (10mm), birch (3mm) and weed (4mm) pollen, compared to the negative control.

The patient began POIT treatment at four years-of-age based on published protocol in pre-school children.³ She developed four episodes of anaphylaxis: two during the build-up phase and two during the maintenance phase. (Figure 1) They were all managed with intramuscular epinephrine injection, antihistamines and a short course of oral corticosteroids. The first episode occurred after one hour, on the first day of up dosing from 12mg to 25mg peanut protein. Her POIT updose was administered in office after 2 weeks on her previous dose and was given immediately after a snack. The second episode of anaphylaxis that occurred in the clinic during the build-up phase was caused by a parental peanut dosing error. The other two episodes occurred one and fourteen months after starting maintenance phase, which were during the grass pollen season in Victoria between May and July. The latter two episodes occurred 4 and 1.5 hours after the ingestion of maintenance dose of peanut. These episodes were not related to recent missed doses, intercurrent illnesses, physical activities or an empty stomach. Except for these acute episodes of anaphylaxis, the patient only developed mild symptoms during POIT dose escalation, and continued maintenance dosing of 300mg peanut protein daily.

Since our patient's grass pollen allergy was likely to be an extrinsic factor driving anaphylaxis while on POIT, her parents were advised for 2021 to follow grass pollen count reports in Victoria. Since she has already been on anti-histamines, a plan following

her last anaphylactic episode was made to reduce her dose of POIT to 150mg of peanut protein when the grass pollen level is moderate or higher, and continue on 300mg peanut protein daily once the grass pollen season is over.

Our patient developed breakthrough episodes of anaphylaxis between May and July in three consecutive years, during the typical grass pollen season in Victoria, Canada.¹ The anaphylaxis episodes occurred in the latter part of the each grass pollen season (mid-June to July) suggesting a priming effect and particular risk due to accumulated exposure and inflammation later in the season. While it's possible these three episodes of anaphylaxis occurred during the same 3 week period in 3 consecutive years randomly, this likelihood is quite low ($0.33\% = 3/52 \times 3/52$). This case demonstrates the importance of considering the seasonal timing of anaphylaxis while on OIT, and the role of grass pollen sensitization and exposure as a possible additional extrinsic anaphylaxis risk factor.

Co-factors are exposures to extrinsic factors that lower the threshold dose to an antigen causing anaphylaxis at a dose of the antigen which would previously be tolerated or only induce mild reactions. However, the pathophysiology remains uncertain. Common co-factors include exercise, drugs, alcohol, viral infections, hormones, emotional stress, exposure to specific additional allergens and concomitant diseases such as mastocytosis.⁷ In an adult POIT study, there was a 45% reduction in threshold dose following exercise and sleep deprivation.⁸ Large scale randomized controlled trials during and outside of the grass pollen season for children with and without grass pollen allergy undergoing OIT is warranted to confirm that grass pollen is a potential anaphylaxis co-factor for OIT patients.

This is the first report of grass pollen as an anaphylaxis co-factor in a patient undergoing oral immunotherapy to food based on temporal correlations with the grass pollen season. We predict that additional aeroallergens such as other species of pollen, dust mite, and cockroach will be identified as co-factors in future cases as well. Exposure to animal dander (Cat) has already been identified as an anaphylaxis co-factor for OIT patients.⁹

Allergists may wish to reinforce the use of adrenaline autoinjectors for children that have demonstrated sensitivity to co-factors, especially during pollen season, following a pass of an OFC to a full serving of peanut. Alternatively, it may be advisable to perform the OFC during the peak pollen season if the intent is to reassure the patient they can tolerate peanut as desired, without a concern for aeroallergen co-factors. While studies have shown that the risk of OIT discontinuation due to adverse events was lower with anti-histamine co-treatment,¹⁰ more evidence is needed for whether anti-histamine use in OIT patients would benefit breakthrough anaphylaxis due to co-factor exposures, and whether performing concurrent aeroallergen immunotherapy to children with concomitant aeroallergen allergies undergoing food OIT could reduce the risk of breakthrough allergic reactions.

As more pediatric patients are offered OIT for their food allergies, we will see patients who previously tolerated a dose of their allergen have anaphylaxis even while on maintenance dosing due to co-factor exposure. While preschool POIT has been shown to be safe, anaphylaxis while on maintenance occurs in about 0.8% of pre-schooler children per year.⁴ A thorough consideration of possible anaphylaxis co-factors is

essential for patients. This will enable allergists to provide risk reduction strategies through co-factor avoidance, immunotherapy to the aeroallergen co-factor, or adjusting the OIT doses when exposure to the co-factor is inevitable.

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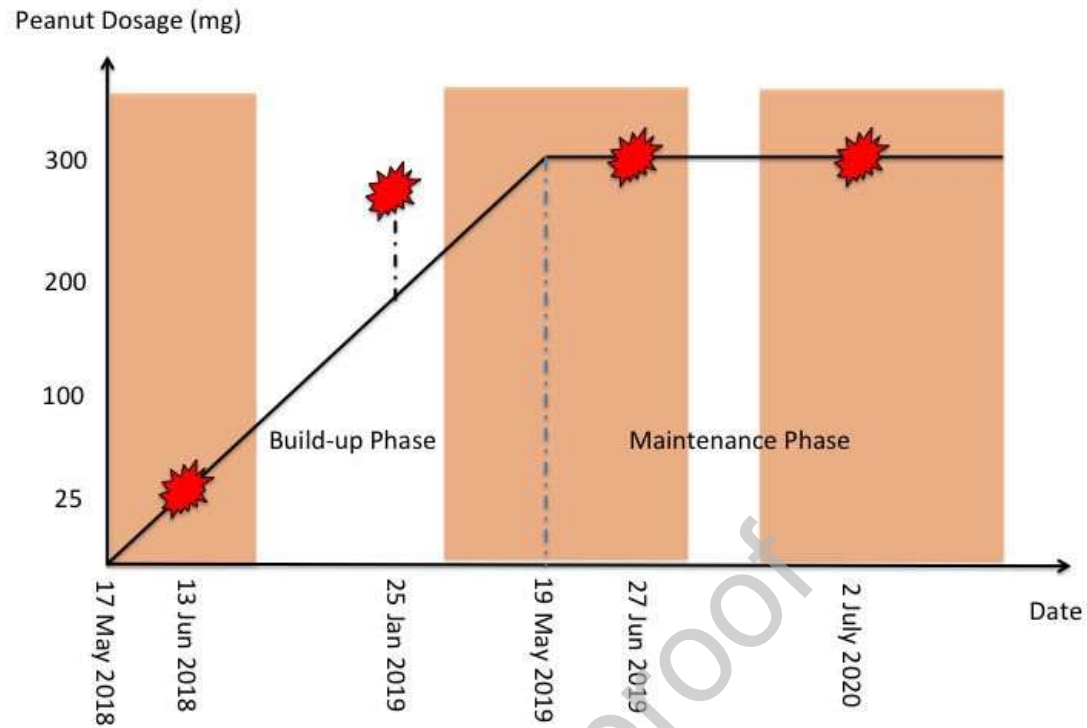


Figure 1. Schematic diagram of the anaphylaxis episodes (red stars) in relationship to the peanut oral immunotherapy and grass pollen seasons in Victoria, Canada (orange boxes). The blue dotted line represents the transition point from the updosing to maintenance stage of oral immunotherapy.