Prevention of Food Allergy: From Pre-conception to Early Post-Natal Life

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The Allergic Diathesis

Atopic dermatitis (Eczema)

Gastrointestinal symptoms

Food Allergy

Asthma (cough; wheeze)

Anaphylaxis

Failure to thrive
Sleep deprivation
Irritability

Allergic rhinoconjunctivitis (hay fever)
Age Relationship Between Food Allergy and Atopy

Adapted from Holgate et al 2001

![Graph showing the relative incidence of asthma, rhinitis, eczema, and food allergy over age](image-url)
Perceived Risks Associated with Infant Food Allergy

- Anaphylaxis – may be life-threatening
- Nutritional insufficiency and failure to thrive
- Promotion of the “allergic march”:

  Food allergy
  ↓
  Atopic dermatitis/eczema
  ↓
  Asthma
Prevention of Food Allergy in Clinical Practice

Requirement:

• Practice guidelines for:
  – Prevention of sensitization to food allergens
  – Prevention of expression of allergy

• Consensus for practice guidelines using evidence-based research

Current status:

• Lack of consensus
Possible Confounding Variables in Studies and Subjects

- Variability in genetic predisposition of infant to allergy
- Mother’s allergic history
- Role of in utero environment and exposure to allergens
- Exclusivity of breast-feeding
- Inclusion of infant’s allergens in mother’s diet
- Dietary exposure not recognized in infant or mother
- Exposure to inhalant and contact allergens
Immune Response in Allergy
The Hypersensitivity Reactions:
Antigen Recognition

- The first stage of an immune response is recognition of a “foreign antigen”
- T cell lymphocytes are the “controllers” of the immune response
- T helper cells (CD4+ subclass) identify the foreign protein as a “potential threat”
- Cytokines are released
- The types of cytokines produced control the resulting immune response
There are two subclasses of T-helper cells, differentiated according to the cytokines they release:

- Th1
- Th2

Each subclass produces a different set of cytokines.
Cytokines of the T-Cell Subclasses

• TH1 subclass produces:
  » Interferon-gamma (IFN-γ)
  » Interleukin-2 (IL-2)
  » Tumor necrosis factor alpha (TNFα)

• TH2 subclass produces:
  » Interleukin-4 (IL-4)
  » Interleukin-5 (IL-5)
  » Interleukin-6 (IL-6)
  » Interleukin-8 (IL-8)
  » Interleukin-10 (IL-10)
  » Interleukin-13 (IL-13)
T-helper cell subtypes

- Th1 triggers the *protective response* to a pathogen such as a virus or bacterium
  - IgM, IgG, IgA antibodies are produced

- Th2 is responsible for the *Type I hypersensitivity reaction (allergy)*
  - IgE antibodies are produced
TH1 ↔ TH2 Interactions

Factors promoting:

**Th1**
- Bacterial and viral infections
- Maturation of the immune system
- Antigen tolerance

**Th2**
- Parasite infestations
- Immature immune system
- Sensitization to antigen
TH1 ↔ TH2 Interactions

Factors promoting:

Th1
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- Maturation of the immune system
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Th2
- Parasite infestations
- Immature immune system
- Sensitization to antigen

Predisposing factors:
- Genetic inheritance
- Early exposure to allergen
- Increased antigen uptake
Example of Interaction of Cytokines

• When Th1 predominates, Th2 is suppressed: the “hygiene theory” of allergy
• Conversely, Th2 cytokines (allergy) suppress Th1 cytokines (protection against infection)
  – Results in decrease in the level of immune protection against microorganisms
  – Infection by normally harmless bacteria can occur
Example of Interaction of Cytokines (continued)

- Clinical example:
  - In atopic dermatitis (eczema) the Th2 response in skin tissues suppresses the protective Th1
  - Increase in IL-4; decrease in INF-γ
  - Results in high potential for infection by normally harmless bacteria on the skin
Does Atopic Disease Start in Fetal Life?

[Jones et al 2000]

- Fetal cytokines are skewed to the Th2 type of response
- Suggested that this may guard against rejection of the "foreign" fetus by the mother’s immune system
- IgE occurs from as early as 11 weeks gestation and can be detected in cord blood
Does Atopic Disease Start in Fetal 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 Fetal 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 Fetal 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 fetal/maternal interface
- Fetus 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 fetus in utero
- Evidence that low dose exposure to food antigens tolerizes
- Exposure to small quantities of food antigens from mother’s diet thought to tolerize the fetus, by means of IgG1 and IgG3, within a “protected environment”
Significance in Practice  continued

- Atopic mother’s immune system may dictate the response of the fetus to antigens in utero
- The allergic mother may be incapable of providing sufficient IgG1 and IgG3 to downregulate fetal 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
Immune System of the Normal Neonate

- Is immature
- Major elements of the immune system are in place
- But do not function at a level to provide adequate protection against infection
- The level of immunoglobulins (except maternal IgG) is a fraction of that of the adult
Immune System of the Normal Neonate

- Phagocytes can engulf foreign particles
- But their killing capacity is negligible during the first 24 hours of life
- The function of the lymphocytes is not fully developed
- Human milk provides the deficient components
Breast-feeding and Allergy

Studies indicating that breast-feeding is protective against allergy report:

– A definite improvement in infant eczema and associated gastrointestinal complaints when:
  • Baby is exclusively breast-fed
  • Mother eliminates food allergens from her diet
– Reduced risk of asthma in the first 24 months of life
Breast-feeding and Allergy

- Other studies are in conflict with these conclusions:
  - Some report no improvement in symptoms
  - Some suggest symptoms get worse with breast-feeding and improve with feeding of hydrolysate formulae
  - Japanese study suggests that breast-feeding increases the risk of asthma at adolescence
  - Why the conflicting results?
Immunological Protection

• Agents in human milk:
  – Provide passive protection of the infant against infection during lactation
    • Mother’s system provides the protective factors
  – Stimulate the immune system of the baby to provide active protection
    • Infant’s own system makes the protective factors
  – The effects may last long after weaning
Characteristics of Protective Factors Provided by Breastfeeding

- Persist throughout lactation
- Resist digestion in the infant’s digestive tract
- Protect by non-inflammatory mechanisms
- Stimulate maturation of the infant’s immune system
- Are the same as at mucosal sites (e.g. in the lining of the digestive tract)
- Promote establishment of a protective microbial population in the infant’s digestive tract
Immunological Factors in Human Milk that may be Associated with Allergy: Cytokines and Chemokines

- Atopic mothers tend to have a higher level of the cytokines and chemokines associated with allergy in their breast milk

- Those identified include:
  - IL-4 - IL-5
  - IL-8 - IL-13
  - Some chemokines (e.g. RANTES)

- Atopic infants do not seem to be protected from allergy by the breast milk of atopic mothers
Immunological Factors in Human Milk that may be Associated with Allergy: TGF-β1

- Cytokine, transforming growth factor-β1 (TGF-β1) promotes tolerance to food components in the intestinal immune response
- TGF-β1 in mother’s colostrum may influence the type and intensity of the infant’s response to food allergens
- A normal level of TGF-β1 is likely to facilitate tolerance to food encountered by the infant in mother’s breast milk and later to formulae and solids
• TGF-β1 in mothers of infants who developed IgE-mediated CMA (+challenge; + SPT) lower than in:
  – Mothers of infants with non-IgE mediated CMA (+ challenge; - SPT)
  – Mothers of infants without CMA (- challenge; - SPT)

[Saarinen et al 1999]
Immunological Factors in Human Milk that may be Associated with Allergy: SIgA

- TGF-β1 seems to be involved in antibody class-switching to IgA
- Inhibits class switch to IgE
- Lower TGF-β1 therefore might lead to lower sIgA, and thus less protection at the mucosal surface of the infant’s digestive tract
- May result in sensitization to allergens in foods via increased IgE production
- Some studies show no evidence of lower SIgA in allergic infants
Significance in Practice

• Colostrum should be the first fluid encountered by the neonate, regardless of the atopic status of the mother
  – Provides sIgA as well as other protective and maturation factors

• Atopic mothers should avoid:
  – Their own allergens during pregnancy and lactation
  – In addition, the most highly allergenic foods during lactation, starting about 2 weeks prior to delivery
Significance in Practice (continued)

• Non-atopic mothers need not restrict their diet
  – exposure to small quantities of food antigens in breast milk should tolerize infant
• Exclusive breast-feeding for at least 4-6 months for infants with potential for allergy to avoid sensitization from external food allergens
• Non-atopic mother needs to avoid foods only if the infant has already been sensitized to them and demonstrates obvious signs of allergy
Development of Allergy in Breast-Fed Infants:
Cow’s Milk Allergy as a Model

- CMA tends to be the first food to elicit symptoms of allergy
- Usually cow’s milk antigens are the first foreign proteins encountered by the infant
- Symptoms of CMA commonly appear during the first year of life
- In 75%-90% of allergic infants within the first month
- Symptoms appear within days or weeks after the infant’s first exposure to cow’s milk
- Incidence of CMA in breast-fed infants who have never been given cow’s milk is reported 0.4%-0.5%
Diagnosis of Cow’s Milk Allergy in the Breast-Fed Infant

• No laboratory tests have proven to be diagnostic of clinical disease
  – Skin prick tests (SPT) are reported as positive in about 45%-47% of infants with immediate-onset symptoms
  – SPT positive in only 17% with delayed-onset symptoms
  – Infants under 6 months may have immediate-onset symptoms on challenge, but SPT negative
  – SPT may become positive in second half of the first year
  – Some practitioners suggest skin-prick test with mother’s breast milk as allergen
Diagnosis of Food Allergy in the Breast-Fed Infant

• Reliable diagnosis is based on elimination and challenge:
  – All sources of cow’s milk or suspect food allergen protein are eliminated from the infant’s and the mother’s diet
  – Symptoms of allergy in the infant resolve
  – Identical symptoms occur during food challenge
  – Symptoms again disappear on elimination of all sources of the suspect food
  – In suspected CMA, lactose intolerance must be ruled out
Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Challenge is implemented two to four weeks after elimination of cow’s milk or food allergen
  - Before feeding, place drop of the food on outer border of infant’s bottom lip
  - Observe for 20 minutes for reddening, irritation
  - If irritation occurs do not give food by mouth
Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

• Cow’s milk and other food challenges can be carried out directly by feeding the food to the infant in incremental doses:
  – Place a drop on the infant’s tongue and monitor for symptoms for an hour
  – Feed small quantities at one hour intervals:
    2.5 mL (½ teaspoon)
    5 mL (1 teaspoon)
    10 mL (2 teaspoons)
Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

• **Challenge via mother’s breast milk**
  – Mother consumes increasing doses of the suspect allergen at one-hour intervals:
    100 mL or \( \frac{1}{4} \) cup
    200 mL or \( \frac{1}{2} \) cup
    400 mL or 1 cup
  – Ad lib feedings of breast milk by the infant
  – Continues over the next day with free consumption of the food by the mother

• **Double-blind Placebo-controlled food challenge (DBPCFC)** is usually unnecessary in infants under one year of age
Diagnosis of Food Allergy in the Breast-Fed Infant (continued)

- Symptoms can be caused by as little as 5mL cow’s milk ingested by the mother
- Other foods may be more, or less, allergenic
- More commonly several hundred mLs are needed to elicit symptoms
- Symptoms usually occur 20 minutes to several hours after breast-feeding
- May appear only after accumulated doses on the second day
Suggested Sources of Sensitizing Food Allergens

• Present thinking is that sensitization occurs predominantly from external sources
• The antigens in mother’s milk then elicit symptoms in the previously sensitized infant
• However, new research suggests that sensitization via breast milk may occur in the atopic mother and baby pair: this remains to be proven
Suggested Sources of Sensitizing Food Allergens (continued)

• Suggested food sources of allergens:
  – Infant formulae, especially in the new-born nursery before first feeding of colostrum
  – Solid foods
  – Covertly by caretakers
  – Accidentally

• Inhalation of allergens
Suggested Non-Fed Sources of Sensitizing Food Allergens

• Through the skin (especially when eczema is present)
  – In eczema creams and ointments (especially peanut protein)
  – Milk proteins in non-food articles e.g. diaper rash ointment; paper coating; cosmetics; pet foods
  – Kissing on cheek after consumption of food e.g. milk; peanut butter
  – Skin prick tests
Summary of the Protective Effect of Breastfeeding on Development of Allergy

• Differing reports on the role of breastmilk in protecting against the development of allergy:
  
  Food allergy; Eczema; Asthma; Rhinitis;

• May reflect the combined effect of inheritance and atopy in the mother

• Recent research seems to suggest that when the infant inherits atopy from the father, mother’s breastmilk is protective against allergy

• When inherited from the mother, breastmilk is not protective against the development of allergy
Implications of Research Data

• Exclusive breast-feeding with exclusion of infant’s known allergens will protect the child against allergy if it is inherited from the father

• Exclusive breast-feeding with exclusion of mother’s and baby’s allergens will reduce signs of allergy in the first 1-2 years

• Reduction or prevention of early food allergy by breast-feeding does not seem to have long-term effects on the development of asthma and allergic rhinitis
Foods Most Frequently Causing Allergy

1. Egg
   » white
   » yolk
2. Cow’s milk
3. Peanut
4. Nuts
5. Shellfish
6. Fin fish
7. Wheat
8. Soy
9. Beef
10. Chicken
11. Citrus fruits
12. Tomato
Current Recommendations for Practice

• If mother is atopic:
  – Mother eliminates all sources of her own allergens during pregnancy to attempt to reduce IgE and IgG4 in the uterine environment
  – Continues to avoid her own allergens during lactation
  – Mother consumes adequate quantities of ω-3 oils, especially fish
    • if she is allergic to fish substitute soy oil, canola oil
  – Exclusive breast-feeding without exposure of infant to external sources of food allergens for 6 months
Current Recommendations for Practice (continued)

• If father is atopic, but mother is not:
  – No recommendations for mother to restrict her diet during pregnancy
  – No recommendations for mother to restrict her diet during lactation unless the baby shows signs of allergy
  – Exclusive breast-feeding for 4-6 months
Current Recommendations for Practice (continued)

- If infant demonstrates overt signs of allergy (eczema; gastrointestinal complaints; rhinitis; wheeze)
  - Identify specific food trigger by elimination and challenge
  - Exclusive breast-feeding with mother excluding her own and baby’s food allergens
- Careful monitoring of mother’s diet for nutritional adequacy, especially of vitamins and trace elements
Current Recommendations for Practice (continued)

- Allergic mother may need to avoid the most highly allergenic foods during lactation, even if she is not allergic to them:
  - Peanuts
  - Tree nuts
  - Cow’s milk
  - Eggs
  - Shellfish

- Benefits of this remain to be proven, but at present the strategy is indicated and recommended
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 ($\text{PGE}_3$), 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 PGE₂

Inhibits IFNγ (associated with Th1 response)
Allows up-regulation (increase) in IL-4 (Th2 response)

 ALLERGIC REACTION PROMOTED

Omega-3 Fatty acids

↓

EPA

↓

DCHA

↓

Prostaglandin PGE₃

PGE₂ is reduced
IFN-γ is not inhibited

 ALLERGIC REACTION REDUCED
Sources of ω-6 and ω-3 Fatty Acids

• ω-6 Fatty Acid Sources:
  – Meats, especially red meat
  – Milk and milk products, including butter, cheese, yogurt

• ω-3 Fatty Acids
  – α-linolenic acid:
    • Canola oil; Soy oil; Wheat germ oil;
  – Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DCHA):
    • Fish, especially oily fish
    • Salmon; Trout; Mackerel; Halibut
    • Cod and Halibut liver oils
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
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-β 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
  – Degree of avoidance of eggs and milk remains controversial
    • Shellfish
    • Fish
    • Eggs
    • Milk proteins
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 ∙ Shellfish ∙ Eggs
    • Tree nuts ∙ Fish ∙ 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