

Nahrungsmittelallergien bei Kindern: Management und Prävention

Caroline Roduit, MD, MPH, PhD
27 August 2018

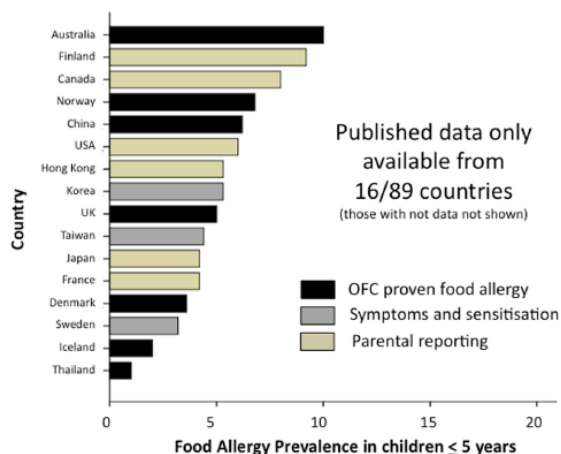


Immune System-Mediated Adverse Food Reaction

	IgE-Mediated	Mixed	Non-IgE-Mediated
Systemic	- Anaphylaxis - Food-associated, exercise-induced anaphylaxis		
Skin	Urticaria/angioedema	Atopic dermatitis	Dermatitis herpetiformis
Gastrointestinal	- Immediate GI symptoms - Pollen-food allergy syndrome	Eosinophilic esophagitis/gastroenteritis	- Celiac disease; enteropathy - Food-induced enterocolitis syndrome - Allergic proctocolitis
Respiratory	Bronchospasm	Asthma	Heiner's syndrome

Nahrungsmittelallergien steigen an: „second wave of the allergy epidemic“

Studies reporting Food Allergy Prevalence
in preschool children ≤ 5 years



Prescott, S. et al., WAO journal 2013

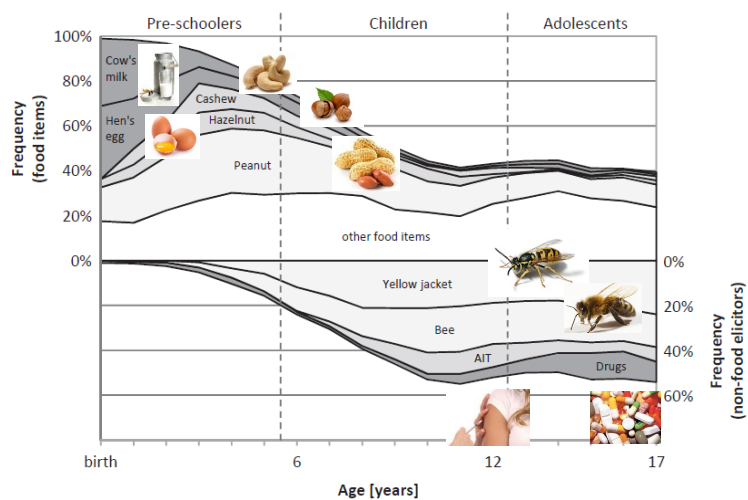
Nahrungsmittelallergien steigen an: „second wave of the allergy epidemic“

Prävalenz **Nahrungsmittelallergien:**

- Kinder: 6% - 8%
- Erwachsene: 2% - 3%

Sicherer SH, Sampson HA. JACI 2014

Die häufigsten Allergene bei Anaphylaxie



Grabenhenrich et al. J Allergy Clin Immunol 2016

Anaphylaxie durch Nahrungsmittel

Although food-related anaphylaxis is relatively common, fatalities remain rare, with a reported range of:
- 0.03 to 0.3 deaths per million person years in the general population

Annual incidence of fatal anaphylaxis in an unselected population

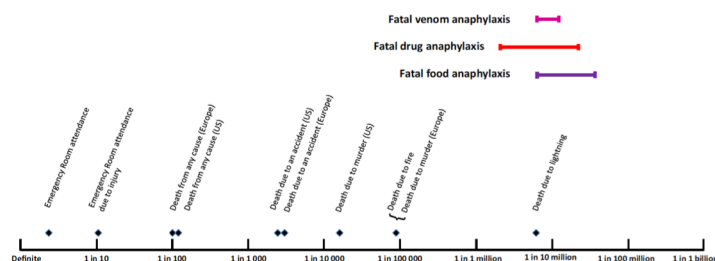


FIGURE 1. Estimated rates of fatal drug, food, and venom anaphylaxis compared with other risks for the general population. Reference risks are for the US population, unless otherwise stated. Bars represent the range of estimates from recent population-based studies of fatal anaphylaxis.

Turner P. et al J Allergy Clin Immunol in Pract. 2017

1. Diagnostik bei Nahrungsmittelallergien und Follow-up
2. Therapie von Nahrungsmittelallergien: was ist neu?
3. Prävention

1. Diagnostik bei Nahrungsmittelallergien und Follow-up

Diagnostik

- die Bestimmung von spezifischem IgE und die Hauttestung sind grundsätzlich als gleichwertig zu betrachten.

Skin Prick Test

- geringe Kosten
- bessere Sensitivität (vor allem mit frischen Lebensmitteln)
- sofortige Resultate
- semi-quantitativ

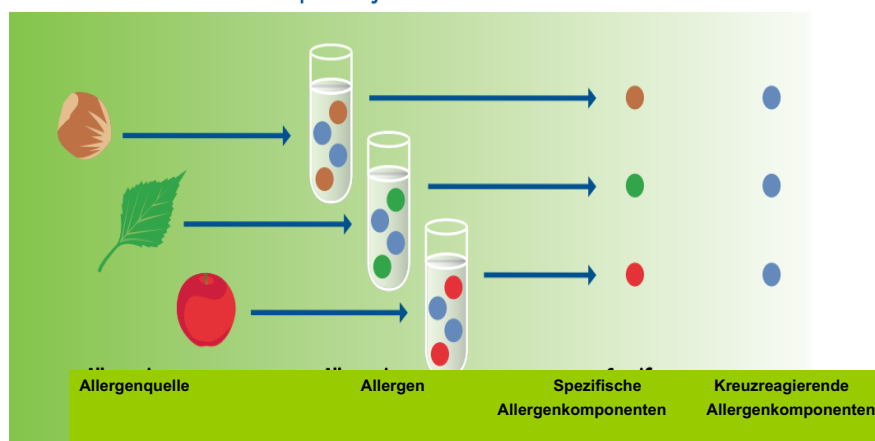
Spezifisches IgE (Blut)

- kein Einfluss bei Medikamenten
- keine Exposition zum Allergen
- ca. 20% falsche negative Resultate
- besser als Hauttest bei: Dermographismus oder Ekzem
- quantitative Resultate
- molekulare Allergiediagnostik

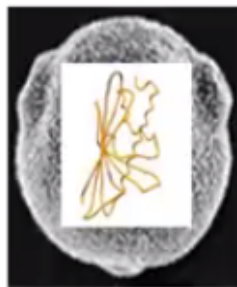
Molekulare Allergiediagnostik

= Komponente basierte Allergendiagnose (CRD)

Component diagnostics: The molecular view of sensitization.



Molekulare Allergiediagnostik



Bet v 1



Api g 1

Molekulare Allergiediagnostik

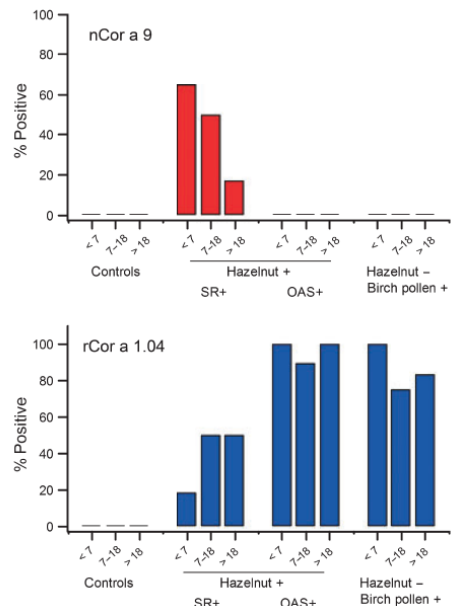
Spezifisches IgE:
gegen molekulare Allergenkomponente

Beispiel:

□ **Ara h 2** (Erdnuss)

- Ersten drei Buchstaben vom Genus (Arachis)
- Erster Buchstabe von der Spezies (hypogaea)
- Nummerierung entsprechend der Entdeckungsreihenfolge

Molekulare Allergiediagnostik



De Knop et al. PAI 2011

Molekulare Allergiediagnostik

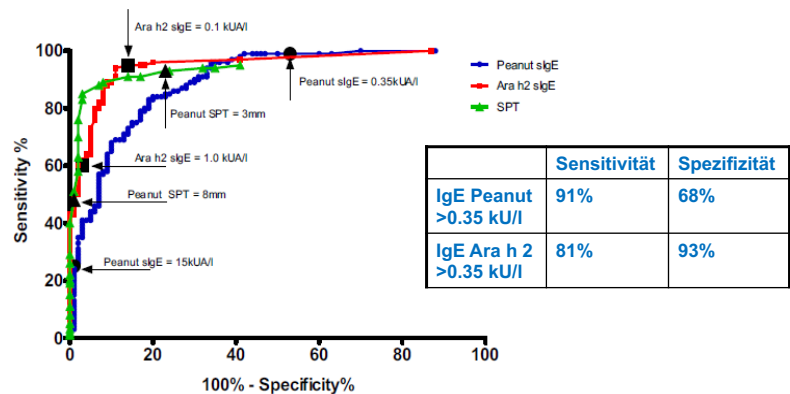
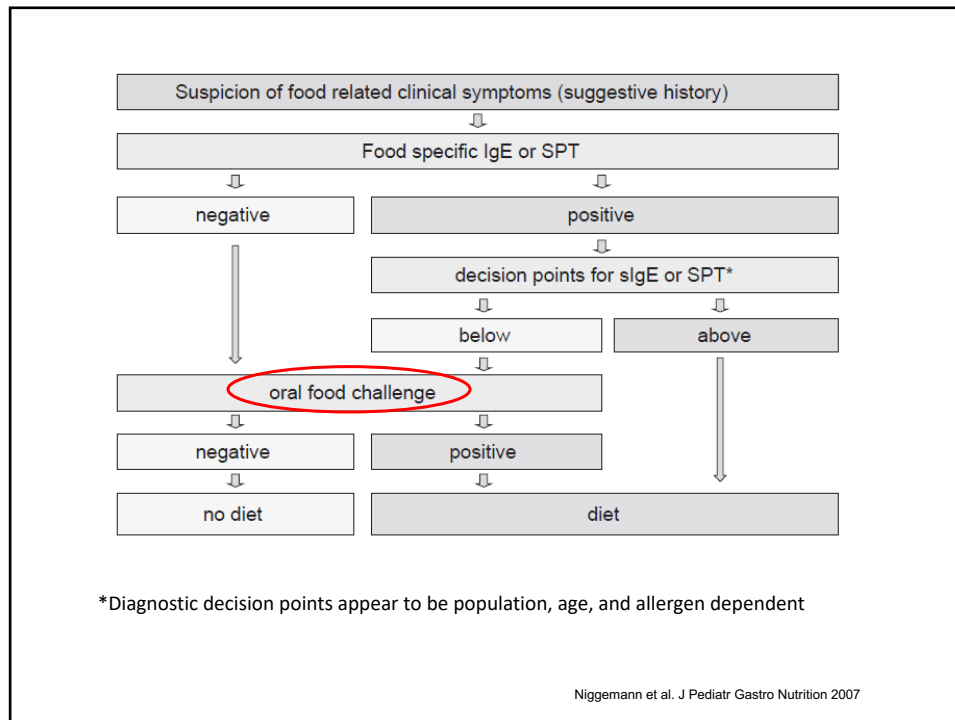


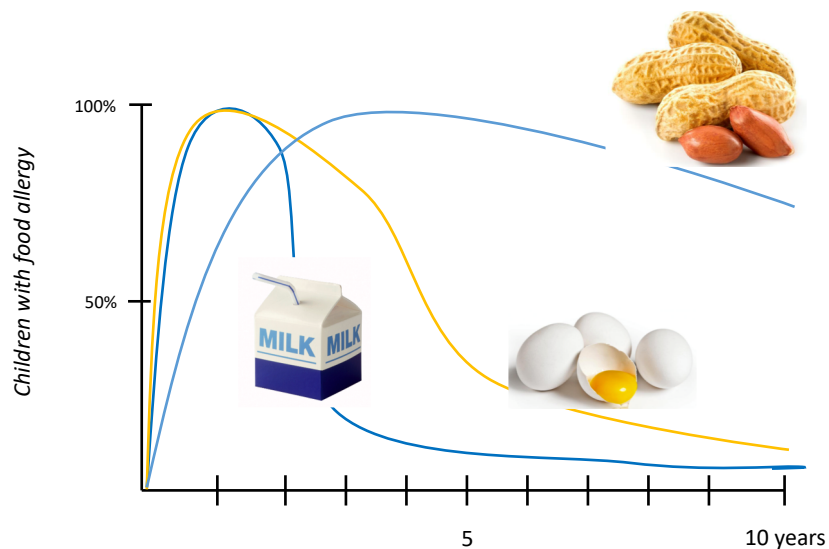
FIG 2. ROC curves showing true-positive rates (sensitivity) plotted against the false-positive rate (specificity) for different cutoff points of the quantified components of Ara h 2 (red squares) and whole peanut extract (blue circles). The points highlighted are the current conventional SPT (3 and 8 mm) and whole peanut slgE (0.35 and 15 kU_A/L) thresholds. The points highlighted for Ara h 2 indicate putative levels for determining sensitization (0.1 kU_A/L) and peanut allergy (1.0 kU_A/L). The area under the curve is 0.95, 0.94, and 0.89 for Ara h 2 slgE, peanut SPT, and peanut slgE, respectively.

Dang et al. JACI 2012



Nahrungsmittelallergie-Follow-up:

Natürlicher Verlauf: Nahrungsmittelallergie



Kindern mit Nahrungsmittelallergie: Follow-up

1x/Jahr*:

- spezifisches IgE und/oder SPT
- Information über unbeabsichtigte Expositionen einholen

➤ Um die Entwicklung der oralen Toleranz zu bestimmen: OPT (1x/5-10 Jahren)

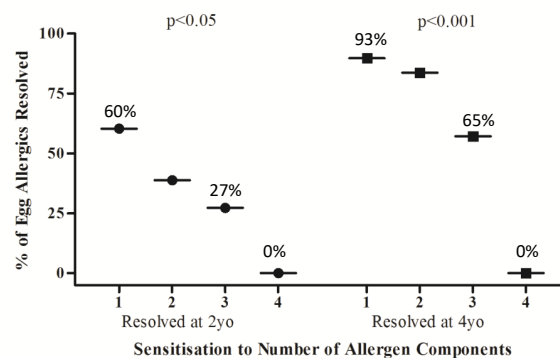
*Kann abhängig vom Nahrungsmittel variieren (Allergie auf bestimmte Nahrungsmittel wie Milch, Hühnerei, Weizen und Soja verschwinden im Kindesalter allgemein schneller als Erdnuss, Walnuss, Fisch und Schalentiere) und weniger häufige Tests wenn die Werte besonders hoch sind (z.Bsp. >20-50kU/L)

Anzeichen von persistierender Nahrungsmittelallergie sind:

- Hohe spezifische IgE-Werte
- Grosse Reaktion beim Skin Prick Test (SPT)
- Gleichzeitiges Auftreten von atopischen Erkrankungen

Anzeichen von persistierender Allergie auf Hühnerei sind:

- Population: food challenge-proven egg allergic and egg sensitised tolerant (n=451)
- **Pos. sIgE auf Gal d 1 (Ovomucoid) at 1 year of age increased risk of persistent egg allergy at 4 years by 2.5 fold**
- The production of **specific IgE to all four egg allergens (Gal d 1, 2, 3 or 5)** increased the risk of having persistent raw egg allergy 4-fold



Dang T. et al. Allergy July 2018

2. Therapie von Nahrungsmittelallergien: Was ist neu?



Potentieller immuntherapeutischer Effekt von gebackener Milch und Ei



- Etwa 70% der Kuhmilch- und Hühnerei-allergischen Kinder tolerieren gebackene Milch und Ei.
- Die Toleranz gegenüber gebackener Milch und Ei in der Nahrung kann die **Lebensqualität erhöhen**, da weniger Einschränkung notwendig ist.
- «Konsum von gebackener Milch und Ei **könnte die Zeit zur Toleranz auf normale Milch und Ei reduzieren**».

Leonard et al. JACI August 2012

Pecora et al. *World Allergy Organization Journal* (2018) 11:11
<https://doi.org/10.1186/s40413-018-0191-6>

World Allergy
Organization Journal

DEBATE

Open Access

Debates in Allergy Medicine: Does oral immunotherapy shorten the duration of milk and egg allergy? The pro argument



Valentina Pecora*, Rocco Luigi Valluzzi, Maurizio Mennini, Vincenzo Fierro and Lamia Dahdah

Loh and Tang *World Allergy Organization Journal* (2018) 11:12
<https://doi.org/10.1186/s40413-018-0189-0>

World Allergy
Organization Journal

DEBATE

Open Access

Debates in Allergy Medicine: Oral immunotherapy shortens the duration of milk and egg allergy - the con argument



Wenyin Loh^{1,2} and Mimi L. K. Tang^{1,3,4*}

Please see related Debate article: Debates in allergy medicine: Does oral immunotherapy shorten the duration of milk and egg allergy? The pro argument, <https://doi.org/10.1186/s40413-018-0191-6>.

Potentieller immuntherapeutischer Effekt von gebackener Milch und Ei

DEBATE

Open Access

Debates in Allergy Medicine: Does oral immunotherapy shorten the duration of milk and egg allergy? The pro argument



- 84 patients (6 months-3 years old) diagnosed with **allergy to cow's milk** and were **tolerated baked milk** (OFC with muffin)
- Control group: avoidance of any milk products for one year
- Intervention group: consume baked milk in the form of muffin for 6 months, and then to consume baked cheese in the form of pizza for another 6 months
- **Results: after one year tolerance to unheated milk:**
 - **Intervention group: 88.1 % (37/42)**
 - **Control group: 66.7 % (28/42)**

Esmailzadeh et al. PAI 2018

Potentieller immuntherapeutischer Effekt von gebackener Milch und Ei

DEBATE

Open Access



Debates in Allergy Medicine: Oral immunotherapy shortens the duration of milk and egg allergy - the con argument

- Double blind RCT, children 6mo-5yrs with **IgE mediated egg allergy**, and **tolerant to baked egg**
- Control group: n=22, egg free diet
- Intervention group: n=21: 1.3g Protein (1/4 egg) 2-3x/week for 6 months
- **Results: after 6 months raw egg tolerance :**
 - **Intervention group: 23.5% (4/17)**
 - **Control group: 33.3% (6/18)**
- No difference between 2 groups regarding sIgE

Netting M. et al. WOA Journal 2017

Immuntherapie für Nahrungsmittelallergien- die Zukunft?

Die Behandlung hat zwei Ziele:

1. Klinische **Desensibilisierung**: tolerieren von grösserer Menge, bevor eine allergische Reaktion stattfindet
2. Andauernde klinische **Toleranz** : nach Behandlung
-> **Sustained Unresponsiveness**

Immuntherapie für Nahrungsmittelallergien: Vergleich von verschiedenen Verabreichungswege

Table 4. Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Feature	Oral Immunotherapy	Sublingual Immunotherapy	Epicutaneous Immunotherapy
Form of study product (protein dose)	Allergen powder (300–4000 mg per day)	Allergen extract drops (2–7 mg per day)	Allergen patch (100–500 µg per day)
Clinical effect			
Desensitization	Large effect	Moderate-to-small effect	Variable effect
Sustained unresponsiveness	Occurs in subgroups of persons	Not known (studies under way)	Not known
Side effects	Oral or gastrointestinal; potential for anaphylaxis in persons with fever, infection, or menses and during exercise after receipt of a dose of oral immunotherapy	Oral or pharyngeal (local effects)	Skin (local effects)
Immune modulation: antibody and cellular changes	Substantial	Small or moderate	Small or moderate

Jones SM and Burks WA, NEJM 2017

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OIT

Jones SM and Burks WA, NEJM 2017

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SLIT

Jones SM and Burks WA, NEJM 2017

Immuntherapie für Nahrungsmittelallergien: Vergleich von verschiedenen Verabreichungswege

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EPIT

Jones SM and Burks WA, NEJM 2017

Immuntherapie für Nahrungsmittelallergien: Vergleich von verschiedenen Verabreichungswege

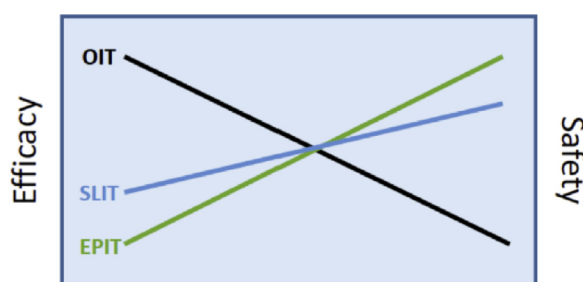
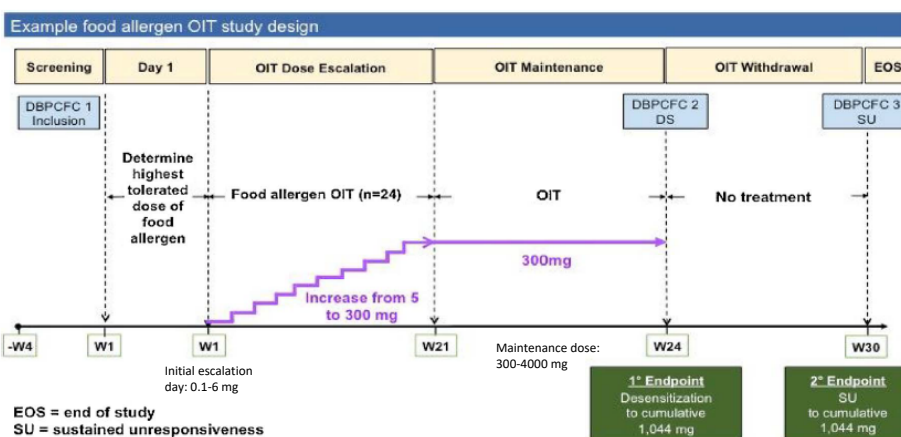


Fig. 1. Efficacy and safety have an inverse relationship as related to food immunotherapy. Oral immunotherapy (OIT) is most efficacious in inducing desensitization, while the highest rate of adverse reactions is observed, some of which are severe. Sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) are generally less efficacious and associated with fewer total adverse events, none of which have been severe.

Kobernick AK and Burks WA, Allergy International 2016

Oral ImmunoTherapy (OIT) for food allergy



Hussey Freeland and al., Seminars in Immunology 2017



Allergen Immunotherapy Guidelines
Part 2: Recommendations

Translating knowledge into clinical practice



European Academy of Allergy and Clinical Immunology

3

EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

IgE-MEDIATED FOOD ALLERGY

*Giovanni B Pajno¹, *Montserrat Fernandez-Rivas², Stefania Arasi^{1,3}, Graham Roberts⁴, Cezmi A Akdis⁵, Montserrat Alvaro-Lozano⁶, Kirsten Beyer⁷, Carsten Bindslev-Jensen⁸, Wesley Burks⁹, Motohiro Ebisawa¹⁰, Philippe Eigenmann¹¹, Edward Knol¹², Kari C Nadeau¹³, Lars K Poulsen¹⁴, Ronald van Ree¹⁵, Alexandra F Santos¹⁶, George du Toit¹⁶, Sangeeta Dhami¹⁷, Ulugbek Nurmatov¹⁸, Yanne Boloh¹⁹, Mika Makela²⁰, Liam O Mahony², Nikolaos Papadopoulos²¹, Cansin Sackesen²², Ioana Agache²³, Elizabeth Angier²⁴, Susanne Halken²⁵, Marek Jutel^{26,27}, Susanne Lau³, Oliver Pfaar^{28,29}, Dermot Ryan³⁰, Gunter Sturm³¹, Eva-Maria Varga³², Roy Gerth van Wijk³³, Aziz Sheikh³⁰, Antonella Muraro³⁴, on behalf of EAACI Allergen Immunotherapy Guidelines Group

Pajno GB et al. Allergy Sept. 2017

Oral ImmunoTherapy (OIT) for food allergy

EAACI guidelines:

- Immuntherapie für Nahrungsmittelallergien könnte empfohlen werden: für eine Desensibilisierung bei **Kindern ab 4-5 Jahre mit Kuhmilch-, Ei-, oder Erdnuss-Allergie.**

Oral ImmunoTherapy (OIT) for food allergy: Efficacy

- Für IgE-vermittelte Nahrungsmittelallergie
- **Desensibilisierung: 80%** (bei OIT mit Kuhmilch-, Ei-, oder Erdnuss-Allergie).
- **Toleranz (sustained unresponsiveness) wird nur in etwa 30-50% der Fälle erreicht**

Oral ImmunoTherapy (OIT) for food allergy: Safety

- **10-20% reagieren mit schweren allergische Reaktionen**, die eine Injektion von Adrenalin notwendig machen
- **hohe Non-Compliance** aufgrund von Reaktionen (häufig gastrointestinale Nebenwirkungen) und den langen Zeitperioden der Desensibilisierung
- Erhöhtes Risiko für Eosinophile Oesophagitis (EoE) (2.7%)

Virkud JACI 2017

Peanut allergy could be cured with probiotics

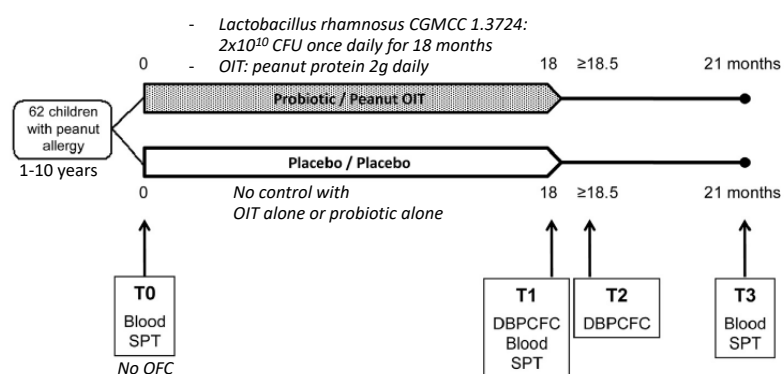
By [Ana Sandoiu](#) | Published Friday 18 August 2017

A new study shows that a treatment for peanut allergy in children that was trialed and proven successful 4 years ago continues to protect children from allergic reactions to peanuts years later.



The research, as well as the initial trial, was led by Prof. Mimi Tang, of the University of Melbourne's Department of Pediatrics in Australia. The [findings](#) were published in the journal *The Lancet Child & Adolescent Health*.

Oral ImmunoTherapy (OIT) for food allergy: Probiotics



Desensitization (T1) after 18 months:

- Probiotic/OIT: 90% to 4g peanut
- Placebo/placebo: 7% to 4g peanut

SU (T2) after 2-5 weeks discontinuation:

- Probiotic/OIT: 82%
- Placebo/placebo: 3%

Tang M. et al. JACI 2015

3. Prävention:

HOME NEWS TECHNOLOGY SPACE PHYSICS HEALTH EARTH HUMANS LIFE TOPICS EVENTS JOBS

DAILY NEWS 19 October 2015

Should babies be given solids earlier to prevent food allergies?



By Clare Wilson

Is this one of the worst wrong turns in the history of parenting advice? Telling people to delay the age they start their babies on solid food might be contributing to the rise in food allergies.

40

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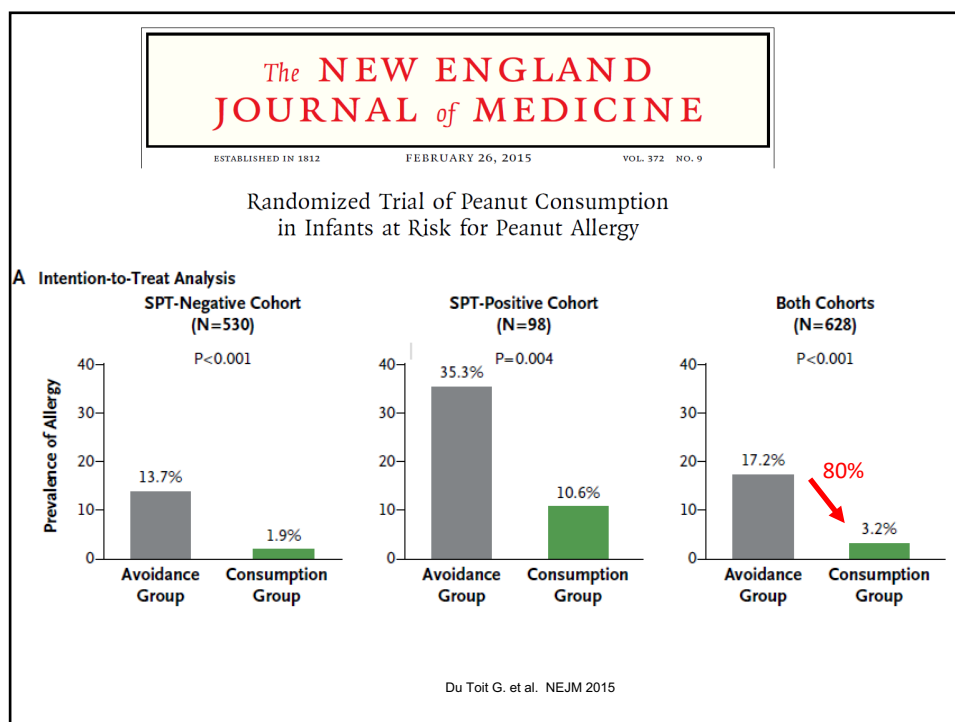
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

LEAP (Learning Early About Peanut allergy) Study:

- Randomisierte klinische Studie, um Strategie zur Prävention von Erdnussallergie bei Kindern zu finden.
- **640 Kinder im Alter zwischen 4 und 11 Monaten, mit erhöhtem Risiko für Erdnussallergie: Hühnereiallergie und/oder schwerem Ekzem**

Studiengruppe:	Instruktionen bis zum Alter von 5 Jahren:
Einnahme (Consumption group)	Einnehmen von erdnusshaltigem Snack 3x pro Woche (6 gr. Erdnussprotein wöchentlich)
Vermeidung (Avoidance group)	Keine erdnusshaltigen Nahrungsmittel essen



Duale Allergen Expositions-Hypothese:

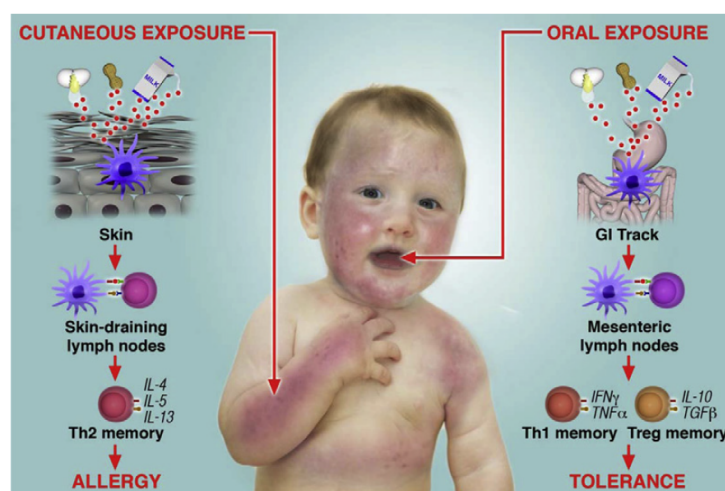


FIG 1. Dual-allergen exposure hypothesis for the pathogenesis of FA. Allergic sensitization results from cutaneous exposure, and tolerance occurs as a result of oral exposure to food. GI, Gastrointestinal. Reprinted with permission from Lack.¹

Lack G. JACI 2012

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D., Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D., Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H., Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*

ABSTRACT

BACKGROUND

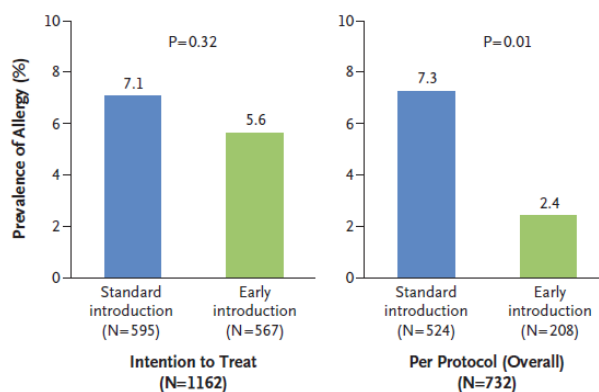
The age at which allergenic foods should be introduced into the diet of breast-fed infants is uncertain. We evaluated whether the early introduction of allergenic foods in the diet of breast-fed infants would protect against the development of food allergy.

METHODS

We recruited, from the general population, 1303 exclusively breast-fed infants who were 3 months of age and randomly assigned them to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current practice recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard-introduction group). The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age.

Perkin M. et al. NEJM, May 2016

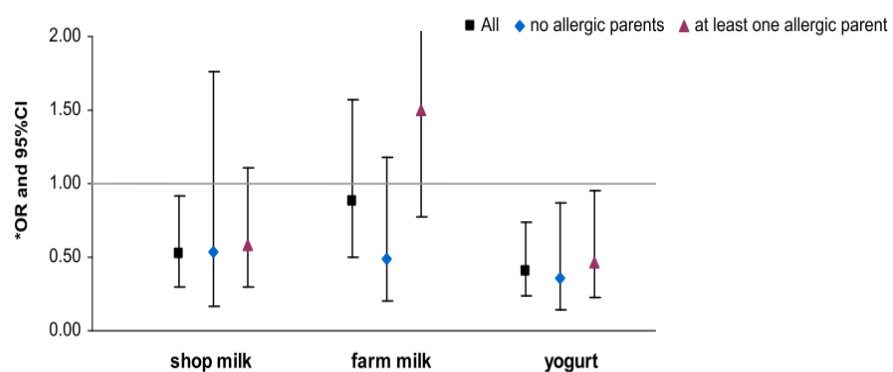
A One or More Foods



- 20% tieferes relatives Risiko für Nahrungsmittelallergie in der Gruppe mit früher Einführung, in einer Intention-to-treat Analyse, obwohl statistisch nicht signifikant.
- In der Per-Protocol Analyse bestand ein signifikantes 67% tieferes relatives Risiko für Nahrungsmittelallergie

Perkin M. et al. NEJM, May 2016

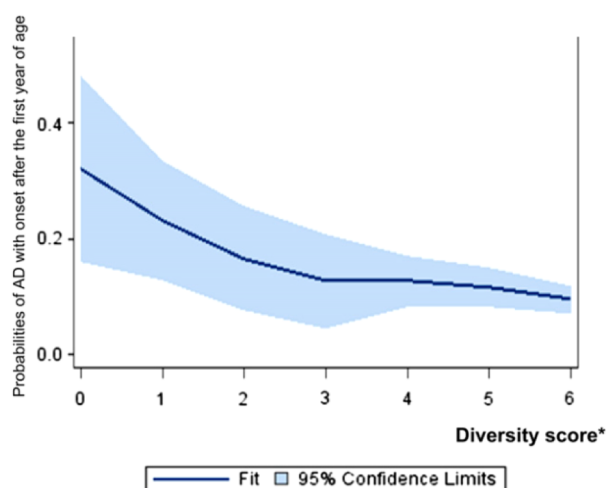
Einführung von Beikost im ersten Lebensjahr und atopische Dermatitis: PASTURE Studie



*adjusted for farmer, center breastfeeding, parental history of allergies

Roduit et al. JACI 2012

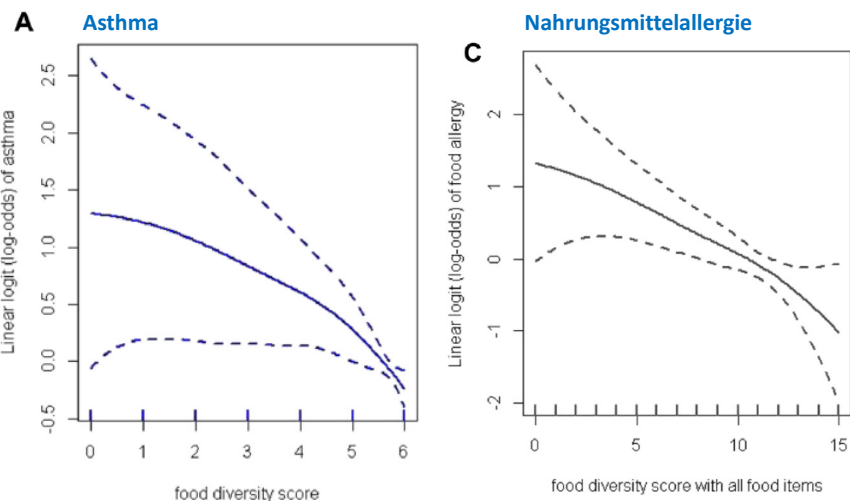
Nahrungsmittel-Diversität im 1. Lebensjahr und atopische Dermatitis



*Diversity score with major food items: vegetables or fruits, any cereals, meat, bread, cake and yogurt

Roduit et al. JACI 2012

Nahrungsmittel-Diversität im 1. Lebensjahr und Asthma und Nahrungsmittelallergie



Roduit et al. JACI 2014

Take home message:

- Nahrungsmittelallergien steigen an
- Molekulare Allergiediagnostik: bessere Spezifität
- Potentieller immuntherapeutischer Effekt von gebackener Milch und Ei: unklar
- OIT ist eine potentielle Therapie für Kinder mit Kuhmilch-, Ei-, oder Erdnussallergie
- Frühe Einführung von Beikost könnte einen präventiven Effekt gegen Nahrungsmittelallergien haben (Ei/Erdnuss)

Vielen Dank für Ihre Aufmerksamkeit

