Weaning: the Optimal Time for Solid Food Introduction for Allergy Prevention

- Introduction
- Starting point
- Old recommendations
- New findings
- Dietary antigens properties
- Development of tolerance
- Other possible mistakes
- Not only allergy
- Allergy development?
- What can be done?
- Conclusions

Food Allergy Among Children in the United States
Branum Pediatrics 2009;124:1549

- A cross-sectional survey of data on food allergy among children <18 yrs
- In the 1997-2007

PREVALENCE OF FOOD ALLERGY IN CHILDREN

~ 4%

% Increase in reported food allergy from 1997 to 2007

18%
P < 0.01
In general, resolution of allergy to egg, milk, wheat, and soy can be expected, although sensitivity can persist into the second decade of life, which is longer than previously appreciated.

In contrast, most patients allergic to peanut, tree nuts, and seafood will not outgrow their disease and must maintain strict elimination diets.

Spontaneous development of clinical tolerance to foods
Vickery BP  JACI 2011;127:576

Weaning: the Optimal Time for Solid Food Introduction for Allergy Prevention

Attilio Boner
University of Verona, Italy

Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study.

OR for eczema by age 10 yrs

in children exposed to ≥ 4 different types of solid food before 6 months.
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Recommended Approaches to Allergy Prevention

• No maternal dietary restriction during pregnancy (peanuts?)
• breastfeeding,
• dietary restrictions while breastfeeding,
• the use of hypoallergenic formulas, and
• delays in the introduction of certain foods into the infant’s diet

Pediatrics 2000;106:346

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University of Verona, Italy
Breast feeding


A cohort of 516 children with a family history of asthma in Sydney, Australia, followed from birth to age 5 years.

In children of asthmatic mother OR for eczema at 5 yrs

Breastfeed > 6 months

2.30

P=0.044

In children of asthmatic mother OR for eczema at age 5 yrs

Breast fed for ≥ 6 months

0.71 to 1.42


A cohort of 516 children with a family history of asthma in Sydney, Australia, followed from birth to age 5 years.
Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years.

- 200 unselected healthy newborns (42% has a family history of allergy)
- Follow up at ages 5 (n=163), 11 (n=150) and 20 years (n=164) with clinical examination and skin prick testing

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The Introduction of Solids in Relation to Asthma and Eczema

- 642 children recruited before birth and followed to the age 5 1/2 years
- Retrospective evaluation of solid foods introduction performed at age 12 months

---

Solid foods: Milk - Egg
The Introduction of Solids in Relation to Asthma and Eczema
Zutavern Arch Dis Child 2004;89:303

- 642 children recruited before birth and followed to the age 5 1/2 years
- Retrospective evaluation of solid foods introduction performed at age 12 months

Prevalence of eczema at age 5 1/2

<table>
<thead>
<tr>
<th>Milks</th>
<th>p=0.032</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 mo</td>
<td>32.3%</td>
</tr>
<tr>
<td>&gt;6mo</td>
<td>41.2%</td>
</tr>
</tbody>
</table>

Solid Food Introduction in Relation to Eczema: Results from a Four-Year Prospective Birth Cohort Study.
Filipiak J Pediatr 2007;151:352

- Introduction of solid foods in the first 12 months (birth cohort)
- Occurrence of eczema during the first 4 years of life
- Intervention group (n=2252) (allergenic food such as cow’s milk and dairy products, eggs, fish, tomatoes, nuts, soy products, and citrus fruits were to be avoided entirely during the first year)
- Nonintervention group (n=3739)

In this large population-based prospective birth cohort study, there was no evidence for a protective effect in relation to eczema from delayed introduction of solids beyond the fourth month and of most potentially allergenic solids beyond the sixth month of life.

Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study.

- 2558 infants in an ongoing prospective birth cohort study in the Netherlands
- Introduction of cow milk products and other food products
- Follow-up: 2 years

OR for Atopic Dermatitis (UK-WP)

<table>
<thead>
<tr>
<th>Age of introduction of cow milk products (mo)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1.0</td>
</tr>
<tr>
<td>4-6</td>
<td>0.65</td>
</tr>
<tr>
<td>7-9</td>
<td>0.64</td>
</tr>
<tr>
<td>&gt;9</td>
<td>1.43</td>
</tr>
</tbody>
</table>
Can early introduction of egg prevent egg allergy in infants? A population-based study

Koplin JACI 2010;126:807

- Population-based cross-sectional study.
- 2589 infants.
- To determine whether confirmed egg allergy in 12-month-old infants is associated with:
  1. duration of breast-feeding and
  2. ages of introducing egg and solids

OR for development of egg allergy in total population

<table>
<thead>
<tr>
<th>Age (mo) of introduction</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-6</td>
<td>1.0</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td></td>
<td></td>
<td>3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td></td>
<td></td>
<td></td>
<td></td>
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- Population-based cross-sectional study.
- 2589 infants.
- To determine whether confirmed egg allergy in 12-month-old infants is associated with:
  1. duration of breast-feeding and
  2. ages of introducing egg and solids

These findings persisted even in children without risk factors (OR = 3.3; 10-12 mo.)

To avoid reverse causality

OR for development of egg allergy in total population

<table>
<thead>
<tr>
<th>Age (mo) of introduction</th>
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<th>1.0</th>
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<tbody>
<tr>
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<td>3.4</td>
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<tr>
<td>&gt;12</td>
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In children exposed at age 4 to 6 months to cooked eggs vs those exposed to eggs in backed goods

- OR for development of egg allergy in total population

<table>
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<th>Age (mo) of introduction</th>
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- In children exposed at age 4 to 6 months to cooked eggs vs those exposed to eggs in backed goods
Age at the Introduction of Solid Foods During the First Year and Allergic Sensitization at Age 5 Years
Nwaru Pediatrics 2010;125:50

- 994 children
- age at the introduction of solid foods
- adjustment for potential confounders
- allergen-sIgE at 5 years

Late introduction of:
- potatoes (>4 months),
- oats (>5 months),
- rye (>7 months),
- wheat (>6 months),
- meat (>5.5 months),
- fish (>8.2 months),
- eggs (>10.5 months)

was significantly directly associated with sensitization to food allergens.

OR for sensitization to inhalant allergens

<table>
<thead>
<tr>
<th>Food</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes &gt;4 mo</td>
<td>2.56</td>
</tr>
<tr>
<td>Milk &gt;4 mo</td>
<td>1.51</td>
</tr>
<tr>
<td>Fruits &gt;4 mo</td>
<td>1.70</td>
</tr>
<tr>
<td>Wheat &gt;6 mo</td>
<td>1.49</td>
</tr>
<tr>
<td>Meat &gt;6 mo</td>
<td>1.65</td>
</tr>
<tr>
<td>Rye &gt;7 mo</td>
<td>2.30</td>
</tr>
<tr>
<td>Fish &gt;8 mo</td>
<td>2.42</td>
</tr>
<tr>
<td>Egg &gt;10 mo</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Development of atopic dermatitis according to age of onset and association with early-life exposures
Roduit JACI 2012;130:130

- Introduction to complementary food in the first year of life.
- Development of atopic dermatitis, taking into account the reverse causality.
- 1041 children birth cohort study.
- Feeding practices reported by parents in monthly diaries between the 3rd and 12th months of life.

OR for having atopic dermatitis with onset after the first year of life

<table>
<thead>
<tr>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.76</td>
</tr>
</tbody>
</table>
Development of atopic dermatitis according to age of onset and association with early-life exposures

- Introduction to complementary food in the first year of life.
- Development of atopic dermatitis, taking into account the reverse causality.
- 1041 children birth cohort study.
- Feeding practices reported by parents in monthly diaries between the 3rd and 12th months of life.

Association between increasing numbers of different major food items (n = 6) introduced in the first year of life and atopic dermatitis (AD) with onset after the first year of life.

- OR for having atopic dermatitis with onset after the first year of life
  - Yogurt in the first year of life

Timing of infant feeding in relation to childhood asthma and allergic diseases

- 3781 consecutively born children.
- Dietary exposures.
- Asthma, allergic rhinitis, and atopic eczema, IgE antibodies at the age of 5 years.

Median duration (months) of

- Breast-feeding

- Exclusive

- Total breastfeeding
Timing of infant feeding in relation to childhood asthma and allergic diseases. Nwaru JACI 2013;131:78

Introduction of wheat, rye, oats, or barley at 5 to 5.5 months was inversely associated with asthma and allergic rhinitis, whereas introduction of other cereals at 4.5 months increased the risk of atopic eczema. Median duration (months) of exclusive and total breastfeeding.

Timing of infant feeding in relation to childhood asthma and allergic diseases. Nwaru JACI 2013;131:78

Introduction of egg at 11 months or less was inversely associated with asthma, allergic rhinitis, and atopic sensitization, whereas introduction of fish at 9 months or less was inversely associated with allergic rhinitis and atopic sensitization. Median duration (months) of exclusive and total breastfeeding.

Gluten
Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. Norris JM, JAMA. 2005;293:2343–2351

- Development of celiac disease autoimmunity (CDA)
- 1560 children at increased risk for celiac disease or type 1 diabetes, as defined by possession of either HLA-DR3 or DR4 alleles, or having a first-degree relative with type 1 diabetes.
- Follow-up: 4.8 years.

EFFECT OF BREAST FEEDING ON RISK OF COELIC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES Akobeng Arch Dis Child 2006; 91: 39

- 6 case-control studies

<table>
<thead>
<tr>
<th>OR for Coeliac Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHILDREN WHO WERE BREST-FED AT THE TIME OF GLUTEN INTRODUCTION</td>
</tr>
<tr>
<td>0.48</td>
</tr>
</tbody>
</table>

Timing of initial exposure to cereal grains and the risk of wheat allergy. Poole JA, Pediatrics 2006; 117:2175–2182

- 1612 children enrolled at birth
- Followed to the mean age of 4.7 years.
- Questionnaire data and dietary exposures were obtained at 3, 6, 9, 15, and 24 months and annually thereafter.

<table>
<thead>
<tr>
<th>OR for Wheat Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age exposed to cereal grains (wheat, barley, rye, oats)</td>
</tr>
<tr>
<td>3.8</td>
</tr>
</tbody>
</table>
Fish consumption during the first year of life and development of allergic diseases during childhood. 
Kull I. Allergy. 2006;61:1009-15

- birth cohort of 4089 new-born infants in Sweden
- follow-up: 4 years
- Parental questionnaires at ages 2 months, 1, 2 and 4 years

OR for multiple allergic disease by age 4

0.56

Fish consumption during the first year of life (≥2-3 times a month vs ≤1 times a month)

0.5

0

Early introduction of fish decreases the risk of eczema in infants 
Alm Arch Dis Child 2009;94:11

- 8176 families.

OR for having eczema by age 1 year

0.76

FISH BEFORE 9 MO. OF AGE
Early complementary feeding and risk of food sensitization in a birth cohort. Joseph JACI 2011;127:1203

- Introduction of complementary food <4 months.
- IgE to egg, milk, and peanut allergen at 2 yrs.
- 594 maternal-infant pairs.

Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. Du Toit JACI 2008;122:984

- Questionnaire.
- Primary schoolchildren (5171 in the UK and 5615 in Israel).
- Peanut consumption and weaning in Jewish infants (77 in the UK and 99 in Israel).
Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy.

Du Toit JACI 2008;122:984

- Questionnaire.
- Primary schoolchildren (5171 in the UK and 5615 in Israel).
- Peanut consumption and weaning in Jewish infants (77 in the UK and 99 in Israel).

Median monthly consumption of peanuts in infants aged 8 to 14 months (g peanut protein/month)

<table>
<thead>
<tr>
<th>ISRAEL</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>0</td>
</tr>
</tbody>
</table>

p<0.001

Household peanut consumption as a risk factor for the development of peanut allergy

Fox JACI 2009; 123:417

- Background:
  Most children with peanut allergy (PA) react on first known oral exposure to peanut.

- Recent data suggest cutaneous exposure as a route of sensitization.

- Objectives:
  This study aimed to establish the relevant route of peanut exposure in the development of allergy.

Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort.

Maslova JACI 2012;130:724

- Danish National Birth Cohort (n=61,908).
- Maternal peanut and tree nut intake during pregnancy and allergic outcomes in children at 18 months and 7 years of age.

OR for asthma in children aging 18 months

<table>
<thead>
<tr>
<th>PEANUTS</th>
<th>TRE NUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.79</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort (Maslova JACI 2012;130:724).

Higher tree nut intake was inversely associated with a medication-related asthma diagnosis (OR, 0.81) and self-reported allergic rhinitis (OR, 0.80).

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- The follicle-associated epithelium (FAE), which comprises columnar epithelial cells and also contains microfold (M) cells, dendritic cells (DCs), T cells, B cells and macrophages, separates the intestinal lumen from Peyer's patches.
- Peyer's patches are aggregates of secondary lymphoid tissue present in the submucosa of the small intestine. The area immediately beneath the FAE ('dome') is rich in DCs.

**effector sites: villi**

a) Normal small intestine showing the characteristic architecture of finger-like villi that are covered by a single layer of columnar epithelial cells, which encloses the central lamina propria (LP) (effector sites)


The process begins with antigen sampling and recognition at inductive sites and ends with the generation of antigen specific secretory IgA at effector sites which is actively transported to the mucosal surface.

MECHANISMS OF TOLERANCE
Burks JACI 2008;121:1344

There are 2 primary effector mechanisms for inducing oral tolerance:

1) Low doses of antigen favor tolerance driven by regulatory cells, which suppress immune responses through soluble or cell surface-associated downregulatory cytokines, such as IL-10, and TGF-β (active suppression).

1) Active Suppression by regulatory T cells

or

2) Deletion or Anergy
MECHANISMS OF TOLERANCE
Burks JACI 2008;121:1344

There are 2 primary effector mechanisms for inducing oral tolerance:

1) Active Suppression by regulatory T cells or
2) Deletion or Anergy

2) High-dose tolerance is mediated by lymphocyte anergy or clonal deletion.

Anergy can occur through T-cell receptor ligation in the absence of costimulatory signals.

Clonal deletion occurs by means of FAS-mediated apoptosis (CD95).

Apoptotic T cells release TGF-β in both latent and bioactive forms, and macrophages produce TGF-β on ingesting apoptotic cells. The secretion of TGF-β through the various mechanisms of clonal anergy and deletion can contribute to an immunosuppressive environment in the gut.
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Iron Deficiency Anemia and Cognitive Function in Infancy
Carter Pediatrics 2010;126:e427
- Effects of iron deficiency anemia (IDA) on specific domains of infant cognitive function
- IDA was defined as hemoglobin level<110 g/L, with ≥2 abnormal iron deficiency indicators (mean corpuscular volume, red cell distribution width, zinc protoporphyrin, transferrin saturation, and ferritin)
- At 9 and 12 months, the Fagan Test of Infant Intelligence (FTII); A-not-B task; Emotionality, Activity, and Sociability Temperament Survey; and Behavior Rating Scale

Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children
Chang Pediatrics 2011;127:e927
- Children with iron-deficiency anemia (IDA) in infancy whose anemia was not corrected before 24 months (chronic IDA) (n=27)
- Children with IDA in infancy whose anemia was corrected before 24 months (corrected IDA) (n=70)
- Children who were non-anemic in infancy and at 24 months (n =64)

Infants with IDA showed poorer recognition memory
- The Behavior Rating Scale orientation/engagement measure partially mediated these effects

Children who had chronic IDA in infancy displayed:
1. less positive affect and frustration tolerance;
2. more passive behavior and physical self-soothing in the stranger approach;
3. delay of gratification
Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children

Chang Pediatrics 2011;127:e927

In contrast, the behavior and affect of children whose anemia was corrected before 24 mo of age were comparable to those of children who were non-anemic throughout infancy.

- Children with iron-deficiency anemia (IDA) in infancy whose anemia was not corrected before 24 months (chronic IDA) (n=27).
- Children with IDA in infancy whose anemia was corrected before 24 months (corrected IDA) (n=70).
- Children who were non-anemic in infancy and at 24 months (n=64).

Higher serum folate levels are associated with a lower risk of atopy and wheeze

Matsui JACI 2009;123:1253

- Serum folate and total IgE levels.
- 8083 subjects 2 years of age and older.

Or in the 5° quintile of Folate vs the 1° quintile

<table>
<thead>
<tr>
<th>IgE LEVEL +100 KU/L</th>
<th>ATOPY</th>
<th>WHEEZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.70</td>
<td>0.69</td>
<td>0.60</td>
</tr>
</tbody>
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Epidemiologic risks for food allergy
Lack, JACI 2008;121:1331-6

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Breastfeeding
Formula feeding
Effects of different formula
Breast-feeding and Allergy

- Protective effect of exclusive breast-feeding for 4-6 months on the risk of allergic disease (eczema and asthma) in early childhood, particularly in high-risk infants (positive family history).
- However, there is no evidence that exclusive breast-feeding for more than 6 months prevented asthma, eczema or atopy at 5 years of age, and with prolonged breast-feeding, the risk of atopic dermatitis and atop, and particularly the risk of asthma in later life, may even increase.

Breastfeeding and allergies: time for a change in paradigm?

- Although breastfeeding is strongly recommended for its multiple benefits on child health, most recent studies do not confirm the 'conventional wisdom' that breastfeeding is protective against allergy and asthma.
- Early reduction in childhood wheezing may reflect protection from viral infections, but allergies and asthma at later ages may be increased.

Timing of solid foods introduction
There is mounting concern that the current recommended practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk of immune disorders.

Tolerance to food allergens appears to be driven by regular, early exposure to these proteins during a "critical early window" of development (most likely to be between 4 and 6 months of life). Delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and autoimmunity.

There is also evidence that other factors such as favourable colonization and continued breastfeeding promote tolerance and have protective effects during this period when complementary feeding is initiated.

Delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and autoimmunity.

Immune-modulating micronutrients antioxidants
Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. Nurmatov U, JACI. 2011;127:724

Weaning: the Optimal Time for Solid Food Introduction for Allergy Prevention

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University of Verona, Italy
Key points underlying changes in complementary feeding practices.

- There is little evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy, and there have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy.
- There is insufficient evidence to support previous advice to specifically delay or avoid potentially allergenic foods (such as egg, peanuts, nuts, wheat, cow's milk and fish) for the prevention of food allergy or eczema.
- This also applies to infants with siblings who already have allergies to these foods.

Feeding advice based on current evidence

Infant formulas before 4 months:
If complementary formula is required before solid foods are started, recommendations vary:

- Where there is no family history of allergic disease in the infant's parents or siblings, a standard cow's milk formula may be used.
- Infants with a family history of allergy (parents or siblings) should be started on a partially hydrolysed cow's milk formula (usually labelled "HA" or hypo-allergenic). For known cow's milk allergy, these formulas are not suitable; elemental formulas are used instead.
- Soy milk and other mammalian milks (eg, goat's milk) are not recommended for allergy prevention or for infants with known cow's milk allergy.

Starting complementary foods:

- From 4-6 months onwards when a child is ready, parents should consider introducing a new food every 2-3 days, according to what the family usually eats (regardless of whether the food is thought to be highly allergenic).
- In this way, reactions can be more clearly identified and the food excluded (or continued) as a part of a varied diet.
- Infants are unlikely to develop a new allergy to any food that is already tolerated, if it is given regularly.
- Breast milk or an appropriate infant formula should remain the main source of milk until 12 months of age, although cow's milk can be used in cooking or with other foods.
Thank you for your attention
FORMAT 23-24/05/2014