

Allergieprävention und Desensibilisierung

Die Ernährung von Säuglingen ist ein möglicher Ansatzpunkt für die Verhinderung von Allergien, wie sie in den vergangenen Jahrzehnten immer häufiger aufgetreten sind. Nur wenige Massnahmen haben sich bisher als wirklich effizient erwiesen. Heute ermutigt man die Mütter zum Stillen ihrer Kinder gemäss den Empfehlungen der WHO. Sollte dies nicht möglich sein, ist eine hydrolysierte Säuglingsnahrung bzw. Milch von wissenschaftlich erwiesener Wirkung zu empfehlen. Andererseits sollte eine werdende oder stillende Mutter während der Schwangerschaft oder in der Stillzeit keine Diät machen. Der Übergang zur Beikost und damit zu potentiell allergieauslösenden Lebensmitteln sollte, genau wie bei Kindern ohne Allergierisiko, schrittweise erfolgen.

Für möglicherweise auftretende Lebensmittelallergien gibt es derzeit noch kein Heilmittel. In den vergangenen Jahren erforschte man die Möglichkeit der Induktion einer oralen Toleranz. Bei manchen Patienten war sie teilweise erfolgreich und führte zu einer vorübergehenden Desensibilisierung. Eine breit angelegte Anwendung ist jedoch noch nicht zu empfehlen.

Prévention des allergies et désensibilisation

L'alimentation du nourrisson est une cible potentielle pour la prévention des allergies, leur prévalence ayant constamment augmenté au cours des dernières décennies. Peu de mesures ont été prouvées comme étant réellement efficaces. Actuellement, la maman est encouragée à allaiter l'enfant selon les recommandations de l'OMS. En cas d'impossibilité, un lait hydrolysé avec un effet scientifiquement prouvé peut-être recommandé. Par contre, un régime chez la maman pendant la grossesse ou pendant l'allaitement n'est pas souhaitable. L'introduction des solides, et des aliments potentiellement allergéniques peut se faire progressivement comme chez les enfants sans risque d'allergie.

En cas d'allergie alimentaire, aucun traitement curatif n'est actuellement disponible. L'induction de tolérance orale est une mesure qui a été étudiée ces dernières années. Une efficacité partielle menant à une désensibilisation temporaire a été observé chez certains patients. Une application à large échelle n'est néanmoins pas encore recommandable.

Prof. Dr. med. Philippe Eigenmann, Hôpitaux Univ. Genève / wissenschaftlicher Beirat aha!

Philippe Eigenmann hat sowohl sein Abitur als auch seinen Hochschulabschluss in Genf erworben. Nach einer FMH-Ausbildung im Fach Pädiatrie spezialisierte er sich auf Kinder-Allergologie. Dieses Studium führten ihn auch an die Johns Hopkins-Universität in Baltimore (USA). Heute leitet er die kinderallergologische Einheit innerhalb des Dienstes für pädiatrische Spezialgebiete der Abteilung für Kinder und Jugendliche, wo er die Prävention und Behandlung von Lebensmittelallergien erforscht.

Prof. Dr. med. Philippe Eigenmann, Hôpitaux Univ. Genève / Comité scientifique aha!

Philippe Eigenmann a fait toutes ses études secondaires et universitaires à Genève. Après une formation FMH en pédiatrie, sa spécialisation en allergologie pédiatrique le conduit à Johns Hopkins University, Baltimore USA. Il est actuellement responsable de l'unité d'allergologie pédiatrique, au service des spécialités pédiatriques du département de l'enfant et de l'adolescent où il mène des recherches sur la prévention et le traitement des allergies alimentaires.

Prévention des allergies et désensibilisation

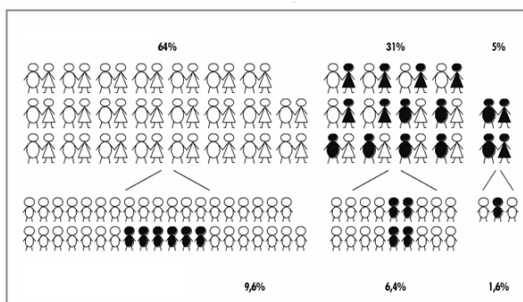
Philippe Eigenmann,
Unité d'Allergologie Pédiatrique



Prevention - Outline

- Who is the target population ?
- When is prevention effective ?

Prevalence of atopy in the first 2 years of life and cumulative prevalence in parents.



Criteria for atopy

- Positive family history (in general 2 atopics)
- Definite positive screening tests
- Atopic disease

Total IgE titers in atopics and non atopics

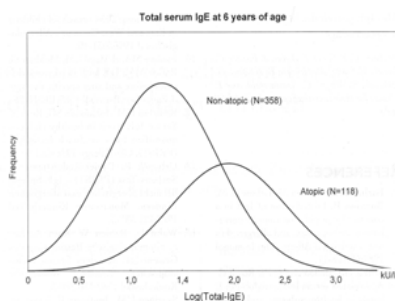


Fig 2. Density distributions of total serum IgE in atopic and nonatopic children at 6 years of age (N_{total} = 476; IgE values were log-transformed because the data were positively skewed).

Kullig M J Pediatr 1999

Which test(s) detect atopy ?

- Family History
- (Cord blood IgE)
- ~~Total IgE~~
- Specific IgE Abs

Prevention - Outline

- Who is the target population ?
- When is prevention effective ?

REVIEW ARTICLE

Primary prevention of food allergy in children and adults: systematic review

D. de Silva¹, M. Geromi¹, S. Halcken², A. Host², S. S. Panesar³, A. Muraro⁴, T. Werfel⁵, K. Hoffmann-Sommergruber⁶, G. Roberts^{7,8,9}, V. Cardona¹⁰, A. E. J. Dubois¹¹, L. K. Poulsen¹², R. Van Ree¹³, B. Vlieg-Boerstra¹⁴, I. Agache¹⁵, K. Grimshaw³, L. O'Mahony¹⁶, C. Venter¹⁷, S. H. Arshad² & A. Sheikh¹⁸ on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group^{*}
Allergy 2014; **69**: 581-588

POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy

A. Muraro^{1,2}, S. Halcken^{2,3}, S. H. Arshad^{3,4,5}, K. Beyer⁶, A. E. J. Dubois⁷, G. Du Toit⁸, P. A. Eigenmann⁹, K. E. C. Grimshaw³, A. Hoest², G. Lack⁶, L. O'Mahony¹⁰, N. G. Papadopoulos^{11,12}, S. Panesar¹³, S. Prescott¹⁴, G. Roberts^{14,5}, D. de Silva¹³, C. Venter¹⁵, V. Verhasselt¹⁶, A. C. Akdis¹⁷ & A. Sheikh^{18,19} on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group
Allergy 2014; **69**: 590-601.

REVIEW ARTICLE

Allergy and asthma prevention 2014

Antonio Nieto¹, Ulrich Wahn², Albrecht Bufe³, Philippe Eigenmann⁴, Susanne Halcken⁵, Gunilla Hedlin⁶, Arne Hagst⁷, Jonathan Hourihane⁷, Jocelyne Just⁸, Gideon Lack^{9,10}, Susanne Lau², Paolo Maria Matricardi², Antonella Muraro¹¹, Nikos Papadopoulos^{12,13}, Graham Roberts^{14,15,16}, Angela Simpson¹⁷, Errika Valovirta¹⁸, Stephan Weidinger¹⁹, Magnus Wickman²⁰ & Angel Mazon¹
Pediatr Allergy Immunol 2014; **25**: 516-533.

Dietary interventions, when ?

- Pregnancy**
arguments: presence of specific IgE Abs and specific T cells in cord blood.
- Lactation**
arguments: allergy tests can be positive before any known ingestion.
- Formula**
- Introduction of solid foods**

Is a diet during pregnancy and/or lactation useful ?

	Studies (high quality)	Preventive effect
Diet during pregnancy	5 (1/5)	One systematic review (9) and two randomized trials (10, 11) found no benefit
Diet during breastfeeding	2 (0/2)	Two nonrandomized comparisons found no evidence of a protective effect for food allergy
	Recommendations	Evidence level
	Dietary restrictions are not recommended for all pregnant or lactating mothers.	I-II

Breast-feeding or bottle feeding, and which formula should it be ?

	Studies (high quality)	Preventive effect
Breastfeeding	11 (1/11)	One systematic review found that most studies of breastfeeding in those at high risk identified a protective benefit . Two cohort studies suggested no benefit and that exclusive breastfeeding may even increase the risk of food allergy.
Formula feeding	18 (8/18)	Benefit from <u>extensively</u> hydrolyzed whey or casein formula (4 studies), although one study found no benefit. Benefit from <u>partially</u> hydrolyzed formula compared with cows' milk formula (4/6 studies).

Breast-feeding or bottle feeding, and which formula should it be ?

Recommendations	Evidence level
If breastfeeding is insufficient or not possible: High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months.	I

Criteria for hypoallergenicity

AAP: a formula can be labeled *hypoallergenic* if tolerated by 90% of infants with cow's milk allergy.

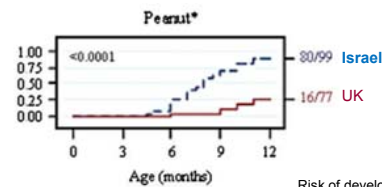
European Union: a formula can be labeled *hypoallergenic* if the content of immunoreactive proteins are < 1% of total nitrogen containing substances.

At what age should solid foods be introduced ?

	Studies (high quality)	Preventive effect
Introduction of solid foods	7 (1/7)	Two cohort studies found no benefit from delaying the introduction of solid foods longer than 4 months.
Delayed exposure to allergenic foods	6 (2/6)	One randomized trial found no benefit from withholding cows' milk or foods made with cow's milk during the first 4 months of infancy

At what age should solid foods be introduced ?

Recommendations	Evidence level
Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity.	II-III
No withholding or encouraging exposure to 'highly allergenic' foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced.	II-III



Risk of developing a peanut allergy in the UK compared with Israel

	Peanut	RR (95% CI)	P value
All individuals			
Unadjusted		10.8 (5.2-22.3)	<.001
Adjusted for age, group ^a and sex ^b		10.4 (4.8-22.2)	<.001
Adjusted for age, group ^a , sex, food allergy, and atopy ^c		5.8 (2.8-11.8)	<.001

Du Toit et al. J Allergy Clin Immunol 2008;122:984

THE NEW ENGLAND JOURNAL of MEDICINE

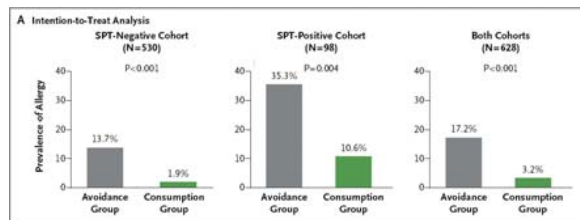
ORIGINAL ARTICLE

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. Bahnsen, 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*

This article was published on February 23, 2015, at NEJM.org.

> 640 infants (med. age 7 months) with a high risk of peanut allergy
 > Randomized to eating 8 peanuts 3x/week, or avoidance until 5 yrs of age



This article was published on February 23, 2015, at NEJM.org.

What we suggest for allergy prevention

- No tobacco smoke exposure
- Breast feeding, or hydrolyzed formula in high risk groups until 4-6 months of age
- In symptomatic children (i.e. atopic eczema), early diagnostic work-up

Summarized in „Die Ernährung während den ersten 1000 Lebenstagen – von pränatal bis zum 3. Geburtstag“
Eidgenössische Ernährungscommission – 2015 (in press) -

Specific oral tolerance induction- SOTT



Oral immunotherapy

Patriarca et al. Aliment Pharmacol Ther 2003;17:459-465

- 59 patients (adults + children)
- 29 milk, 18 egg, 11 fish, 9 other food allergies.
- protocols stretched over 60 to 84 days.
- successful treatments:
24/29 milk
13/15 egg
8/11 fish
- but: no control group, no blinding, side effects in some patients.

Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction

Allergy 2007; 62: 1261-1269

U. Staden¹, C. Reinck-Werninghaus¹,
F. Brewe¹, U. Wahn¹,
B. Niggemann¹, K. Beyer¹

Table 1. Scheme for the Specific oral tolerance induction phase with cow's milk

Concentration milk + water	Day	Quantity	OM protein (mg)	Concentration milk + water	Day	Quantity	OM protein (mg)
1 + 99 ml	1	1 drop	0.02	1 + 99 ml	25	5 drops	0.50
	2	2 drops	0.03		26	8 drops	0.17
	3	3 drops	0.05		27	8 drops	0.17
	4	4 drops	0.07		28	14 drops	0.34
	5	5 drops	0.08		29	14 drops	0.34
	6	6 drops	0.10		30	23 drops	0.69
	7	7 drops	0.12		31	23 drops	0.69
	8	8 drops	0.13		32	34 drops	1.06
	9	9 drops	0.15		33	34 drops	1.06
	10	10 drops	0.17		34	34 drops	1.06
	11	14 drops	0.23		35	23 drops	0.69
	12	20 drops	0.33		36	20 drops	0.69
1 + 9 ml	13	3 drops	0.50		37	34 drops	1.06
	14	4 drops	0.66		38	34 drops	1.06
	15	5 drops	0.83		39	34 drops	1.06
	16	6 drops	1.00		40	34 drops	1.06
	17	7 drops	1.2		41	34 drops	1.06
	18	8 drops	1.3		42	34 drops	1.06
	19	10 drops	1.7		43	34 drops	1.06
	20	14 drops	2.3		44	34 drops	1.06
	21	20 drops	3.3		45	34 drops	1.06
Pure milk	22	3 drops	5.0		46	34 drops	1.06
	23	4 drops	6.6		47	34 drops	1.06
	24	5 drops	8.3		48	34 drops	1.06

SOTT-group (n = 25)		Control-group (n = 20)	
Pattern	n (%)	Result	n (%)
I Responder (natural course or SOTT)	9 (36)	Tolerant	7 (35)
II Responder (with regular daily intake)	3 (12)		
III Partial responder	4 (16)		
IV No responder	9 (36)	Allergic	13 (65%)

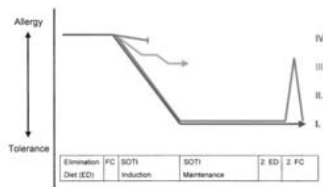
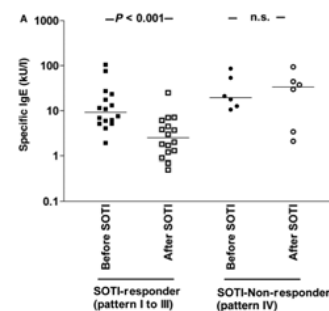


Figure 1. The four clinical patterns of reactions observed during specific oral tolerance induction (SOTT) treatment. ED: elimination diet, FC: food challenge.

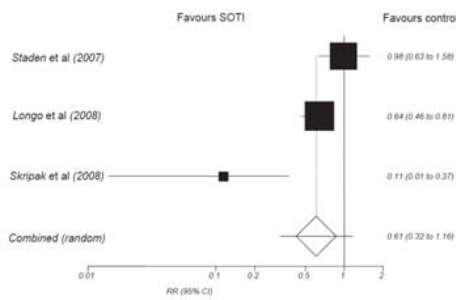
Allergy 2007; 62: 1261-1269



Allergy 2007; 62: 1261-1269

Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?

H R Fisher, G du Toit, G Lack



Arch Dis Child 2011;96:259-264

Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial

www.thelancet.com Published online January 30, 2014

Katherine Anagnostou, Sabita Islam, Yvonne King, Loraine Foley, Laura Pisoni, Simon Bond, Chris Palmer, John Deighton, Pamela Ewan, Andrew Clark

- Peanut allergic children (7-16 years), 50 allergics/50 controls
- SOTI with 2 → 800 mg prot for 26 weeks
- Successful if 1400 mg prot tolerated at 6 months

	Control (n=46)	Active (n=39)	P
First phase			
Number desensitised	0	24	-
Number not desensitised	46	15	-
Proportion desensitised	0 (0 to 0.091)	0.62 (0.45 to 0.78)	-
Proportion able to tolerate daily ingestion	0	0.84 (0.70 to 0.93)	-
Median absolute change in NOAEL, mg	0 (-95 to 45)	1345 (45 to 1400)	0.002, +0.001†
Median fold change in NOAEL, mg	0.81 (0.05 to 1.82)	25.5 (1.82 to 280)	0.003, +0.001†
Median NOAEL after first phase, mg/l	5 (5 to 400)	1400 (100 to 1400)	<0.001‡
Second phase			
Proportion desensitised	0.54 (0.35 to 0.72)	-	-
Proportion able to tolerate daily ingestion	0.91 (0.79 to 0.98)	-	-
Median change in FAQLQ-PF score from baseline to post-treatment	-1.41 (-4.83 to 1.38)¶	-1.61 (-4.87 to 0.24)¶	+0.001, +0.001**

Data are proportion (95% CI) or median (range). NOAEL=no observed adverse effect level. FAQLQ-PF=Food Allergy Quality of Life Questionnaire-Parent Form for 5-12 years. †From Fisher's exact test. ‡From Wilcoxon signed rank tests. §Median difference in NOAEL between groups was 1305 mg (95% CI 235 to 1395); p=0.001 (from Mann-Whitney U test). ¶From Mann-Whitney U test. ¶n=20. ||n=19. **From Wilcoxon signed rank tests.

Table 1: Clinical endpoints for first and second phases

www.thelancet.com Published online January 30, 2014

Symptoms	Participants who experience an adverse event	Adverse events per dose of OIT
Mouth itch	76 (81%)	1121 (6.30%)
Abdominal pain	54 (57%)	460 (2.59%)
Nausea	31 (33%)	393 (2.21%)
Vomiting	31 (33%)	134 (0.75%)
Diarrhoea	1 (1%)	5 (0.03%)
Urticaria	12 (13%)	29 (0.16%)
Angio-oedema	18 (19%)	71 (0.40%)
Erythema	20 (21%)	41 (0.23%)
Rhinitis	23 (24%)	65 (0.37%)
Wheezing	21 (22%)	73 (0.41%)
Laryngeal oedema	1 (1%)	1 (0.01%)
Cardiovascular collapse or fainting	0	0
Outcome		
Admission to intensive-care unit, serious adverse reaction, or serious unexpected suspected adverse reaction	0	0
Use of inhaled β2 agonist	18 (19%)	63 (0.35%)
Use of intramuscular adrenaline	1 (1%)	2 (0.01%)

Data are n (%). Total doses were 12 793. OIT=oral immunotherapy.

Table 3: Adverse events during treatment presented

www.thelancet.com Published online January 30, 2014

Long-term follow-up of oral immunotherapy for cow's milk allergy

Corinne A. Keet, MD, MS^{1,2}

Shannon Seysa, BS¹

Sarah Knorr, RN, MPH, CCRP¹

To the Editor:

- 32 patients with SOTI to cow's milk → 5 yrs
- 9/32 eat ><< 1 serving >>/day +/- local sx
- 3/32 unlimited cow's milk without sx
- Symptoms increase in some patients over time.

Food allergy therapy - What can be achieved-

- Desensitization
- **Partial (temporary) tolerance**
- Total tolerance -cure