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Article type : News & Views: Algorithms in Allergy and Clinical Immunology

Medical Algorithm: Early Introduction of Food Allergens in High Risk Populations

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14717](https://doi.org/10.1111/ALL.14717)

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Word Count: 602

Tables: 0

Figures: 1

1 Oral Tolerance Induction (OTI) is the only RCT-proven effective intervention for preventing childhood food
2 allergy.(1, 2) OTI to peanut is highly effective in a high-risk population with an 81% relative risk ratio
3 (RRR) to peanut allergy .(3) OTI also reduced egg allergy in the general population in a per protocol
4 analysis.(1) These published RCT findings have changed practice and many governmental and allergy
5 societies now recommend introducing peanut in infancy; some suggest that other foods, such as well-
6 cooked egg, are also introduced. Only National Institute of Allergy and Infectious Diseases (NIAID) stratify
7 their recommendations according to food allergy (FA) risk level.

8 In countries where food allergy is a public health concern, choosing which infants should undergo OTI, at
9 what age, to which foods, and under which circumstances is critical for successful OTI prevention. Infants
10 with moderate to severe eczema are at increased risk of food allergy but infants with no or mild eczema
11 contribute the most cases at a population level; the Health Nuts study found 28% of children with one FA
12 had no current or past medical history of eczema. (4) Risk of food sensitisation or food allergy increases
13 with age (5) suggesting the window of opportunity for OTI is both small and likely diminishes during the
14 first year of life. Oral tolerance induction from 4 months of age, is safe for nutrition, growth and general
15 child health (6) when completed using allergenic foods in a form often consumed by the family (NB egg
16 must be well-cooked). Commencing multiple food OTI at 4 months of age has no detrimental effect on
17 established breastfeeding.(6,7) All children may adopt a diverse weaning diet (8), including allergenic
18 foods such as well-cooked egg and peanut, as soon as weaning commences. High-risk children may start
19 weaning and actively include peanut and well-cooked egg as soon as developmentally ready, usually at
20 about 4 months of age (Fig 1).

21 A dosing regimen of approximately 2g/week of peanut and well-cooked egg in early infancy is more
22 effective in inducing oral tolerance than later introduction.(9) A lower dosing regimen has not been
23 shown to be effective in preventing allergy in children who are not already sensitised to the allergen at
24 commencement of OIT (see reference 9 for in-depth discussion) but, importantly, does not increase
25 allergy risk above that of children who introduce allergenic foods in later infancy.(7) There are limited
26 data regarding the efficacy of OTI to other allergenic foods, or the dose required.(1) All infants could
27 therefore aim to consume at least 2g of peanut protein and well-cooked egg per week; parents of high-
28 risk infants should give peanut more diligently aiming for the LEAP Study regimen of 2g of peanut protein
29 3 times per week. Given the protective benefit observed for peanut and well-cooked egg, it is reasonable
30 for all weaning infants to additionally incorporate similar quantities of other common and nutritious food
31 allergens; cow's milk (e.g. as yoghurt), wheat, fish and sesame.

Whether children should undergo allergy testing and/or have their first feed of peanut under medical supervision is contested. This cautious approach, potentially requiring large numbers of children to access specialist allergy care with associated cost and feasibility implications (10), must be balanced against the risks of severe allergic reaction, particularly as most allergic reactions occur on first known oral exposure (11). There were no cases of anaphylaxis during the first complementary food introduction of any of the allergens investigated in LEAP and, notably, EAT for which oral food challenges (OFC) were conducted regardless of SPT results in the early introduction group (3,7). However, anaphylaxis has been described during peanut introduction outside of the research setting (12) and has also occurred in trials of OTI, which used pasteurised whole egg powder (13, 14, 15, 16, 17). Children with no food allergy risk factors do not require testing prior to, or medical supervision during, their first consumption of peanut, well-cooked egg or other common food allergens (Figure 1). In the absence of clinical trials to the contrary, we recommend children with moderate to severe eczema or with an existing food allergy undergo allergy testing +/- OFC at a specialist allergy centre (18). Where rapid access to allergy services is not available, these children should undergo SptIgE through their GP or paediatrician and, if ≥ 0.35 kU/L, will require referral for OFC (Figure 1). If negative (<0.35 kU/L) the food may be introduced at home with the following precautionary measures for the first feeding: child is well; parent is aware of the signs of IgE mediated reaction, has access to medical support if required and age-appropriate form of the food is given incrementally.

Conflicts of Interest: Dr. Fisher reports grants from NIAID ITN, during the conduct of the study; personal fees from Aimmune Therapeutics, outside the submitted work; Dr. Lack reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), other from Food Allergy & Research Education (FARE), other from MRC & Asthma UK Centre, other from UK Dept of Health through NIHR, other from National Peanut Board (NPB), grants from UK Food Standards Agency (FSA), grants from Action Medical Research, during the conduct of the study; other from DBV Technologies, other from Mighty Mission Me, personal fees from Novartis, personal fees from Sanofi-Genzyme, personal fees from Regeneron, personal fees from ALK-Abello, outside the submitted work; Dr. Roberts reports grants from National Institutes of Health, outside the submitted work; and Coordinator of the EAACI Food Allergy Prevention Guideline; Henry Bahnson reports personal fees from King's College London, during the conduct of the study; grants from Immune Tolerance Network, grants from DBV Technologies, outside the submitted work; Dr. Du Toit reports income from grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, and National Peanut Board (NPB).

64 References

- 65 1. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet
66 and risk of allergic or autoimmune disease: A systematic review and meta-analysis. *JAMA*
67 2016;**316**(11):1181-1192.
- 68 2. de Silva, D, Halken, S, Singh, C, et al.; on behalf of European Academy of Allergy, Clinical
69 Immunology Food Allergy, Anaphylaxis Guidelines Group. Preventing food allergy in infancy and
70 childhood: Systematic review of randomised controlled trials. *Pediatr Allergy*
71 *Immunol.* 2020; 00: 1– 14.
- 72 3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut
73 consumption in infants at risk for peanut allergy. *New England Journal of Medicine* 2015;**372**(9):803-813.
- 74 4. Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from
75 a population based cohort. *Clinical & Experimental Allergy* 2014;**45**(1): 255-64
- 76 5. Du Toit G, Roberts G, Sayre P et al. Identifying infants at high risk of peanut allergy: The Learning Early
77 about Peanuts (LEAP) screening study. *Journal of Allergy and Clinical Immunology* 2013; **131**(1):153-143
- 78 6. Feeney M, Du Toit G, Roberts G, Sayre PH, Lawson K, Bahnson HT, et al. Impact of peanut consumption
79 in the LEAP Study: Feasibility, growth, and nutrition. *Journal of Allergy and Clinical*
80 *Immunology*;**138**(4):1108-1118.
- 81 7. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized Trial of Introduction of
82 Allergenic Foods in Breast-Fed Infants. *New England Journal of Medicine* 2016;**374**(18):1733-1743.
- 83 8. Venter C, Greenhawt M, Meyer RW et al. EAACI position paper on diet diversity in pregnancy, infancy
84 and childhood: Novel concepts and implications for studies in allergy and asthma. *Allergy* 2020; 75(3):497-
85 523.
- 86 9. Fisher HR, Du Toit G, Bahnson HT, Lack G. The challenges of preventing food allergy: Lessons learned
87 from LEAP and EAT. *Annals of Allergy, Asthma & Immunology* 2018;**121**(3):313-319.

- 88 10. Koplin JJ, Peters RL, Dharmage SC, et al. Understanding the feasibility and implications of
89 implementing early peanut introduction for the prevention of peanut allergy. *Journal of Allergy and*
90 *Clinical Immunology* 2016;**138**(4):1131-1141
- 91 11. Brough HA, Kull I, Richards K, et al. Environmental peanut exposure increases the risk of peanut
92 sensitization in high risk children. *Clinical and Experimental Allergy* 2018; **48**(5):586-93
- 93 12. Rabinovitch N, Shah D, Lanser BJ. Look before you LEAP: Risk of anaphylaxis in high-risk infants with
94 early introduction of peanut. *Journal of Allergy and Clinical Immunology* 2015;**136**(3):822
- 95 13. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksünger Ö, Kalb B, et al. Randomized placebo-
96 controlled trial of hen's egg consumption for primary prevention in infants. *Journal of Allergy and Clinical*
97 *Immunology*; **139**(5):1591-1599.e1592.
- 98 14. Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of
99 age in infants at risk for egg allergy. *J Allergy Clin Immunol.* 2017;**139**:1621–1628
- 100 15. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption
101 for primary prevention in infants. *J Allergy Clin Immunol.* 2017;**139**:1591–1599. e1592.
- 102 16. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: a
103 randomized controlled trial. *J Allergy Clin Immunol.* 2013;**132**:387–392. e381.
- 104 17. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular
105 egg intake to prevent egg allergy. *J Allergy Clin Immunol.* 2017;**139**:1600–1607
- 106 18. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR, Beck LA, et al. Addendum guidelines for the
107 prevention of peanut allergy in the United States. *Pediatric Dermatology* 2017;**34**(1):5-12.

