Targeting the Skin for Food Allergy Prevention

Dr Helen Brough
Consultant & Reader in Paediatric Allergy

Table of Content

<table>
<thead>
<tr>
<th></th>
<th>Eczema and epicutaneous sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Microbial therapies</td>
</tr>
<tr>
<td>3</td>
<td>Skin barrier therapies</td>
</tr>
<tr>
<td>4</td>
<td>Anti-inflammatory therapies</td>
</tr>
</tbody>
</table>
Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? Allergy. 2020; 75 (9):2185-2205

1) Skin barrier impairment due to environmental pollutants, detergents, infections, and genetics

2) Skin barrier impairment leads to skin inflammation and clinical AD

3) Exposure to food allergens through skin that has an impaired barrier (dry) or clinical AD leading to sensitization and FA

Brough H.A. et al. Allergy 2020; 75 (9):2185-2205

Early intervention and prevention of allergic diseases

Allergy 2021 – under review

Table of Content

1. Eczema and epicutaneous sensitization
2. Microbial therapies
3. Skin barrier therapies
4. Anti-inflammatory therapies
### Microbial applications on the skin

- **Cosmetic products** using a variety of formulations and diverse bacterial strains have filed for patents.

- **Targeted microbiome transplant via topical probiotic cream** for the treatment of AD:
  - Enrolled very limited numbers of subjects
  - Insufficient evidence currently reported
  - No safety concerns reported

- **Larger scale, randomized, controlled trials** are underway.

---


**Early intervention and prevention of allergic diseases**

**Allergy 2021 – under review**

---

**Boxberger M et al. Challenges in exploring and manipulating the human skin microbiome.**


**Ambrożej D et al. The use of probiotics and bacteria-derived preparations in topical treatment of atopic dermatitis-A systematic review.**

Table of Content

1. Eczema and epicutaneous sensitization
2. Microbial therapies
3. Skin barrier therapies
4. Anti-inflammatory therapies

<table>
<thead>
<tr>
<th>Element or Characteristic</th>
<th>AD vs. healthy skin</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin Microbiome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial diversity</td>
<td>↑</td>
<td>Influenced by host genetics, local immune response, environmental factors (pH, temperature, humidity, hygiene practices and exposure to antibiotics)</td>
</tr>
<tr>
<td>S. aureus colonization (including MRSA)</td>
<td>↑</td>
<td>Correlates with severity of AD</td>
</tr>
<tr>
<td>S. aureus virulence factors</td>
<td>↑↑</td>
<td>Superantigens, biofilms, alpha-toxin, protein A, and exogenous proteases</td>
</tr>
<tr>
<td>Commensal bacteria Malassezia spp.</td>
<td>↓</td>
<td>Streptococcus, coagulase negative Staphylococcus, Corynebacterium and Curtobacterium spp. Seen in sebaceous dermatitis in infants and in adults with IgE to Malassezia</td>
</tr>
<tr>
<td><strong>Skin Barrier</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flagging gene expression and breakdown products including natural moisturizing factor</td>
<td>↑</td>
<td>Complex genetic and environmental interactions play a major role in the pathogenesis of AD and risk for FA in AD</td>
</tr>
<tr>
<td>Skin pH</td>
<td>↑</td>
<td>A loss of acidity leads to enhanced adhesion, altered lipid structure, and susceptibility to S. aureus</td>
</tr>
<tr>
<td>Transdermal water loss (TEWL)</td>
<td>↑↑</td>
<td>Causes skin dehydration, can be used as a noninvasive skin assessment</td>
</tr>
<tr>
<td>Tight junction expression and function</td>
<td>↑</td>
<td>Impaired barrier function and enhanced allergen exposure</td>
</tr>
<tr>
<td>Organization of the lipid bilayer and fatty acid chain length</td>
<td>↑</td>
<td>The lipid bilayer is disorganized with altered ceramides with short-chain fatty acids which have anti-microbial and anti-inflammatory properties</td>
</tr>
<tr>
<td><strong>Inflammatory Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-4, -13, and other Th2 cytokines</td>
<td>↑ ↑</td>
<td>Allows for S. aureus colonization, central role in AD shown by the successful treatment with biocidation by diphenphenameth</td>
</tr>
<tr>
<td>Thymic Stromal Lymphopoietin (TSLP)</td>
<td>↑</td>
<td>A pro-inflammatory, IL-7-like cytokine</td>
</tr>
<tr>
<td>IL-31</td>
<td>↑</td>
<td>The key component of the itch-scratch cycle and primary driver of pruritus in AD</td>
</tr>
<tr>
<td>IL-33 &amp; ILC2s</td>
<td>↑</td>
<td>IL-33 increases with skin trauma (scratching), which leads to increased intestinal ILC2s, which may be an important link between AD and FA</td>
</tr>
</tbody>
</table>


Early intervention and prevention of allergic diseases

Allergy 2021 – under review
Effects of Cream Application in Childhood on Skin Barrier and Development of Atopic Diseases


Skin barriers book
Accepted for publication

Eczema by 1-3 years: Skin care intervention vs. standard skin care/no skin care intervention

• Large proportion of children being moisturised in EAT study:
  • 70.7% of babies with no visible eczema at 3 months at least once a week often for massage
  • 89.7% of those with visible eczema at 3 months at least once a week

Perkin et al. J Allergy Clin Immunol 2021;147:967-76

### Types of moisturiser used in the EAT study

<table>
<thead>
<tr>
<th>Moisturiser Type</th>
<th>Frequency</th>
<th>% (Cumulative %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil</td>
<td>151</td>
<td>23.1 (23.1)</td>
</tr>
<tr>
<td>Johnson’s baby oil</td>
<td>74</td>
<td>11.3 (34.5)</td>
</tr>
<tr>
<td>E45</td>
<td>39</td>
<td>6.0 (40.4)</td>
</tr>
<tr>
<td>Johnson’s baby lotion</td>
<td>36</td>
<td>5.5 (45.9)</td>
</tr>
<tr>
<td>Olatum</td>
<td>29</td>
<td>4.4 (50.4)</td>
</tr>
<tr>
<td>Aqueous cream</td>
<td>27</td>
<td>4.1 (54.5)</td>
</tr>
<tr>
<td>Diprobene</td>
<td>18</td>
<td>2.8 (57.3)</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>16</td>
<td>2.5 (59.7)</td>
</tr>
<tr>
<td>Aveeno</td>
<td>15</td>
<td>2.3 (62.0)</td>
</tr>
<tr>
<td>Almond oil</td>
<td>13</td>
<td>2.0 (64.0)</td>
</tr>
<tr>
<td>Epaderm</td>
<td>13</td>
<td>2.0 (66.0)</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>12</td>
<td>1.8 (67.6)</td>
</tr>
<tr>
<td>Doublebase</td>
<td>12</td>
<td>1.8 (69.7)</td>
</tr>
<tr>
<td>Sudocrem</td>
<td>12</td>
<td>1.8 (71.5)</td>
</tr>
<tr>
<td>Ceteben</td>
<td>9</td>
<td>1.4 (72.9)</td>
</tr>
<tr>
<td>Baby oil</td>
<td>8</td>
<td>1.2 (74.1)</td>
</tr>
<tr>
<td>Neal’s yard baby oil</td>
<td>8</td>
<td>1.2 (75.3)</td>
</tr>
<tr>
<td>Vegetable oil</td>
<td>8</td>
<td>1.2 (76.6)</td>
</tr>
<tr>
<td>Vaseline</td>
<td>6</td>
<td>0.9 (77.5)</td>
</tr>
<tr>
<td>Weleda calendula lotion/oil</td>
<td>6</td>
<td>0.9 (78.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moisturiser Type</th>
<th>Frequency</th>
<th>% (Cumulative %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil</td>
<td>49</td>
<td>18.2 (18.2)</td>
</tr>
<tr>
<td>Diprobene</td>
<td>27</td>
<td>10.0 (28.3)</td>
</tr>
<tr>
<td>Aqueous cream</td>
<td>18</td>
<td>6.7 (43.1)</td>
</tr>
<tr>
<td>Olatum</td>
<td>15</td>
<td>5.6 (48.7)</td>
</tr>
<tr>
<td>Aveeno</td>
<td>14</td>
<td>5.2 (53.9)</td>
</tr>
<tr>
<td>Epaderm</td>
<td>13</td>
<td>4.8 (58.7)</td>
</tr>
<tr>
<td>E45</td>
<td>12</td>
<td>4.5 (63.2)</td>
</tr>
<tr>
<td>Johnson’s baby oil</td>
<td>12</td>
<td>4.5 (67.7)</td>
</tr>
<tr>
<td>Ceteben</td>
<td>11</td>
<td>4.1 (71.8)</td>
</tr>
<tr>
<td>Johnson’s baby lotion</td>
<td>6</td>
<td>2.2 (74.0)</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>5</td>
<td>1.9 (75.6)</td>
</tr>
<tr>
<td>Hydromol</td>
<td>6</td>
<td>1.9 (77.7)</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>5</td>
<td>1.9 (79.6)</td>
</tr>
<tr>
<td>Dermol</td>
<td>4</td>
<td>1.5 (81.0)</td>
</tr>
<tr>
<td>Emulsifying ointment</td>
<td>3</td>
<td>1.1 (82.2)</td>
</tr>
<tr>
<td>Baby lotion</td>
<td>2</td>
<td>0.7 (82.9)</td>
</tr>
<tr>
<td>Boots baby moisturier</td>
<td>2</td>
<td>0.7 (83.6)</td>
</tr>
<tr>
<td>Boots baby oil</td>
<td>2</td>
<td>0.7 (84.4)</td>
</tr>
<tr>
<td>Burt’s bees lotion</td>
<td>2</td>
<td>0.7 (85.1)</td>
</tr>
</tbody>
</table>
Frequent moisturizer use in early infancy and food allergy

- Due to dose-response between AD severity and moisturizing frequency?
  - Analysis adjusted for eczema severity and filagrin status

- Because infants who had moisturizers applied had eczema / dry skin before enrolment?
  - Persisted when infants whose parents reported eczema/dry skin were excluded

- Because the moisturisers damage the skin barrier?
  - TEWL also increased with each increase in application of moisturiser
  - Olive oil - top moisturizer applied in children with and without eczema
  - Olive (and other vegetable oils) impede the development of lamellar structures
  - Sodium lauryl sulfate (e.g. aqueous cream) disrupts the skin barrier

- Because oils facilitate transfer of allergen to the skin?
  - Mouse models oils facilitate penetration of a model chemical

---

**TEWL after petrolatum vs trilipids for 5 weeks**

Sindher T et al. Pilot Study Measuring TEWL in Children Suggests Trilipid Cream Is More Effective Than a Paraffin-Based Emollient. 2020 Allergy
IgG4/IgE in infants with AD/dry skin: Aveeno vs trilipid

Sindher T et al. Increases in plasma IgG4/IgE with trilipid vs paraffin/petrolatum-based emollients for dry skin/eczema 2020 PAI

PEBBLES pilot study preventative trilipid therapy


ITT: Visible AD at 12m 16% vs. 5% (p=0.15)

<table>
<thead>
<tr>
<th>Food</th>
<th>Control (n=36)</th>
<th>Epiceram ITT (n=34)</th>
<th>Epiceram PP (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>5.6%</td>
<td>2.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Egg</td>
<td>16.7%</td>
<td>5.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Peanut</td>
<td>8.3%</td>
<td>2.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Any food</td>
<td>19.4%</td>
<td>8.8%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Moisturisers and prevention of AD and FA

• Petrolatum based emollients
  • No effect for AD prevention, severity, time of onset
  • Increase in skin infections (BEEP)
  • Trend towards sensitisation and food allergy (BEEP)

• Frequency of moisturisers associated with food allergy
  • Predominantly olive oil used for baby massage

• Trilipid based emollients
  • Positive results on pilot study for AD and SPT
  • PEBBLES RCT (NCT 03667651) 760 high-risk infants (Aus)

Table of Content

1. Eczema and epicutaneous sensitization
2. Microbial therapies
3. Skin barrier therapies
4. Anti-inflammatory therapies
Effects of Cream Application in Childhood on Skin Barrier and Development of Atopic Diseases


Skin barriers book

Accepted for publication
Early proactive topical steroids associated with reduced FA

45% reduction in food allergy by 2 yrs (egg, milk, wheat, soy, peanut, fish)

60% reduction in egg allergy in egg sensitized patients

Miyaji Y et al. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. J Allergy Clin Immunol Pract. in press.

Secondary prevention study in AD infants

- Multicenter, investigator-blinded, RCTI (PACI Study, Japan, n=650)

- Twice daily emollient therapy from 7-13 weeks
  - Heparinoid cream (Hirudoid® Soft ointment) twice daily

- Proactive steroid treatment from 7-13 weeks (BD for 2/52 then twice weekly BD)
  - Face: Alclometasone dipropionate (low potency)
  - Body: Betamethasone valerate (intermediate potency)

- OFC proven IgE mediated egg allergy at 6 months

UMIN000028043 doi.org/10.1186/s13601-018-0233-8
SEAL study: Stopping Eczema and Allergy U01 # AI147462 National Institutes of Health

Adaptive trial design with two intervention arms:
1) Aveeno + proactive fluticasone propionate cream 0.05%
2) Epiceram + proactive fluticasone propionate cream 0.05%
3) Control arm – standard of care – reactive care

Outcome: Food allergy (DBPCFC) by 36 months (egg, cow’s milk, peanut, sesame, fish, wheat and five tree nuts)

Proactive treatment with emollients and topical steroids

*If child < 3 months: Use 1% hydrocortisone ointment instead of FP

Topics for future research

• Characterize molecular mechanisms underlying the phenotypes of skin barrier dysfunction (SBD) that place some, but not all patients with AD at increased risk for atopy
• Evaluation of environmental exposures including irritants, pollution, pollen, bacteria, viruses and fungi
• Identify targeted treatment approaches to heal the SBD which specifically predispose to atopy
• Determine whether moisturisers facilitate food and aeroallergen uptake and whether effects are limited to certain types of moisturiser or to specific susceptible individuals

Thank-you for your attention
Acknowledgements

- King’s College London
  - Gideon Lack
  - Susan Chan
  - George Du Toit
  - Alexandra Santos

- Stanford University
  - Kari Nadeau
  - Sayantani Sindher
  - Vanitha Sampath
  - Shifaa Alkotob

- University of Colorado, Denver
  - Carina Venter

- National Institutes of Health

- National Jewish Denver
  - Donald Leung
  - Bruce J Lanser

- Benaroya Research Institute
  - Tee Bahnson

- University of Chicago
  - Christina Ciaccio
  - Joyce Teng
  - Cathy Nagler

- Northwestern University Feinberg School of Medicine
  - Ruchi Gupta

- Icahn School of Medicine at Mount Sinai
  - Emma Guttman-Yassky

Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment full time / part time</td>
<td>Guy’s and St. Thomas’ NHS Foundation Trust</td>
</tr>
<tr>
<td>Research-Grant (P.I., collaborator or consultant; pending and received grants)</td>
<td>National Institutes for Health (P.I.), Aimmune (subinvestigator), DBV Technologies (subinvestigator)</td>
</tr>
<tr>
<td>Other research support</td>
<td>None</td>
</tr>
<tr>
<td>Speakers Bureau / Honoraria</td>
<td>DBV Technologies, Sanofi</td>
</tr>
<tr>
<td>Ownership interest (stock, stock-options, patent or intellectual property)</td>
<td>None</td>
</tr>
<tr>
<td>Consultant / advisory board</td>
<td>None</td>
</tr>
</tbody>
</table>

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (e.g. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.
Can the Microbiome be Manipulated to Prevent Food Allergy

Carina Venter PhD RD
Associate Professor Allergy and Immunology
University of Colorado/Children's Hospital Colorado

We can not ignore the bigger picture

- Early life nutrition is associated with gut microbiome composition and function
- Early life gut microbiome and metabolites associated with food allergies
- Early life (cord blood) epigenetics associated with food allergies


Martini et al. Frontiers 2017, PMID: 28879172
We have seen changes in food allergy prevention guidelines

Past and present—Guidelines on diagnosis and management


Past and present—Guidelines on prevention


Our knowledge base is increasing
Infant microbiome and microbial diversity: CMA allergic vs. no CMA

• Children with CMA have lower gut microbiota diversity and an elevated Enterobacteriaceae to Bacteroidaceae (E/B) ratio compared with healthy controls (P = 0.0002).


• In food allergic infants, several studies show the presence of altered gut microbiota, or ‘dysbiosis’ (a breakdown in the balance of intestinal bacteria).

Outgrowing cow’s milk allergy: Differences in microbial diversity

• Gut microbiome composition at age 3 to 6 months was associated with milk allergy resolution by age 8 years (PERMANOVA P = .047), with enrichment of Clostridia and Firmicutes in the infant gut microbiome of subjects whose milk allergy resolved.

Cow’s milk allergic infants exhibit significantly increased diversity and altered composition

- Differential feature selection and generalized linear model fitting revealed that the CMA infants have a diverse gut microbial community structure dominated by Lachnospiraceae (20.5±9.7%) and Ruminococcaceae (16.2±9.1%).

- After LGG treatment: Blautia, Roseburia and Coprococcus were significantly enriched – both butyrate producing bacteria.

Berni Canani et al. 2016, ISME J. 10(3): 742–750
The bigger picture

We are beginning to understand that not only the levels of single nutrients are important, but also their interactions are key, and this can change depending on host-specific factors such as background genetics.

Both nutrient excesses (e.g. high fat, highly processed dietary patterns and deficiencies (e.g. fiber) may have dramatic effects on the microbiome and immune system functions.

The “complicated tango” between nutrients, microbiome, epithelial barriers, metabolism, epigenetics and the immune system may be just as important for disease prevention as for disease treatment.


Fat intake matters
– Infants
- Fat intake associated with reduced microbial diversity

Laursen MF, mSphere. 2016;1(1)
Fat intake in mice

- Murine models: high-fat diet induces changes to gut microbiota that increase food allergy risk.
- On a high fat diet, mice developed decreased gut bacterial diversity.
- Transfer of the high fat diet-associated microbiome from the mice to germ-free mice enhanced food allergy susceptibility to the recipient mice.


Fiber and the microbiome

- Fecal microbiota of the Burkina Faso children was rich in Actinobacteria and Bacteroidetes but had lower levels of Firmicutes.
- EU children were rich in Proteobacteria and had over twice the relative abundance of Firmicutes to Bacteroidetes vs. African children.
- The African children exhibited increased richness and biodiversity in their fecal microbiota.

Fiber and allergy
“There were no food allergy or food sensitization studies identified that examined fiber or prebiotic interventions. “

Emulsifiers and Microbiota

Emulsifiers are compounds used in ice cream, margarine, packaged bread, commercial mayonnaise, creamy sauces, candy and many processed e.g. polysorbate 80 and carboxymethylcellulose.

Destroy the epithelial mucous layer in the gut, alter gut microbial composition and promote inflammation in mice.


In humans: “We conclude that dietary emulsifiers can severely impact the gut microbiota, and this seems to be proportional to their emulsifying strength, rather than emulsifier type or origin. As biotechnological emulsifiers were especially more impactful than chemical emulsifiers, caution is warranted when considering them as more natural alternatives for clean label strategies.”

Miclotte et al. 2020 https://doi.org/10.3389/fmicb.2020.577474
Protection Against Allergy Study in Rural Environments (PASTURE)\textsuperscript{1,2}

Probabilities of AD with onset after the first year age

Numbers of food items*

Increased Diet Diversity

Decreased Allergic Disease

Early life diet increases butyrate production

Diet in early life

Yogurt

Butyrate

Propionate

Up to 6 years:

\downarrow Atopic sensitization

\downarrow Asthma

\downarrow Food allergy

\uparrow T reg

The association between four different measures of DD during infancy and development of FA over the first 10 years of life

DD were defined using four measures:
1. The WHO definition of minimum diet diversity at 6 m,
2. Number of foods introduced: food diversity (FD) at 3, 6 and 9 m,
3. Number of food allergens introduced: food allergen diversity (FAD) at 3, 6, 9, 12 m and
4. Number of fruit and vegetables introduced: fruit and vegetable diversity (FVD) at 3, 6 and 9 m.

Food Diversity at 6 Months/Food Allergen Diversity at 12 Months vs. Food Allergy

A: Food diversity at 6 months versus food allergy over 10 years. Multivariate analysis showed that food diversity at 6 months ($p=0.0111$) significantly reduced the odds of food allergy over the first 10 years of life (holding introduction of solids at the mean and ever having eczema: yes).

B: Food allergen diversity at 12 months versus food allergy over 10 years. Multivariate analysis showed that food allergen diversity at 12 months ($p=0.0005$) significantly reduced the odds of food allergy over the first 10 years of life (holding introduction of solids at the mean and ever having eczema: yes).

Dotted line: 95% confidence interval; solid line: p value.
In summary...

1) The gut microbiome is important in prevention via its effect on the immune system and epigenome

2) We need more data on diversity, composition and function of the microbiome
Actionable points

1) Diet and nutrition has a profound effect on the gut microbiome
2) Based on the data available advise patients, to:
   1) Limit fat intake
   2) Eat more high fiber foods
   3) Eat more home-cooked/less ultra processed foods
   4) Focused in varied dietary intake

Any questions?
Innovative approaches to food allergy prevention

Jennifer Koplin, PhD
Co-Group Leader, Population Allergy, MCRI
Director, Centre for Food and Allergy Research

Food Allergy in Australia

Prevalence of allergic diseases:
- <1%
- 1-5%
- 5-10%
- >10%
- No data

Renz H. et al. Nat. Rev. Dis. Primers 2018
Prescott S. et al. WAO Journal 2014

HealthNuts study
Melbourne, Australia 2007-2011
Peanut allergy 3%
Prevention of Food Allergy: The 5D’s

Dry skin

Diet

Vitamin D

Dogs (external microbial exposure)

Dribble (internal microbial milieu)


Prevention of Food Allergy: The 5D’s

Dry skin

Diet

Vitamin D

Dogs (external microbial exposure)

Dribble (internal microbial milieu)
Earlier peanut introduction prevents peanut allergy (in RCTs)

- Early introduction of peanut (4-11 months vs 5 years)
- Reduced peanut allergy at 5 years. (Du Toit, 2015)
- Early introduction could decrease the population peanut allergy prevalence by 44-64%. (Koplin, 2016)

However:
High risk infants: severe eczema, egg allergy, or both.
Excluded those with SPT> 4mm at entry.
3 or more times/week (6g total)

Early introduction of egg also reduced egg allergy in a combined analysis of multiple randomized controlled trials
Possibly less effective than early peanut introduction
History of Australian infant feeding guidelines

- 1990s: Guidelines recommended avoidance of allergenic foods until age 1-3 years
  - Avoidance of peanut in infancy became widespread

- 2008: Removal of advice to delay peanut and other allergenic foods
  - Small shift towards earlier introduction of peanut, but most still delayed
Changes in Australian infant feeding guidelines

Consensus Infant Feeding Guidelines – Australia 2016

- When your infant is ready, at around six months, but not before four months, start to introduce a variety of solid foods, starting with iron rich foods, while continuing breastfeeding.
- All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy and wheat products in the first year of life. This includes infants at high risk of allergy.
- Hydrolysed (partially or extensively) infant formula are not recommended for prevention of allergic disease.

Australasian Society of Clinical Immunology and Allergy Guidelines updated in 2016

NipBub website and resources developed.

---

Infant feeding in Australia after introduction of new guidelines

---

Earlier ingestion of peanut after changes to infant feeding guidelines: The EarlyNuts study

Victoria X. Soriano, BSc (Hons),*† Rachel L. Peters, MPH, PhD,*† Anne-Louise Pensoenby, MBBS, FAPHM, FRACP, PhD,*† Shayneil C. Dharmage, MBBS, MSc, MD, PhD,*† Kirsten P. Perrett, MBBS (Hons), FRACP, PhD,*‡§ Michael J. Field, MBBS, BCom/BA,*† Andrew Knox, BA (Hons), MSc, GCEnv,* Dean Tay, MBBS, FRACP,*‡§ Sasha Odell, BNS (Hons),*† Grace Gell, BSc (Hons),*† Beatriz Caminella Perez, RN, MSc (PHDC), DLSHTA,*† Katrina J. Allen, MBBS, BMedSci, FRACP, FAAAAI, PhD,*‡§ Lyle C. Gurrin, PhD,*‡§ and Jennifer J. Koplitz, PhD*‡§

Parkville, Australia

Journal of Allergy and Clinical Immunology, 2019
Two population-based studies, 10 years apart

*EarlyNuts*, 2017 - 2019, n=860 (n=1,933) and *HealthNuts*, 2007 - 2011, n=5,276

- Same recruitment methods and sampling frame
- Melbourne, Australia

1. Population sample of 12-month-olds
2. Questionnaires
3. Eczema assessment and skin prick test
4. Oral-food challenges for those sensitized

---

Many more families are now introducing peanut before 12 months

*Similar results in infants with eczema*

Introduction of egg is occurring earlier in the first year of life

Most families received advice on early allergen introduction

<table>
<thead>
<tr>
<th>Proportion of families receiving food introduction advice</th>
<th>Advice Received (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solids</td>
<td>97.3</td>
<td>96.5 – 98.1</td>
</tr>
<tr>
<td>Peanut</td>
<td>85.1</td>
<td>83.3 – 86.8</td>
</tr>
<tr>
<td>Dairy</td>
<td>88.1</td>
<td>86.5 – 89.6</td>
</tr>
<tr>
<td>Egg</td>
<td>86.5</td>
<td>84.8 – 88.1</td>
</tr>
<tr>
<td>Other Nuts</td>
<td>74.6</td>
<td>72.5 – 76.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of accurate infant food introduction advice</th>
<th>Advice Accurate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solids</td>
<td>99.0</td>
<td>98.3 - 99.4</td>
</tr>
<tr>
<td>Peanut</td>
<td>94.3</td>
<td>92.8 - 95.5</td>
</tr>
<tr>
<td>Dairy</td>
<td>80.8</td>
<td>78.5 - 82.9</td>
</tr>
<tr>
<td>Egg</td>
<td>96.2</td>
<td>94.9 - 97.2</td>
</tr>
<tr>
<td>Other Nuts</td>
<td>89.1</td>
<td>86.3 - 91.5</td>
</tr>
</tbody>
</table>

The most common source of infant feeding advice (68%) was maternal child health nurses

Tables courtesy of Sasha Odoi
Has earlier peanut introduction reduced the prevalence of peanut allergy?

*EarlyNuts*, 2017 - 2019, n=1,933 and
*HealthNuts*, 2007 - 2011, n=5,276 (**3% peanut allergy**)

- Same recruitment methods and sampling frame
- Melbourne, Australia
- 1. Population sample of 12-month-olds
- 2. Questionnaires
- 3. Eczema assessment and skin prick test
- 4. Oral-food challenges for those sensitized

---

Key demographics change in Melbourne over this time period

<table>
<thead>
<tr>
<th>Parent’s country of birth</th>
<th>HealthNuts 2007-11 % (95% CI)</th>
<th>EarlyNuts 2018-19 % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia, both</td>
<td>59.3 (57.9-60.6)</td>
<td>49.3 (46.9-51.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>East Asia, one or both</td>
<td>10.5 (9.7-11.4)</td>
<td>16.5 (14.8-18.3)</td>
<td></td>
</tr>
<tr>
<td>Other countries</td>
<td>30.2 (29.0-31.5)</td>
<td>34.3 (32.1-36.5)</td>
<td></td>
</tr>
</tbody>
</table>

Peanut allergy over 3 times more common in those with one or both parents born in Asia* 

Key demographics change in Melbourne over this time period

<table>
<thead>
<tr>
<th>Parent’s country of birth</th>
<th>HealthNuts 2007-11 % (95% CI)</th>
<th>EarlyNuts 2018-19 % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia, both</td>
<td>59.3 (57.9-60.6)</td>
<td>49.3 (46.9-51.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>East Asia, one or both</td>
<td>10.5 (9.7-11.4)</td>
<td>16.5 (14.8-18.3)</td>
<td></td>
</tr>
<tr>
<td>Other countries</td>
<td>30.2 (29.0-31.5)</td>
<td>34.3 (32.1-36.5)</td>
<td></td>
</tr>
</tbody>
</table>

- Infant eczema similar after controlling for parent country of birth
- Family history of food allergy more common in EarlyNuts

Small decrease in peanut allergy after controlling for changes in population demographics

<table>
<thead>
<tr>
<th>Peanut allergy prevalence</th>
<th>% (95% CI)</th>
<th>% Change from baseline (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed HealthNuts</td>
<td>3.1 (2.6 - 3.6)</td>
<td>Ref group</td>
<td></td>
</tr>
<tr>
<td>Unadjusted EarlyNuts</td>
<td>3.1 (2.3 - 4.1)</td>
<td>0.1 (-1.0, 1.1)</td>
<td>0.917</td>
</tr>
<tr>
<td>Adjusted EarlyNuts</td>
<td>2.6 (1.8 - 3.4)</td>
<td>-17.2 (-43.0, 13.1)</td>
<td>0.242</td>
</tr>
</tbody>
</table>

*Standardised to baseline study, HealthNuts, distribution: infant ancestry, family history of food allergy, family history of hay fever, dog ownership, number of siblings, and interactions between family history of food allergy and study.
Decrease in peanut allergy only among infants with early eczema

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>% (95% CI)</td>
<td>n/N</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>67/4140</td>
<td>1.6 (1.3-2.1)</td>
<td>22/1090</td>
<td>2.0 (1.3-3.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>73/516</td>
<td><strong>14.1 (11.4-17.4)</strong></td>
<td>20/165</td>
<td>12.1 (7.9-18.1)</td>
</tr>
</tbody>
</table>

Standardised to baseline study, HealthNuts, distribution: infant ancestry, family history of food allergy, family history of hay fever, dog ownership, number of siblings, and interactions between family history of food allergy and study.

*Early onset, moderately-severe eczema, defined as a diagnosis of eczema in the first 6 months of life, treated with topical steroids

Change in peanut allergy prevalence by parent country of birth

<table>
<thead>
<tr>
<th>Infant ancestry</th>
<th>HealthNuts</th>
<th>Unadjusted EarlyNuts</th>
<th>Adjusted EarlyNuts a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>% (95% CI)</td>
<td>n/N</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Australia</td>
<td>67/2935</td>
<td><strong>2.3 (1.8-2.9)</strong></td>
<td>12/636</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>East Asia b</td>
<td>37/493</td>
<td><strong>7.5 (5.5-10.2)</strong></td>
<td>21/220</td>
<td>9.5 (6.3-14.2)</td>
</tr>
</tbody>
</table>

Observed and predicted peanut allergy prevalence in EarlyNuts (2018-2019) compared to HealthNuts (2007-2011), stratified by parents’ country of birth. a) Standardized to baseline study, HealthNuts, variables: family history of food allergy, family history of hay fever, dog ownership, number of siblings, and interactions between family history of food allergy and study. b) Both parents born in East Asia or one parent born in East Asia and one born in Australia.

Soriano et al. Publication in progress
Association between age of peanut introduction and peanut allergy

Both parents born in Australia

One/both born in East Asia

\[ \text{Decreased risk} \]

\[ \text{aOR (95% CI)} \]

\[ 1.09 (0.51 - 2.33) \]

\[ 0.23 (0.02 - 2.20) \]

\[ 0.38 (0.09 - 1.59) \]

\[ 0.09 (0.02 - 0.51) \]

\[ 0.44 (0.06 - 3.25) \]

\[ 0.07 (0.02 - 0.34) \]

\[ \text{Diamonds} \quad \text{HealthNuts} \quad \text{EarlyNuts} \]

\[ \text{Decreased risk} \]

\[ \text{aOR (95% CI)} \]

\[ 0.71 (0.16 - 3.11) \]

\[ 2.05 (0.46 - 9.11) \]

\[ 1.02 (0.23 - 4.59) \]

\[ 2.40 (0.59 - 9.75) \]

\[ 1.00 (0.12 - 8.06) \]

\[ 1.91 (0.51 - 7.22) \]

\[ \text{Diamonds} \quad \text{HealthNuts} \quad \text{EarlyNuts} \]

Association between age of peanut introduction and peanut allergy at 1 year. Reference group is infants who delayed peanut introduction to 12 months or beyond. aOR adjusted for SES, number of siblings, childcare attendance, family history of food allergy.

The current prevalence of peanut allergy in Melbourne might have been much higher if timing of introduction had not changed

<table>
<thead>
<tr>
<th>Peanut allergy prevalence</th>
<th>n/N</th>
<th>% (95% CI)</th>
<th>% Change from baseline (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed HealthNuts (baseline)</td>
<td>156/5080</td>
<td>3.1 (2.6 - 3.6)</td>
<td>Ref group</td>
<td></td>
</tr>
<tr>
<td>Observed EarlyNuts</td>
<td>43/1405</td>
<td>3.1 (2.3 - 4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted EarlyNuts with low peanut introduction *</td>
<td>N/A</td>
<td>5.0 (3.3 - 7.3)</td>
<td>61.7 (1.6, 142.9)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

(a) Standardized to HealthNuts age of peanut introduction only.
Most reactions occurred on first exposure, few severe

- 63/1506 (4.2%) reactions before 12 months
- 51 (80.1%) reacted on first introduction
- 10 consumed again and tolerated
- 41 did not tolerate again (13 reported repeated reactions)
- 26 diagnosed peanut allergic

Symptoms:
- 35 skin only
- 3 skin and gut
- 2 wheeze/breathing difficulties
- 1 possible FPIES*

12 reacted later
- 7 diagnosed allergic (2 prior dr diagnosis)
- 1 missing

2 reacted later
- 10 consumed again and tolerated

Conclusions

- The prevalence of peanut allergy remains high despite good uptake of early peanut introduction
- Small, non-significant, decrease in the prevalence of peanut allergy after controlling for demographic changes over the past 10 years
- The decrease in peanut allergy appeared to be greater among infants with early onset eczema
- Early introduction of peanut is necessary, but not sufficient to eliminate peanut allergy
- East Asian migrants are an important group to target for early peanut introduction and food allergy prevention

*FPIES, food protein-induced enterocolitis syndrome (not IgE mediated food allergy)
Unpublished data
Prevention of Food Allergy: The 5D’s

Dry skin
Diet PrEggNut
Vitamin D VITALITY
Dogs (external microbial exposure)
Dribble (internal microbial milieu)

Prevention Trials in progress

The Vitamin D hypothesis

Ecological and epidemiological evidence suggest a link between vitamin D and food allergy

Vitamin D insufficiency at 12 months was more common in infants with food allergy in the HealthNuts cohort

<table>
<thead>
<tr>
<th></th>
<th>aOR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No food allergy</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Food allergy</td>
<td>3.08 (1.10-8.59)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Vitamin D deficiency is rising in Australia

- High rates of Vitamin D deficiency in Australia
  - 40% of Australian pregnant women develop low vitamin D (Morley MJA 2009, Teale 2010)

Australia (unlike the Northern Hemisphere)
- Does not recommend routine Vitamin D infant supplementation
- Has no vitamin D fortification of the food chain (with the exception of margarine).
- Anti skin cancer campaigns initiated in the 1970s have been highly successful (slip, slop, slap, wrap) in Australia

Can vitamin D supplementation in infants prevent food allergy in the first year of life? The VITALITY Trial

- Study design: Double-blind, randomised, placebo-controlled trial (CIA: A/Prof Kirsten Perrett)
- Participants: 2,739 infants aged 6-8 weeks, breastfed, not already receiving vitamin D
- Intervention: Vitamin D3 (Cholecalciferol) 400IU orally (or placebo) daily to 1 year
- Primary Outcome: Oral food challenge-proven food allergy at 12 months of age

2,604 infants currently enrolled, recruitment ongoing
The PrEggNut Study: RCT of maternal diet rich in eggs and peanuts during pregnancy and breastfeeding

- Study design: Multi-site, parallel, two arm, single blinded RCT (CIA: A/Prof Debbie Palmer)
- Participants: Pregnant women (<23 weeks gestation) whose infants have at least two family members with medically diagnosed allergic disease
- Intervention: High egg and peanut diet or standard (low) egg and peanut diet from <23 weeks’ gestation to 4 months’ lactation
  - **High egg diet:** at least 6 eggs and 60 peanuts per week
  - **Standard diet:** no more than 3 eggs and 30 peanuts per week
- Primary Outcome: Oral food challenge-proven egg and/or peanut allergy at age 12 months

1,171 participants randomised, recruitment ongoing

Thank you
Objectives

• To understand awareness of early introduction guideline implementation among pediatricians and allergists in the U.S.

• To understand barriers of early introduction guideline implementation among pediatricians and allergists in the U.S.

• To discuss recommendations and resources surrounding early introduction
Of children who have a food allergy, 40% are allergic to multiple foods
42% have experienced a severe reaction

8% of US children have a food allergy
~ 2 kids per classroom

Of children who have a food allergy, 40% are allergic to multiple foods
42% have experienced a severe reaction

Of children who have a food allergy, 40% are allergic to multiple foods
42% have experienced a severe reaction

Childhood Food Allergy Prevalence by Age
Physician Diagnosed

<table>
<thead>
<tr>
<th>Age</th>
<th>PEANUT</th>
<th>TREE NUT</th>
<th>MILK</th>
<th>SHELLFISH</th>
<th>EGG</th>
<th>FIN FISH</th>
<th>WHEAT</th>
<th>SOY</th>
<th>SESAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 y</td>
<td>20.2%</td>
<td>9.0%</td>
<td>53.0%</td>
<td>7.1%</td>
<td>13.5%</td>
<td>2.6%</td>
<td>14.9%</td>
<td>15.4%</td>
<td>4.6%</td>
</tr>
<tr>
<td>1 y</td>
<td>24.6%</td>
<td>8.0%</td>
<td>37.8%</td>
<td>5.1%</td>
<td>22.8%</td>
<td>6.4%</td>
<td>6.0%</td>
<td>16.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>2 y</td>
<td>24.5%</td>
<td>10.9%</td>
<td>43.5%</td>
<td>11.5%</td>
<td>14.1%</td>
<td>6.0%</td>
<td>9.9%</td>
<td>8.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>3–5 y</td>
<td>25.1%</td>
<td>15.9%</td>
<td>33.6%</td>
<td>13.0%</td>
<td>15.0%</td>
<td>6.2%</td>
<td>6.6%</td>
<td>6.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>6–10 y</td>
<td>32.8%</td>
<td>17.6%</td>
<td>24.4%</td>
<td>18.4%</td>
<td>10.8%</td>
<td>7.8%</td>
<td>6.4%</td>
<td>6.5%</td>
<td>3.3%</td>
</tr>
<tr>
<td>11–13 y</td>
<td>30.5%</td>
<td>21.3%</td>
<td>14.9%</td>
<td>20.2%</td>
<td>12.8%</td>
<td>7.1%</td>
<td>6.2%</td>
<td>3.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>≥14 y</td>
<td>29.5%</td>
<td>13.3%</td>
<td>16.0%</td>
<td>21.3%</td>
<td>6.6%</td>
<td>7.9%</td>
<td>5.4%</td>
<td>3.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Emergency Department Visits
Among Children with Food Allergy

- 1+ Lifetime ED Visit
- No Lifetime ED Visits
- 1+ Past Year ED Visit
- No ED Visits in Past Year

58% 42%
19% 81%
Prevention Guidelines

AAP Guideline Recommendations

2000
Avoid consuming peanuts until 3 years of age

2008
Recommendations revised; not sufficient data to recommend delay

2015
Learning Early About Peanut Allergy (LEAP) published in the New England Journal of Medicine

2017
Release of addendum guidelines encouraging the introduction of peanuts especially in high risk infants after testing and discussion with their physician
## Guidelines Recommendations By Risk Level

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Addendum Guideline</th>
<th>Infant Criteria</th>
<th>Recommendations</th>
<th>Earliest Age of Peanut Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>“High Risk”</td>
<td>1</td>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider evaluation by sIgE and/or SPT, and if necessary, an oral food challenge. Based on test results, introduce peanut containing foods</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>“Moderate to Low Risk”</td>
<td>2</td>
<td>Mild to moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>“Moderate to Low Risk”</td>
<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>
Role of Pediatricians and Allergists in Early Introduction


Pathway to Guideline Adherence

Awareness → Agreement → Adoption → Adherence
Role of Pediatrician (4- and 6- Month Visits)

1. Discuss and encourage early peanut introduction for infants at low-risk of developing peanut allergy.
2. Order a peanut sIgE and/or refer an infant to an allergist if the infant is at high-risk of developing peanut allergy (severe eczema and/or egg allergy).
3. Provide families with resources to educate and inform early peanut introduction.

### 4-6 month old infants

- **High Risk:** Egg Allergy and/or Severe Eczema
  - **Peanut IgE**
    - *Negative (<0.35 kU/L)*
      - Recommend introduction of peanut products at home per guidelines
    - *Positive (≥0.35 kU/L)*
      - Refer to allergy specialist for consultation/SPT protocol
      - Recommend waiting to introduce peanut pending allergist consultation
- **Moderate to Low Risk:** Mild-to-moderate eczema
  - No eczema or FA
  - Recommend introduction of peanut products at home per guidelines
Allergist Referral

Skin Prick Test

- 0-2 mm wheal
  - Low risk of reaction
  - Introduce peanut products at home OR
  - In office supervised feeding

- 3-7 mm
  - Moderate-high risk of reaction
  - In office supervised feeding OR
  - Oral food challenge

- ≥ 8 mm
  - Likely allergic

Current Guidelines for Solid Food Introduction

- The American Academy of Pediatrics (AAP) Section on Breastfeeding and Committee on Nutrition recommends:
  - introduction of solid foods around 6 months.
  - differs by child and depends on their ability to sit, head control, interest/willingness to eat food

- The AAP and the Centers for Disease Control and Prevention (CDC) recommends:
  - introducing one single-ingredient food at a time
  - observing infant for 3 to 5 days between each new food

- It is unclear what pediatricians are recommending for their patients.

Evaluating Complementary Food Introduction Recommendations Among Pediatric Practitioners

- Study Objective: To characterize pediatric clinician recommendations regarding new food introduction and waiting periods between introductions.

- An electronic survey was administered between February - April 2019.

- N= 563 pediatric practitioners
Pediatric Practitioners' Recommendations for Age of Food Introduction

<table>
<thead>
<tr>
<th>Age in months</th>
<th>Exclusively Breastfed</th>
<th>Non-Exclusively Breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months</td>
<td>31.8%</td>
<td>42.5%</td>
</tr>
<tr>
<td>5 months</td>
<td>17.9%</td>
<td>20.2%</td>
</tr>
<tr>
<td>6 months</td>
<td>47.6%</td>
<td>34.3%</td>
</tr>
</tbody>
</table>

Pediatric Practitioners’ Recommendation for First Food To Introduce to Infant

- No recommendation: 46.9%
- Infant cereal: 40.1%
- Fruits: 8.0%
- Vegetables: 1.4%
- Meats: 0.7%
- Other: 2.8%
Pediatric Practitioner Recommendations for Infants with Food Allergy Risk

Pediatric clinicians recommended waiting longer between food introductions if infant was at risk for food allergy

<table>
<thead>
<tr>
<th>Elapsed Time Before Introducing A New Food</th>
<th>% of Pediatric Practitioners</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 Day *</td>
<td>1.3%</td>
</tr>
<tr>
<td>1 Day</td>
<td>9.9%</td>
</tr>
<tr>
<td>2 Days</td>
<td>8.9%</td>
</tr>
<tr>
<td>3 Days</td>
<td>27.4%</td>
</tr>
<tr>
<td>4+ Days</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

- Recommendations for Infants with Food Allergy Risk
- General Recommendations for Infants

69.4% would change recommendations due if the infant had the following risk factors for FA:
- older siblings with food allergy (68.7%)
- moderate/severe eczema (66.4%)
- family history of food allergy (65.7%)

Pediatric practitioners more frequently recommended waiting three or more days for infants at risk of developing food allergy (66.3% vs. 38.6%, p=0.02)
Pediatric practitioners reported that allergic reactions during food introduction were infrequent

- **55.8%** reported they occurred in <5% of infants

**Recommendations on Complementary Food Introduction Among Pediatric Practitioners**

**Key Findings:**

- 217 (39%) recommended waiting 3 days or longer before introducing new foods

- However, for infants at risk for developing food allergy, 259 (66%) recommended waiting.

- Majority of practitioners (55.8%) noted food allergic reactions happened infrequently during food introduction (<5%)

- Findings indicate that current recommendations could limit infants’ food diversity and additionally could delay early peanut introduction.
## Pediatrician and Allergist Use of PPA Guidelines

<table>
<thead>
<tr>
<th>Response</th>
<th>Pediatricians (n=2,135)</th>
<th>Allergists (N=946)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using the Guidelines as published and rarely deviate from any part</td>
<td>28.7%</td>
<td>64.5%</td>
</tr>
<tr>
<td>Using only parts of the Guidelines</td>
<td>64.2%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Not using the Guidelines</td>
<td>7.2%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>


Objectives

- To survey U.S. pediatricians who provide general care to infants and assess Guideline:
  - Awareness
  - Implementation
  - Barriers and concerns
  - Needs

Methods

- A 29-question online survey was hosted by Qualtrics
  - Eligibility Criteria: Non-retired, U.S. pediatricians in general practice who have an email address on file in a vendor-provided AAP database (N=45,668)
  - Survey launched in Summer/Fall of 2018
  - Total Response Rate: 5.2%
- Survey N=1895

### Barriers/Concerns for Guideline Implementation

<table>
<thead>
<tr>
<th>Parental Concerns</th>
<th>Percent of Survey Sample Using the Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns about allergic reactions</td>
<td>36%</td>
</tr>
<tr>
<td>Concerns about blood draws</td>
<td>20%</td>
</tr>
<tr>
<td>Parents who are not interested</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Guideline Familiarity

<table>
<thead>
<tr>
<th>Guideline Familiarity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding and correctly applying the Guidelines</td>
<td>33%</td>
</tr>
<tr>
<td>The newness of the Guidelines</td>
<td>25%</td>
</tr>
</tbody>
</table>

---


---

### Barriers/Concerns for Guideline Implementation

<table>
<thead>
<tr>
<th>Pediatrician and Practice Related Issues for Implementation</th>
<th>% of Survey Sample Using the Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conducting an in-office, supervised feeding of peanut</td>
<td>32%</td>
</tr>
<tr>
<td>Lack of clinic time</td>
<td>29%</td>
</tr>
<tr>
<td>Conducting peanut-specific IgE antibody testing</td>
<td>15%</td>
</tr>
<tr>
<td>Concerns about allergic reactions</td>
<td>14%</td>
</tr>
<tr>
<td>Legal liability</td>
<td>11%</td>
</tr>
<tr>
<td>Access to an allergist for referrals</td>
<td>9%</td>
</tr>
<tr>
<td>Insufficient insurance coverage or reimbursement</td>
<td>8%</td>
</tr>
</tbody>
</table>

---

Pediatrician Guideline Education/Training

Do you believe you need more education or training on the Guidelines? (Among Survey Sample Aware of Guidelines)

- Yes (68%)
- No (32%)

Practice Aids Identified by Pediatricians

<table>
<thead>
<tr>
<th>Practice Aids for Offices</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A printed or electronic script for explaining the 2017 Guidelines to parents</td>
<td>54.6%</td>
</tr>
<tr>
<td>A printed or electronic handout to guide an in-office supervised introduction of a peanut-containing food</td>
<td>33.4%</td>
</tr>
<tr>
<td>A printed or electronic handout to guide clinical assessments and recommendations</td>
<td>59.9%</td>
</tr>
<tr>
<td>An online tutorial on 2017 Guidelines implementation</td>
<td>52.7%</td>
</tr>
<tr>
<td>Prompts in the electronic medical health record</td>
<td>32.1%</td>
</tr>
</tbody>
</table>
Conclusions

• The majority of pediatricians expressed the need for more education/training.
• Main barriers/concerns for Guideline implementation include:
  - Parental concerns about allergic reactions and blood draws
  - Pediatricians’ understanding and correctly applying the Guidelines
  - Conducting an in-office, supervised feeding of peanut
  - Lack of clinic time
• **Pediatrician education and practice support** are needed to successfully implement the Guidelines
• **Public education** for parents is also warranted.
Survey Objectives

• Among U.S. allergists/immunologists who provide food allergy services to infants, to assess:
  - Awareness
  - Implementation
  - Sources of information
  - Services provided
  - Barriers and concerns
  - Need for training

Survey Methods

• A 33 question electronic survey was developed and delivered to 3281 respondents
• Eligibility Criteria:
  - U.S. physician members of the AAAAI
  - Non-retired
  - Board certified in allergy and immunology
  - Have an email address on file
• Survey launched in Fall 2018
• 825 eligible respondents
Allergist Awareness of Guidelines

Aware (97.1%)

Not Aware (2.9%)

Allergist Implementation of Guidelines

(Among Survey Sample Aware of Guidelines)

% of survey sample

Fully Implementing 64.5

Partially Implementing 34.4

Not Implementing 1.1


Allergist Beliefs on Effectiveness of Early Introduction

Indicate your level of agreement with the following statement: The early introduction of peanut-containing foods is an effective method for the prevention of peanut allergy.

Peanut Allergy Services Offered by Allergists

- Advising parents on peanut allergy prevention: 98.9%
- Peanut-specific SPT: 98.7%
- Peanut-specific IgE: 98.3%
- Graded Oral Food Challenges with Peanut: 87.7%
- Supervised In-Office Introduction of Peanut: 85.8%

Sources of Referrals To Assess Infants

- Pediatrician: 88.1%
- Parent Self-Referral: 78.7%
- Family Medicine: 55.1%
- Dermatologist: 22.5%
- Allergist/Immunologist: 13.8%
- Internist: 6.2%

Of patients referred for early intro, how often is a peanut-specific IgE result provided by referring HCP?

<table>
<thead>
<tr>
<th>Responses</th>
<th>N = 781</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some of the time</td>
<td>74.1%</td>
</tr>
<tr>
<td>None of the time</td>
<td>20.0%</td>
</tr>
<tr>
<td>Most of the time</td>
<td>5.9%</td>
</tr>
</tbody>
</table>
Barriers/Concerns for Guideline Implementation

<table>
<thead>
<tr>
<th>Parental Concerns</th>
<th>Percent of Survey Sample Using the Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns about allergic reactions</td>
<td>47.6%</td>
</tr>
<tr>
<td>Parents who are not interested</td>
<td>28.2%</td>
</tr>
<tr>
<td>Concerns about blood draws</td>
<td>18.7%</td>
</tr>
</tbody>
</table>

Feasibility Issues and Physician Concerns for Implementation

- Lack of referrals: 33.6%
- Concerns about allergic reactions: 21.8%
- Lack of clinic time: 20.9%
- Conducting a graded oral peanut challenge: 19.5%
- Insufficient insurance coverage or reimbursement: 17.9%
- Conducting an in-office, supervised feeding of peanut: 17.6%
- Legal liability: 17.5%
Most Common Deviations from the Guidelines

<table>
<thead>
<tr>
<th>Responses*</th>
<th>N = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td>I consider additional factors (e.g., family history)</td>
<td>50.2%</td>
</tr>
<tr>
<td>I conduct a SPT in children without severe eczema or egg allergy</td>
<td>43.9%</td>
</tr>
<tr>
<td>I conduct an OFC when the Guidelines recommend home introduction or an in-office feeding</td>
<td>31.2%</td>
</tr>
<tr>
<td>I conduct an IgE test in children without severe eczema or egg allergy</td>
<td>30.8%</td>
</tr>
<tr>
<td>I use different peanut wheal size thresholds than in the Guidelines</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

*Responses are out of partial users of the Guidelines

Allergist Guideline Education/Training

Do you believe you need more education or training on the Guidelines?
(Among Survey Sample Using Guidelines)

No (54.3%)  Yes (45.7%)
Summary of Findings - Allergists

• **Essentially all allergists/immunologists** who responded to the survey reported **full or partial guidelines implementation**.

• Parental concerns and lack of referrals are major identifiable barriers.

• Allergists were likely to deviate from the guidelines for the following reasons:
  - Improved guidelines messaging to parents and referring physicians is warranted.

---

**Intervention to Reduce Early Peanut Allergy in Children**

**Goal:** To support pediatrician adherence to the early peanut introduction guidelines through a clinical decision support tool integrated into EMR.

**Ultimate Goal:** To reduce peanut allergy incidence in the U.S.

- NIH Funded U01 (AI138907)
- Practice-based, two-arm, cluster randomized controlled trial.
- Partnering with over 30 clinics in Illinois.
- >300 clinicians and >10,000 infants will be enrolled in the study.

---

**The Start Eating Early Diet Study (SEED)**

- CFAAR will enroll 1,800 infants from diverse pediatric practices in Chicago in order to:
  - Explore early infant introduction of peanut and other common food allergens (milk, egg, cashew, walnut, almond, soy, sesame) in the U.S.
  - Evaluate the impact of early introduction on food allergy development between ages 1-3.
  - Collect microbiome and other biospecimens
  - Collect extensive nutritional data
Impact

- To inform the 2025 USDA Dietary Guidelines for Americans to promote the early introduction of allergenic proteins
- To demonstrate the safety of early introduction and reduce fear among caregivers
- To prevent the development of food allergy around the world

Resources
Feeding Your Baby Solid Foods

When?
Your infant will express interest in eating solid foods between 4 and 6 months of age.

Infant Developmental Skills to Eat Food:
- Good head and neck control
- Sit up with little or no support
- Opens mouth when offered baby food
- Dribbles or takes food

What?
Recommended first foods include:
- Start with one food first. Examples include fortified baby cereal and pureed vegetable or fruit. Gradually offer new single-ingredient purees one at a time.
- Offer thin purees first, advance to mashed consistencies as baby’s palate adjusts to different textures.
- Progress infant’s diet by serving two-ingredient purees such as meat mixed with a vegetable.
- Avoid adding sugar or salt to foods.
- Infant cereal should not be given in a bottle.
- Foods to avoid for the first 12 months of life: cow’s milk, juice and honey.
- Foods to avoid until 4 years of age (choking hazards): hard, round or sticky foods such as nuts, grapes, raw carrots, candy, lollipops and peanuts.

How?
How to introduce solid foods:
- Feed your infant in a high chair and stay with your baby the whole time, watching for signs of choking.
- Allow your baby to sample small amounts of purees first, introducing one new food at a time. Gradually increase amounts offered to respond to baby’s appetite.
- Begin with one feeding per day, increase to three feedings daily with infant’s age.
- Continue to provide breast milk or infant formula during the first year of life.
- Your baby may need to be offered a new food several times before accepting the food.
- Gradually offer a variety of foods as baby adapts to new tastes and textures.

Adding Peanut Protein to Your Baby’s Diet
These are general instructions for feeding peanut-containing foods to your baby. When introducing peanut-containing foods, pick a time when your infant is healthy and able to have your full attention for at least 2 hours to watch for an allergic reaction.

Feeding Your Infant Peanut Foods:
1. Offer a small sample of thinred peanut butter on the tip of a baby’s spoon.
2. Wait 10 minutes to see how your baby responds.
3. If no allergic reaction, offer more peanut containing food. Slowly give the rest of the peanut food as your baby will accept.

Symptoms of an Allergic Reaction:
- Most symptoms include new rash or colored lves especially around the mouth.
- More severe allergic symptoms include:
  - Lip swelling
  - Widespread lves
  - Vomiting/ diarrhea
  - Skin color change
  - Wheezing
  - Receptive coughing
  - Difficulty breathing
  - Sudden fatigue

Concerned about your baby’s response to peanut? Call 911 for medical attention.

Peanut Recipe #1
Thinned, Smooth Peanut Butter
(contains 2 grams of peanut protein)

Directions:
1. Measure 2 teaspoons of smooth peanut butter. Slowly add 2-3 teaspoons of hot water.
2. Stir until peanut butter is mixed in thinned and well blended. Let cool.
3. Increase water or add infant cereal to make mixture as thin or thick as infant likes.

Start with one serving containing 2 grams of peanut protein shown above. Gradually increase to three servings weekly, adapting to your baby’s appetite and taste preferences.

Peanut Recipe #2
Smooth Peanut Butter Puree
(contains 3 grams of peanut protein)

Directions:
1. Measure 2 teaspoons of smooth peanut butter.
2. Add 2-3 teaspoons of pureed fruit or vegetables that your infant has eaten before to the peanut butter.
3. Increase or decrease the amount to make mixture as thin or thick as your infant likes.
PPA Guidelines

Eczema Categorization

Parts of Guidelines Not Used

<table>
<thead>
<tr>
<th>Survey question and responses</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which of the following statements describe parts of the 2017 Guidelines you do NOT use or ways in which you deviate from the 2017 Guidelines? (Select all that apply regardless of whether you do them routinely or occasionally) (N = 253; asked of respondents using only parts of the Guidelines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I consider additional factors, such as family history of food allergy or food allergies other than egg, in deciding whether to recommend the early introduction of peanut</td>
<td>50.2</td>
<td>43.9-56.5</td>
</tr>
<tr>
<td>I conduct a peanut-specific skin prick test in children who do not have severe eczema or egg allergy</td>
<td>43.9</td>
<td>37.7-50.2</td>
</tr>
<tr>
<td>I conduct a graded oral food challenge even when the 2017 Guidelines recommend the introduction of peanut at home or at an in-office feeding</td>
<td>31.2</td>
<td>25.6-37.3</td>
</tr>
<tr>
<td>I conduct a peanut-specific IgE test in children who do not have severe eczema or egg allergy</td>
<td>30.8</td>
<td>25.2-36.9</td>
</tr>
<tr>
<td>I rely on peanut-specific IgE results more than I rely on peanut-specific skin prick test wheal size</td>
<td>22.5</td>
<td>17.5-28.2</td>
</tr>
<tr>
<td>In making decisions about the early introduction of peanut, I use different peanut wheal size thresholds than the ones stated in the 2017 Guidelines</td>
<td>22.5</td>
<td>17.5-28.2</td>
</tr>
<tr>
<td>I do not conduct supervised in-office introductions of a peanut-containing food</td>
<td>15.4</td>
<td>11.2-20.5</td>
</tr>
<tr>
<td>I do not recommend the introduction of a peanut-containing food for a child with severe eczema and/or egg allergy until the child is older than 6 mo</td>
<td>13.4</td>
<td>9.5-18.3</td>
</tr>
<tr>
<td>I do not conduct graded oral food challenges</td>
<td>11.9</td>
<td>8.1-16.5</td>
</tr>
<tr>
<td>I recommend avoidance of peanut even when the 2017 Guidelines recommend the introduction of peanut</td>
<td>7.1</td>
<td>4.3-11.0</td>
</tr>
<tr>
<td>Other</td>
<td>2.4</td>
<td>0.9-5.1</td>
</tr>
</tbody>
</table>
The SEED Study

- A randomized controlled trial comparing the early introduction of multiple commonly allergenic foods vs. standard allergen introduction approaches in a large, representative sample of US infants.
- A total of 1800 infants will be enrolled, 900 in the intervention arm, 900 in the control arm, 250 total will be high-risk
- Allergens will be introduced every week starting at 4 months.
  - Milk, Peanut, Egg, Cashew, Walnut, Sesame, Almond, Soy
- Families will be given a choice of protein powder, protein puff, or a whole/common food option.
- Whole food choices will be determined by the study dietitian team and supplied to study patients and their families when developmentally ready.
- Food Allergy will be assessed at 12, 24, and 36 months
Secondary and Exploratory Outcomes

- To assess the efficacy, safety, and feasibility of early food allergen introduction.
- To assess infant growth and nutrition through 36 months of age and evaluate relationships to gut microbiota and other immune signatures.
- To improve predictive models for pediatric atopy (allergies and asthma) among infants.
- To assess the prevalence of asthma, eczema and allergic rhinitis at repeated time points during the three year follow up amongst the intervention group compared with the control children.
- To assess sleep, screen time use, and relational health in control arm participants.

High Risk Assessment

1000 Infants (Intervention)

- 750 Average Risk
- Start study diet
- If participant reacts to any study food at home, food allergy assessment
- 250 High Risk
  - Peanut PFT
    - ≥ 1 KU/L
      - Start study diet
    - < 3 mm
      - Start study diet
    - 3-7 mm
      - Peanut OFC
      - Controlled feeds of other foods**
  - Peanut Allergic
    - Controlled feeds of other foods**

* Consider ABAH2
** If not already in the infant’s diet