

Management of Pediatric Food Allergy



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Clinical Signs of Food Allergy According to Age in Infancy

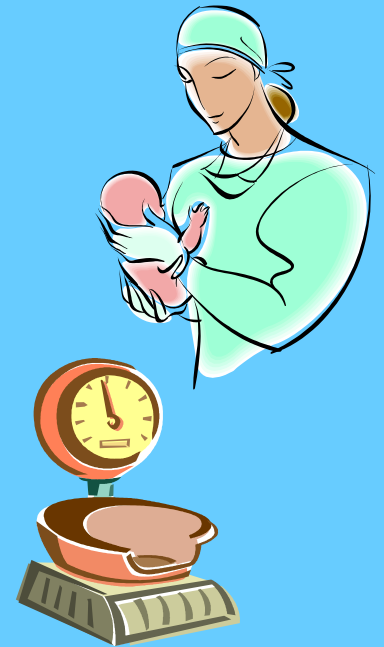
- Less than 20 months of age:
 - Atopic dermatitis (eczema)
 - Gastrointestinal disturbances
 - Immediate food reactions
- Later childhood:
 - Wheezing
- All stages:
 - Rhinitis



Symptoms Suggesting Allergy in the Infant: Digestive Tract

- Persistent colic
- Diarrhea
- Frequent “spitting up”
- Feeding problems

Poor or no weight gain when all other causes have been investigated and ruled out



Symptoms Suggesting Allergy in the Infant: Skin

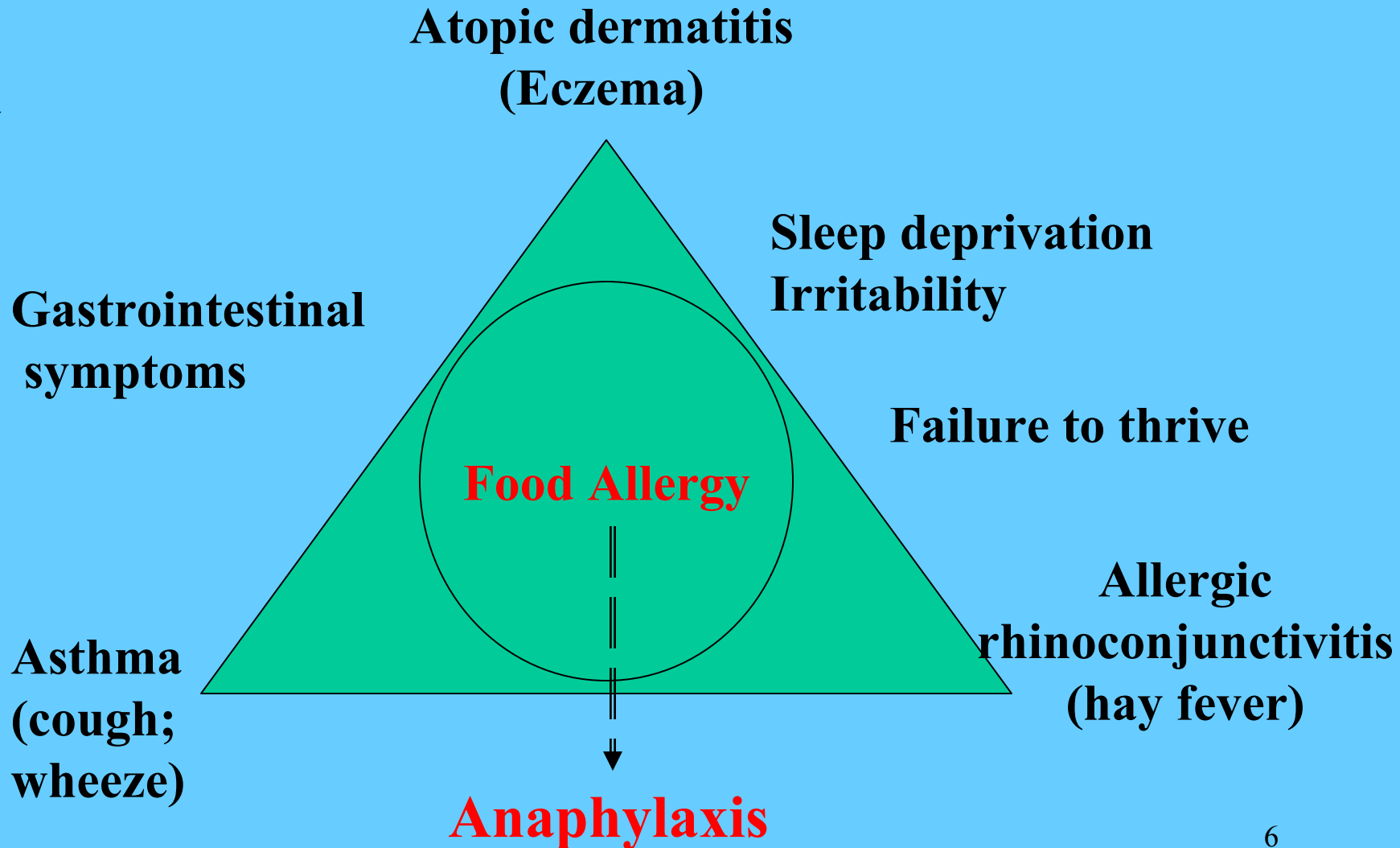
- Urticaria (hives)
- Dry, itchy skin
- Persistent diaper rash
- Redness around anus
- Redness on cheeks
- Scratching and rubbing
- Rash
- Atopic dermatitis/Eczema



Symptoms Suggesting Allergy in the Infant: Respiratory Tract

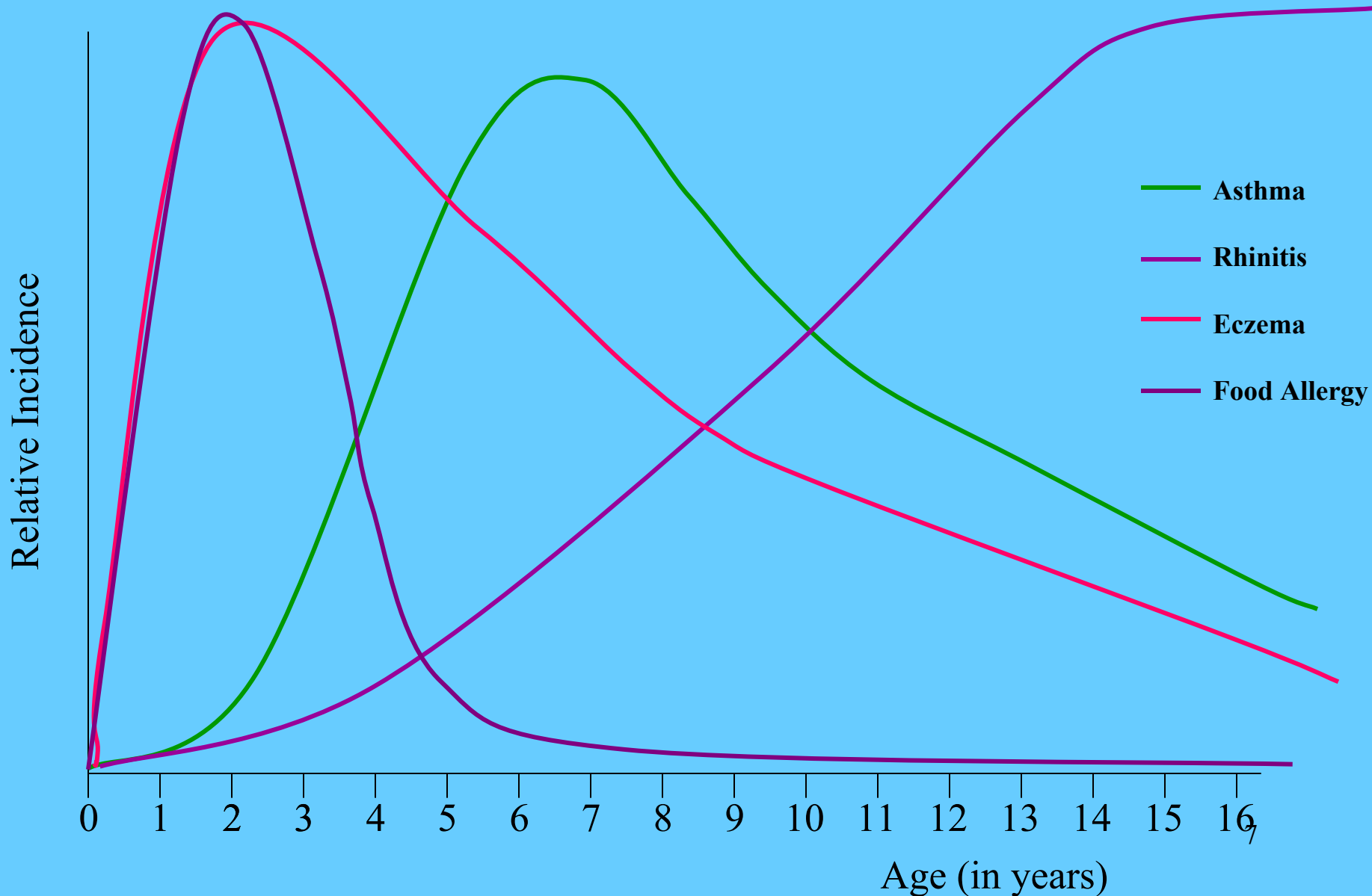
- Rhinitis
- Persistent cough
- Nose rubbing
- Noisy breathing
- Wheezing
- Sneezing
- Itchy, runny, reddened eyes
- Atopic conjunctivitis
- Serous otitis media (earache with effusion)

The Allergic Diasthesis



Age Relationship Between Food Allergy and Atopy

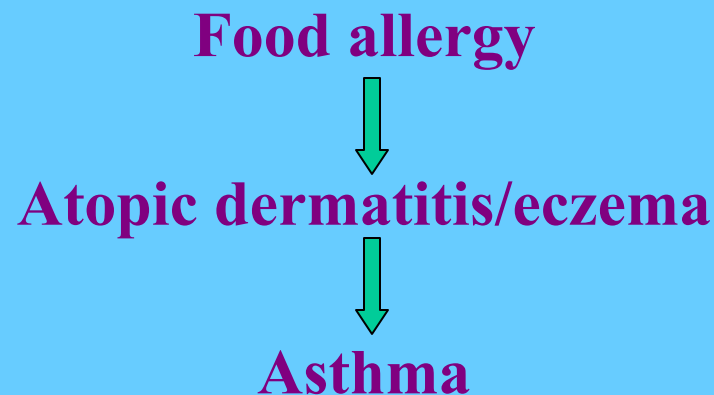
{Adapted from Holgate et al 2001}



Perceived Risks Associated with Infant Food Allergy

Preventable?

- Anaphylaxis – may be life-threatening ✓
- Nutritional insufficiency and failure to thrive ✓
- Disruption of maternal/infant bonding and family dynamics ✓
- Promotion of the “allergic march”:



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Approach to Infant Allergy

- **Prediction**
 - Identification of the atopic baby before initial allergen exposure may allow prevention of allergy
- **Prevention**
 - Measures to prevent initial allergic sensitization of potentially atopic infant
- **Identification**
 - Methods for identification of an established food allergy
- **Management**
 - Strategies for avoiding the allergenic food and providing complete balanced nutrition from alternative sources to ensure optimum growth and development

Prediction: Factors Contributing to Food Allergy in Infants

- **Family history of allergy**
- **Developmental immaturity in:**
 - **Digestive tract**
 - **Immune system**
 - **Enzyme systems**



Prevention of Food Allergy in Clinical Practice

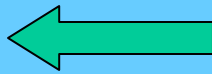
Requirement:

- 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
- 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

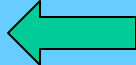
The Hypersensitivity Reactions: Antigen Recognition


- 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

T-helper Cell Subclasses

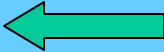

- There are two subclasses of T-helper cells, differentiated according to the cytokines they release:
 - Th1
 - Th2
 - Each subclass produces a different set of cytokines

Cytokines of the T-Cell Subclasses

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

- 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

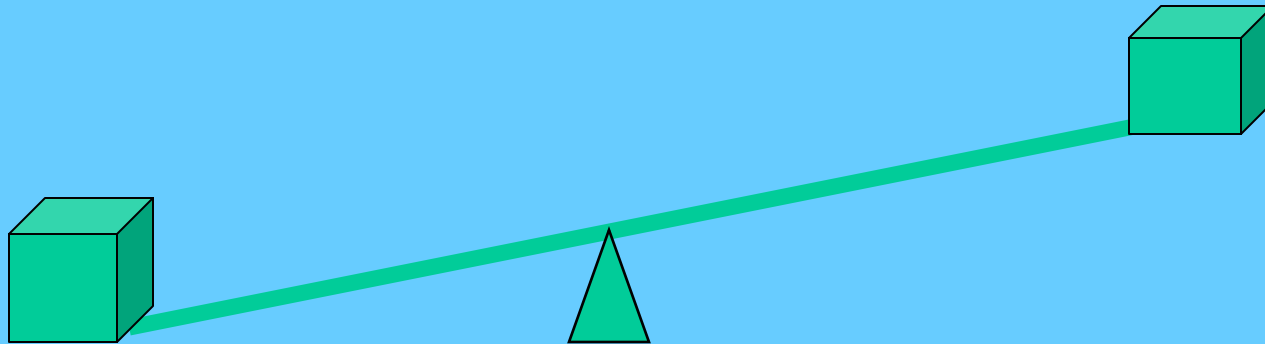
Factors promoting:

Th1

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

Th2

- Parasite infestations
- Immature immune system
- Sensitization to antigen



TH1 ↔ TH2 Interactions

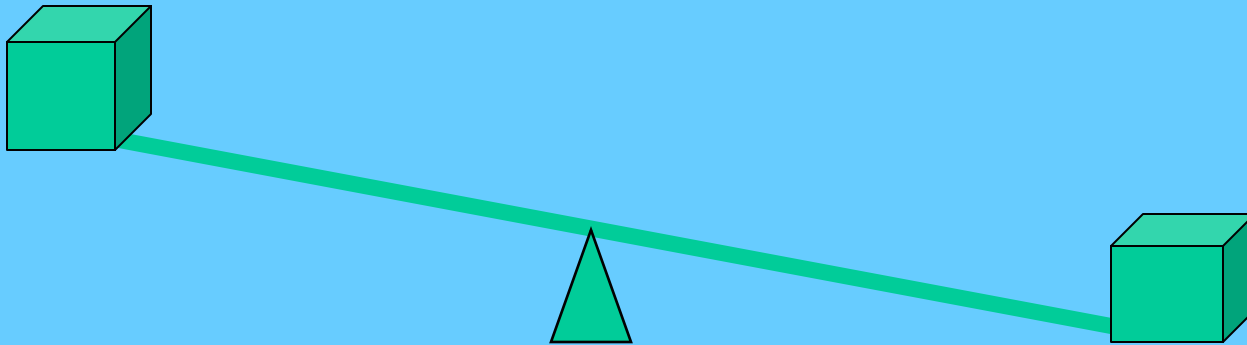
Factors promoting:

Th1

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Th2

- Parasite infestations
- Immature immune system
- Sensitization to antigen



Predisposing factors:

- Genetic inheritance
- Early exposure to allergen
- Increased antigen uptake

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 in *expression* of allergy in the neonate and infant
- IgG crosses the placenta; IgE does not
- Certain sub-types of IgG (IgG1; IgG3) can inhibit IgE 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

- Food proteins demonstrated to cross the placenta and can be detected in amniotic fluid
- Allergen-specific T cells in fetal blood demonstrated to:
 - Ovalbumin
 - Alpha-lactalbumin
 - Beta-lactoglobulin
- 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
 - 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
 - Secretory IgA (sIgA) absent at birth: provided by maternal colostrum and breast milk throughout lactation

The Neonate:

Conditions That Predispose to Th2 Response

- Increased uptake of antigens:
 - Hyperpermeability of the immature digestive mucosa
 - Immaturity of the gut-associated lymphoid tissue (GALT) means reduced effectiveness of antigen processing at the luminal interface
 - Inflammatory conditions in the infant gut (infection or allergy) that interfere with the normal antigen processing pathway

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 highly allergenic foods 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
[Miyake et al 2003]
- Why the conflicting results?

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- β 1

- Cytokine, transforming growth factor- β 1 (TGF- β 1) promotes tolerance to food components in the intestinal immune response
- TGF- β 1 in mother's colostrum may influence the type and intensity of the infant's response to food allergens
- A normal level of TGF- β 1 is likely to facilitate tolerance to food encountered by the infant in mother's breast milk and later to formulae and solids

Immunological Factors in Human Milk that may be Associated with Allergy: TGF- β 1 (continued)

[Saarinen et al 1999]

- TGF- β 1 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)

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
- Exposure to food antigens in breast milk normally tolerizes infant to foods
- However, recent research suggests that sensitization via breast milk may occur in the atopic mother and baby pair: this remains to be proven

Foods Most Frequently Causing Allergy in Babies and Children

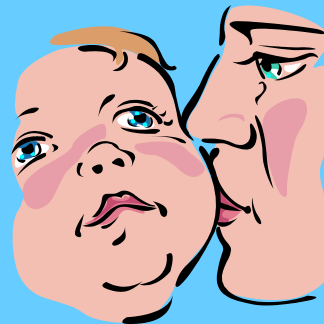
1. Egg
 - » white
 - »yolk
2. Cow's milk
3. Peanut
4. Nuts
5. Shellfish
6. Fin fish
7. Wheat
8. Soy
9. Beef
10. Chicken
11. Citrus fruits
12. Tomato

Sources of Sensitizing Allergens

- Suggested food sources of allergens:
 - Infant formulae, especially in the new-born nursery before first feeding of colostrum
 - Solid foods
 - Covertly by caretakers
 - Accidentally
- Inhaled Allergens
 - Dust and dust mites; Pollens; Molds; Animal danders
 - Tobacco smoke
- Contact
 - Animal danders
 - Dust and dust mites

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 and patch tests



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

From Science to Practice

Identification of Risk Categories

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

Current Recommendations for Practice

Preventive Measures

High Risk

- Mother is atopic:
 - Mother eliminates all sources of her own allergens prior to and during pregnancy to reduce IgE and IgG4 in the uterine environment
 - Continues to avoid her own allergens during lactation
 - Exclusive breast-feeding without exposure of infant to external sources of food allergens for 6 months

Current Recommendations for Practice (continued)

Moderate Risk

- Father and or siblings atopic; mother is non-atopic:
 - 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)

- Some studies suggest that maternal avoidance of the most highly allergenic foods during lactation may reduce sensitization of infant in high and moderate risk categories
- Foods to be avoided:
 - **Peanuts** - **Tree nuts** - **Shellfish**
 - **Fish** - **Eggs** - **Milk**
- Benefits of this remain to be proven
- Hypoallergenic infant formulae if breast-feeding not possible

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**
 - **If breast-feeding is not possible, hypoallergenic infant formulae**
- Careful monitoring of mother's diet during lactation for nutritional adequacy, especially of vitamins and trace elements

From Science to Practice

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

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):

½ 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):

$\frac{1}{4}$ 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 reaction 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:**

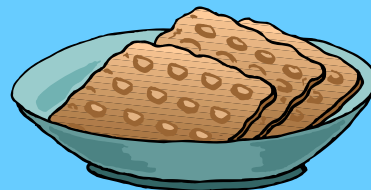
- Rice
 - Tapioca
 - Arrowroot
 - Millet
 - Quinoa
 - Amaranth

- **After 9 months:**

- Barley
 - Oats

- **After 12 months:**

- Corn
 - Wheat



Sequence of Adding Solid Foods for the Allergic Baby

- Fruit and Juices:

- **At 6 months** (cooked at first):

- Pear
 - Plum
 - Apricot
 - Grape
 - Peach
 - Apple

- **after 12 months:**

- Citrus fruits
 - Tomato
 - Berries

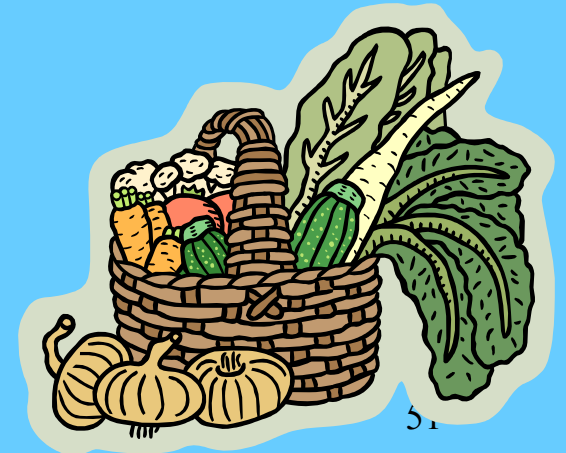


- Banana



Sequence of Adding Solid Foods for the Allergic Baby

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



Sequence of Adding Solid Foods (continued)

- Meat:

- **At six months:**

- lamb • turkey

- **after 9 months:**

- veal

- **after 12 months:**

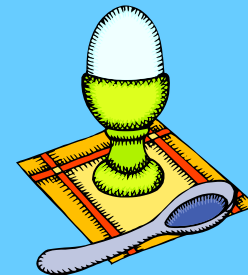
- chicken • beef • pork



- 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



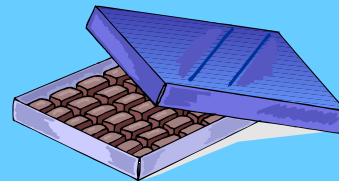
- **After 12 months:**

- Fin fish (not shellfish)



- **After 2 years**

- Shellfish
 - Chocolate
 - Seeds
 - Tree nuts
 - Peanuts*



* Some authorities recommend delaying until after 3 years

Most Common Allergens Relative to Peak Age of Food Sensitivity

[Hannuksela, 1983]

Years

Foods

0-2

Milk, Egg, Soy, Fish, Pea, Banana,

2-7

**Egg, Soy, Fish, Nuts, Apple, Pear, Plum,
Carrot, Celery, Tomato, Spices**

Over 7

**Fish, Nuts, Apple, Pear, Plum,
Carrot, Celery, Tomato, Spices**

Development of Tolerance

[Sampson et al, 1989]

To Specific Foods :

- After 1 year:
 - **26% decrease in allergy to:**
 - Milk
 - Soy
 - Peanut
 - Egg
 - Wheat
 - **2% decrease in allergy to other foods**
- Allergy to some foods more often than others persists into adulthood:
 - Peanut
 - Shellfish
 - Soy
 - Tree nuts
 - Fish

Prognosis

- Most infants will outgrow milk allergy by 3 years of age, but may become intolerant to other foods
- About 25% will develop respiratory allergies

[Study: Bishop et al 1990]

- **Age at which milk was tolerated by milk-allergic children:**
 - 28% by 2 years of age
 - 56% by 4 years of age
 - 78% by 6 years of age
- **Additional observations of children studied:**
 - 50% were also allergic to egg and soy
 - 30% to peanut