Prevention of Food Allergy

From Pre-conception to Early Post-Natal Life
Does Atopic Disease Start in Foetal Life?

[Jones et al 2000]

• Foetal cytokines are skewed to the Th2 type of response
• Suggested that this may guard against rejection of the “foreign” Foetus by the mother’s immune system
• IgE occurs from as early as 11 weeks gestation and can be detected in cord blood
Atopic Disease Start in foetal Life? (continued)

- At birth neonates have low INF-γ and tend to produce the cytokines associated with Th2 response, especially IL-4

- So why do all neonates not have allergy?
Does Atopic Disease Start in foetal Life? (continued)

- New research indicates that the immune system of the mother may play a very important role
- IgG crosses the placenta; IgE does not
- Certain sub-types of IgG (IgG1; IgG3) can inhibit IgE response
- Suggested that IgG anti-IgE antibodies suppress the Th2 response
Does Atopic Disease Start in Foetal Life? (continued)

- IgG1 and IgG3 are the more “protective” subtypes of IgG
- IgG1 and IgG3 tend to be lower than normal in allergic mothers
- In allergic mothers, IgE and IgG4 are abundant
- In mothers with allergy and asthma, IgE is high at the foetal/maternal interface
- Foetus of allergic mother may thus be primed to respond to antigen with IgE production
Significance in Practice

• Allergenic molecules demonstrated to cross the placenta and sensitize the foetus in utero
• Evidence that low dose exposure to food antigens tolerises
• Exposure to small quantities of food antigens from mother’s diet thought to tolerize the foetus, by means of IgG1 and IgG3, within a “protected environment”
• Atopic mother’s immune system may dictate the response of the foetus to antigens in utero
• The allergic mother may be incapable of providing sufficient IgG1 and IgG3 to downregulate foetal IgE
• However – there is no convincing evidence that sensitization to specific food allergens is initiated prenatally
• Current directive: the atopic mother should strictly avoid her own allergens
The Neonate: Conditions That Predispose to Th2 Response

- Inherited allergic potential (maternal and paternal)
- Intrauterine environment
- Immaturity of the infant’s immune system
- Hyperpermeability of the immature digestive mucosa
- Inflammatory conditions in the infant gut (infection or allergy) that interfere with the normal antigen processing pathway
- Increased uptake of antigens
Current Areas of Investigation to Reduce Risk of Allergy

Science to Practice
Fatty Acids and Allergy

• Theory:
  – Linoleic acid (ω-6 FA) is a precursor of arachidonic acid
  – Arachidonic acid is the precursor of secondary inflammatory mediators, especially of the pro-inflammatory prostaglandin E₂ (PGE₂)
  – PGE₂ has a strong inhibitory effect on IFN-γ and increases IL-4; thus promoting the Th2 (allergy) response
Fatty Acids and Allergy

- $\alpha$-linolenic acid, EPA and DCHA are $\omega$-3 fatty acids
- Are precursors to prostaglandins of the 3 series (PGE$_3$), which are less inflammatory than the 2 series
- Will tend to inhibit Th2 and thus promote Th1 (protective) activity
- Thus will down-regulate the allergic response
- Increased intake of fish should reduce allergy
- Old-fashioned idea of taking cod liver oil should help prevent allergy
Fatty Acids and Allergy

Omega-6 Fatty acids
  ↓
  Arachidonic acid
  ↓
  Prostaglandin PGE$_2$
  ↓
Inhibits IFN$\gamma$ (associated with Th1 response)
Allows up-regulation (increase) in IL-4 (Th2 response)
  ↓
ALLERGIC REACTION PROMOTED

Omega-3 Fatty acids
  ↓
  EPA
  ↓
  DCHA
  ↓
  Prostaglandin PGE$_3$
  ↓
PGE$_2$ is reduced
IFN-$\gamma$ is not inhibited
  ↓
ALLERGIC REACTION REDUCED
Sources of $\omega$-6 and $\omega$-3 Fatty Acids

<table>
<thead>
<tr>
<th>$\omega$-6 Fatty Acid Sources:</th>
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<tbody>
<tr>
<td>- Meats, especially red meat</td>
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<tr>
<td>- Milk and milk products, including butter, cheese, yogurt</td>
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<table>
<thead>
<tr>
<th>$\omega$-3 Fatty Acids</th>
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<tbody>
<tr>
<td>- $\alpha$-linolenic acid:</td>
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<tr>
<td>- Canola oil; Soy oil; Wheat germ oil;</td>
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<tr>
<td>- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DCHA):</td>
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<tr>
<td>- Fish, especially oily fish</td>
</tr>
<tr>
<td>- Salmon; Trout; Mackerel; Halibut</td>
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<tr>
<td>- Cod and Halibut liver oils</td>
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Conflict of Results

[Duchen et al 2000; n=120]
• Lower levels of long-chain ω-3 fatty acids in mature breast milk of mothers of atopic as compared to non-atopic infants (atopy measured during first 18 months)

[Stoney et al 2004 (n=620)]
• Higher levels of long-chain ω-3 fatty acids in colostrum of mothers of infants sensitized to foods (cow’s milk; egg; peanut: STP +)) at 6 months of age compared to those of non-sensitized infants
• Breast milk fatty acid profile was the same in atopic and non-atopic mothers:
• FA in breast milk results from maternal diet
Vitamin Supplementation and Risk of Allergy

[Milner et al 2004 (n = >8,000)]

• Vitamin supplementation in the first 6 months associated with:
  – Higher risk for asthma in black infants
  – Higher risk for food allergies in formula-fed infants

• Vitamin supplementation at 3 years of age associated with:
  – Increased risk for food allergies but not asthma
  – In both breast-fed and formula-fed children
Vitamin Supplementation and Risk of Allergy (continued)

[Matheu et al 2003 (murine study)]

- Early vitamin D supplementation augmented allergen-induced Th2 response, with production of:
  - IL-4
  - IL-13
  - IgE

- Vitamin D supplementation tends to downregulate Th1 response, with beneficial effects on development of Th1-mediated conditions such as:
  - Airway eosinophilia
  - Type 1 diabetes mellitus
Epicutaneous Exposure to Food Allergens

[Hsieh et al 2003 (murine study)]

• Patch administration of ovalbumin induced:
  – High level of ovalbumin-specific IgE
  – Elevated plasma histamine levels
  – Histological changes in intestine and lung tissue
  – Th2-predominant cellular immune response in lungs after oral challenge

• Significance of epicutaneous exposure to allergens as a result of skin testing?
Role of Micro-organisms in Preventing Food Allergy

- Commensal gut microflora might suppress Th2 response by promoting:
  - Th1 response
  - Protective SIgA production
  - TGF-ß production
- In mouse food anaphylaxis, lactobacillus:
  - Induced IL-12 production
  - Suppressed IgE-response
  - Suppressed anaphylaxis
Probiotics in Prevention of Food Allergy

Human study [Kalliomaki et al 2001]

• Mothers given lactobacillus GG antenatally
• Infants given oral lactobacillus for 6 months post-natally
• Treated group reduced risk of eczema at 2 years
• No difference in treatment and control groups:
  – Total IgE
  – Specific IgE to food allergens
  – Skin-prick tests
Summary of Current Research

1. Identification of Risk Categories

- **High risk:**
  - Atopic mother
- **Moderate risk:**
  - Atopic father
  - Atopic sibling(s)
- **Low risk:**
  - No family history of allergy
Summary of Current Research

2. Preventive Measures

- High risk:
  - Identify mother’s allergens
  - Maternal avoidance of her own allergens from preconception onwards
  - In addition, starting about two weeks prior to delivery mother avoids most highly allergenic foods throughout lactation
    - Peanuts
    - Tree nuts
    - Shellfish
    - Fish
    - Eggs
    - Milk proteins
  - Degree of avoidance of eggs and milk remains controversial
Summary of Current Research

2. Preventive Measures (continued)

• **Moderate risk**
  – No need to restrict mother’s diet prior to, or during most of her pregnancy
  – Starting two weeks prior to delivery, mother avoids the most highly allergenic foods and continues throughout early lactation
    - **Peanuts**
    - **Tree nuts**
    - **Shellfish**
    - **Fish**
    - **Eggs**
    - **Milk proteins**
  – Degree of avoidance of eggs and milk remains controversial
Summary of Current Research

2. Preventive Measures  (continued)

• Low Risk:
  – Good nutrition practices for mother from preconception onwards
  – Good nutrition practices for early infant feeding
  – Breast-feeding is the best possible source of nutrition and protection
  – Allergen avoidance is unnecessary unless the infant demonstrates signs of allergy
Summary of Current Research
2. Preventive Measures (continued)

- Low Risk:
  - Good nutrition practices for mother from preconception onwards
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Routes of Allergen Exposure in Infancy

• **Food Allergens:**
  – Placenta pre-natally (relatively uncommon and not proven)
  – Breast milk during lactation
  – Infant formulae
  – Via the skin e.g. in eczema creams and ointments; skin prick tests
  – Solid foods
  – Covertly by caretakers

• **Inhaled Allergens**
  – Dust and dust mites; Pollens; Molds
  – Tobacco smoke

• **Contact and inhalation**
  – Animal danders; Dust and dust mites
Measures to Reduce Food Allergy in Infants with Symptoms of Allergy or at High Risk Because of Genetic Background

1. Exclusive breast-feeding for the first 6 months
2. Total maternal avoidance of:
   - any food inducing allergy symptoms in the infant
   - any food inducing allergy symptoms in mother
   - eggs
   - cow’s milk and dairy products
   - peanuts
   - nuts
   - shellfish

As a preventive measure initially if not avoided in above categories {clinicians disagree about this}
Measures to Reduce Food Allergy in Infants (continued)

3. Colostrum as soon after birth as possible
4. Avoid infant formulae in the newborn nursery: NO exposure to formulae in the hospital
5. Avoid small supplemental feedings of infant formulae at widely spaced intervals
6. If formula is unavoidable introduce in incremental doses over a 3-4 week period
Measures to Reduce Food Allergy in Infants (continued)

7. Introduce solid foods after 6 months starting with the least allergenic. Use incremental dose introduction to promote oral tolerance.

8. Delay the most allergenic foods until after 12 months:
   - cow’s milk
   - eggs
   - peanuts
   - nuts
   - shellfish
   - fish
   - beef
   - chicken
   - soy
   - wheat
   - citrus fruits
   - tomatoes
Adding Solid Foods

- **Aim:** To induce tolerance and avoid sensitization
- **Method:** Incremental dose introduction of foods

**Day 1:**

**Morning** (breakfast):
0.5 teaspoon of food
Wait four hours. If no reaction:

**Noon** (lunch):
1 teaspoon of food
Wait four hours. If no reaction:

**Evening** (dinner):
2 teaspoons of food
Adding Solid Foods (continued)

Day 2:
Monitor for delayed reactions.
Give none of the new food.

Day 3:
**Morning** (breakfast):
  2 tablespoons of food
  Wait four hours. If no reaction:
**Noon** (lunch):
  ¼ cup of food
  Wait four hours. If no reaction:
**Evening** (dinner):
  As much of the food as baby wants
Adding Solid Foods (continued)

Day 4:

– Monitor for delayed reactions. Give none of the new food

No adverse reactions experienced during the four day introduction period:

– the food can be considered safe and included in the diet

Adverse reaction occurs at any time during the test period:

– STOP
  – do not give any more of the test food

• Wait at least two months before testing that food again
• Wait 48 hours after all symptoms have subsided before starting to introduce another new food
Sequence of Adding Solid Foods for the Allergic Baby

• Cereals:
  – At 6 months:
    • Rice
    • Tapioca
    • Arrowroot
    • Millet
  – After 9 months:
    • Barley
    • Oats
  – After 12 months:
    • Corn
    • Wheat
    • Quinoa
    • Amaranth
Sequence of Adding Solid Foods for the Allergic Baby

• Fruit and Juices:
  – At 6 months (cooked at first):
    • Pear
    • Apricot
    • Peach
    • Plum
    • Grape
    • Apple
  – after 12 months:
    • Citrus fruits
    • Berries
    • Banana
    • Tomato
Sequence of Adding Solid Foods for the Allergic Baby

- **Vegetables**
  - At 6 months (cooked at first):
    - Sweet potato
    - Squashes
    - Parsnip
    - Broccoli
  - After 12 months:
    - Legumes (peas, beans, lentils)
    - Spinach
    - Yam
    - Turnip
    - Carrot
    - Cauliflower
Sequence of Adding Solid Foods (continued)

• Meat:
  – At six months:
    • lamb   • turkey
  – after 9 months:
    • veal
  – after 12 months:
    • chicken   • beef   • pork

• Eggs:
  – after 12 months:
    • test yolk first
    • white later
Sequence of Adding Solid Foods (continued)

• Milk and Milk Products
  – At or after 12 months:
    • Start with full cream milk, full cream yogurt, or equivalent
• After 12 months:
  – Fin fish (not shellfish)
• After 2 years
  – Shellfish
  – Peanuts
  – Tree nuts
  – Seeds
  – Chocolate