

Viewing Time

The program will take up to one hour to complete.

Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

It is the policy of Children's Hospitals and Clinics of Minnesota to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. Our faculty have been asked to disclose to our program audience any real or apparent conflicts of interest related to the content of their presentation. They have also been requested to let you know when any product mentioned in their presentation is not labeled for the use under discussion or is still under investigation.

Faculty Disclosure

Allan Stillerman, MD has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Stillerman** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

Natural History of Food Allergy – An Update

Allan Stillerman, MD
Allergy & Asthma Specialists, P.A.
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Natural History of Food Allergy – An Update

A lecture presenting new information on the natural history of food allergy to cow's milk, egg protein, and peanut, as well as defining the Allergist's approach to determining persistence of food allergy or development of tolerance in the individual patient.

Program Objectives

Upon completion of this program, participants should be able to:

- Recognize the new information on natural history of food allergy to cow's milk.
- Recognize the new information on natural history of food allergy to egg protein.
- Recognize the new information on natural history of food allergy to peanut.
- Recognize an Allergist approach to determining persistence of food allergy or development of tolerance in the individual patient.

Disclaimer

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Accreditation

Children's Hospitals and Clinics of Minnesota is accredited by the Minnesota Medical Association to provide continuing medical education for physicians. Children's Hospitals and Clinics of Minnesota designates this educational activity for a maximum of 1 AMA PRA Category 1 Credits™ toward the AMA Physician's Recognition Award. Each physician should only claim those credits that he/she actually spent in the activity.

Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

Natural History of Food Allergy – An Update
Refining The Diagnosis of Food Allergy - Who Had It.

Allan Stillerman, M.D.
Allergy & Asthma Specialists, P.A.
and
Clinical Research Institute
WestHealth-Plymouth
Medical Arts Bldg-Minneapolis
Maple Grove

Objectives

1. Participant will recognize the new information on
 - a. Natural history of food allergy to peanut
 - b. Natural history of food allergy to egg protein
 - c. Natural history of food allergy to cow's milk.
2. Recognize an Allergist approach to determining
 - a. Persistence of food allergy or
 - b. Development of tolerance in the individual patient.

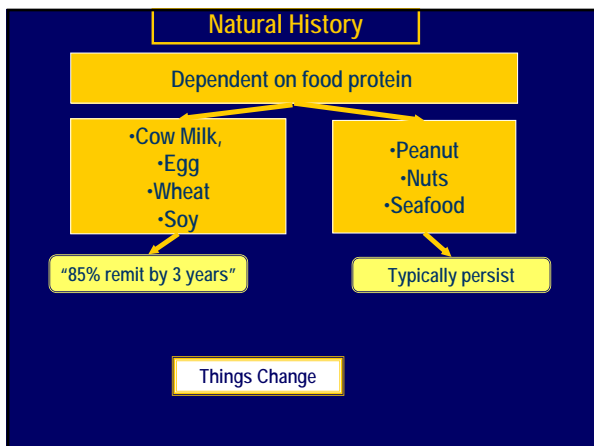
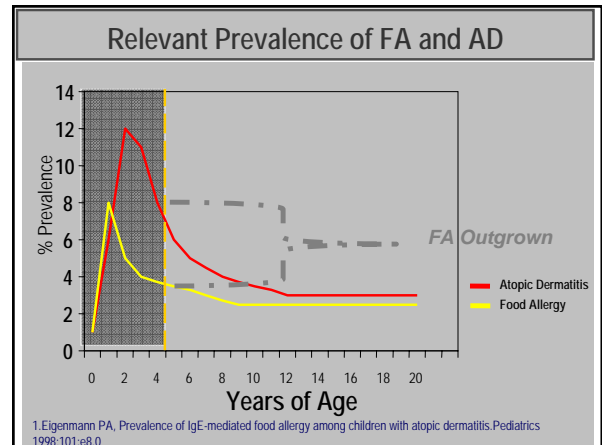
Natural History Of Food Allergy

Natural History

- A collection of facts about the development of a natural process or entity.
 - Develop food tolerance
 - Outgrow food allergy

Natural History

- To a person **uninstructed** in natural history, his country or sea-side stroll is a walk through a gallery filled with wonderful works of art, nine-tenths of which have their faces turned to the wall.
- **Teach** him something of natural history, and you place in his hands a catalogue of those which are worth turning round.
 - **Thomas Henry Huxley** (1825–95)
 - British biologist and educator.



In The Beginning we believed..

- Peanut allergy is **permanent**
- This notion was derived from the observation that:
 - Adults are affected and
 - Study with no resolution of allergy
 - Study of 32 children
 - Aged 1-14 years (mean age 7)
 - Followed 2-14 years with no resolution of allergy.
 - In essence, the study showed that a peanut allergy that was established in later childhood was not likely to resolve.

Bock SA, Atkins FM. The natural history of peanut allergy. J Allergy Clin Immunol 1989; 83:900-4

Peanut Allergy: Is This A Life-long Allergy?
.....*This Notion was challenged!*

- **Subsequent studies** of sensitization and clinical reactivity
 - With **physician-supervised oral food challenges**
 - Show that **young children (generally under age 2) may outgrow the allergy.**
 - *Spergel et al. Resolution of childhood peanut allergy. Ann Allergy*

Peanut Allergy: Is This A Life-long Allergy?
.....*This Notion was challenged!*

- A young child with a documented
- Positive physician-supervised challenge reverted to a negative challenge.
- 10% of children with **positive skin tests**
- at about age 2 1/2 yrs had **negative skin tests** to peanut about 3 years later
 - Zimmerman B, Urch B. Peanut allergy: children who lose the positive skin test response. JACI 2001; 107(3):558-9.

Peanut Allergy: Is This A Life-long Allergy?
.....*This Notion was challenged!*

- **Studied further** Things Change
- Evaluated **children aged 4-20** years with a history of peanut allergy and
- **Offered oral food challenges** to those with serum peanut specific IgE **under 21 kIU/L**
- Two-hundred twenty patients were evaluated,
 - **85 underwent challenges**
 - 41 declined and 97 did not qualify.
- **Forty-eight (21.5%) passed the challenge.**

•Skolnick and colleagues| The natural history of peanut allergy. Jaci 2001; 107(2):367-74

Objective The Natural History of *Egg* Allergy

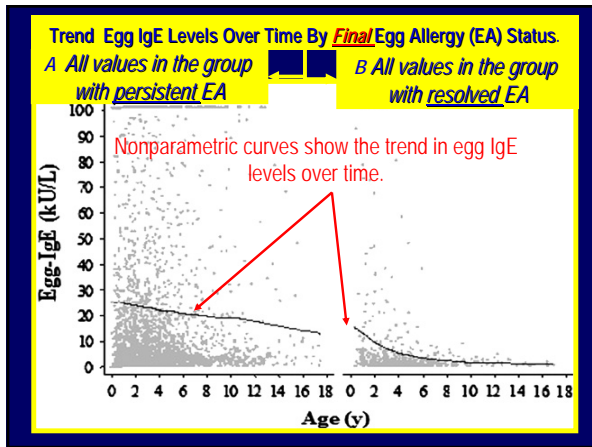
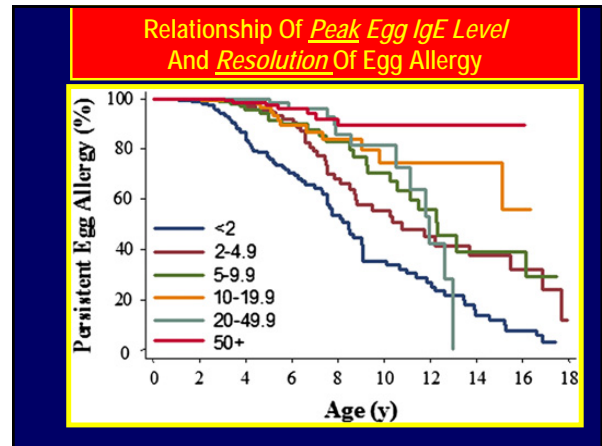
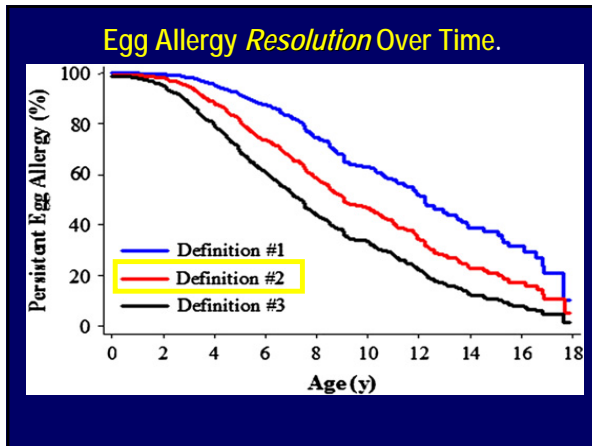
- Estimate the **proportion** of children with egg allergy who **develop egg tolerance** and to
- Identify **predictors of tolerance** development.

Jessica H. Savage, MD, Justin M. Skripak, MD, Robert A. Wood, MD
The natural history of egg allergy. JACI Volume 120, Issue 6, Pages 1413-1417 (December 2007)

Definition of Tolerance to Egg

Definition #2 of Egg Tolerance

- If they passed a formal egg challenge,
- If they had successful home introduction of concentrated egg, **or**
- If their last recorded egg IgE was **<2 kIU/L** and they had no recorded reaction with egg exposure in the last 12 months.



Results **The Natural History of Egg Allergy**

Kaplan-Meier analysis predicted resolution in

- 4% by age 4 years
- 12% by age 6 years
- 37% by age 10 years
- 68% by age 16 years

Jessica H. Savage, MD, Justin M. Skripak, MD, Robert A. Wood, MD
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Results **Natural History Of Egg Allergy: Those with Persistent Egg Allergy**

- Higher egg IgE levels at all ages to age 18 years.
- Factors significantly related to egg allergy persistence.
 - A patient's highest recorded egg IgE,
 - Presence of other atopic disease, and
 - Presence of other food allergy

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 The natural history of egg allergy. JACI Volume 120, Issue 6, Pages 1413-1417 (December 2007)

Conclusion **The Natural History Of Egg Allergy**

- A majority of patients with egg allergy will develop egg tolerance.
- Rate of tolerance development is slower than described previously. **Things Change**
- Egg IgE is
 - Predictive of allergy outcome and
 - should be used in counseling patients on prognosis

Jessica H. Savage, MD, Justin M. Skripak, MD, Robert A. Wood, MD
 The natural history of egg allergy. JACI Volume 120, Issue 6, Pages 1413-1417 (December 2007)

Clinical Implications **The Natural History Of Egg Allergy**

- Most patients with egg allergy are likely to develop egg tolerance by late childhood
 - with the exception of patients with an
 - Egg IgE greater than 50 kU/L, who are unlikely to develop egg tolerance.

Things Change

Jessica H. Savage, MD, Justin M. Skripak, MD, Robert A. Wood, MD
 The natural history of egg allergy. JACI Volume 120, Issue 6, Pages 1413-1417 (December 2007)

Background **Natural History Cow Milk Allergy -(CMA)**

Cow's milk allergy (CMA) is the most common food allergy in infants and young children,

- Affects 2% to 3% of the general population.
- Most studies have shown the prognosis of developing tolerance to cow's milk to be good,
 - with most outgrowing their allergy by age 3 years.
- Some studies had less optimistic results
 - Saarinen et al found 15% of children with previously diagnosed IgE-mediated CMA to have persistent sensitivity at age 8.6 years.
 - Prognosis for developing tolerance in older children with persistent CMA remains less clear.

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Methods **Natural History Cow Milk Allergy -(CMA)**

- 807 patients with IgE-mediated CMA Data collected.
- Clinical history
- Test results &
- Final outcome

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Criteria / Definition of Clinical Tolerance

<i>Clinical Tolerance</i>	<i>Criteria</i>
1	Pass office challenge or home introduction
2	Pass office challenge or home introduction OR cm-IgE <u><3 kU/L</u> and no history of clinical reactivity in previous 12 mo
3	Pass office challenge or home introduction OR cm-IgE <u><15 kU/L</u> and no history of clinical reactivity in previous 12 mo

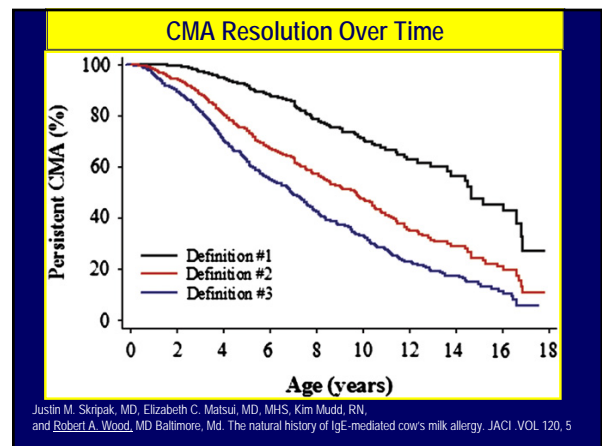
Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

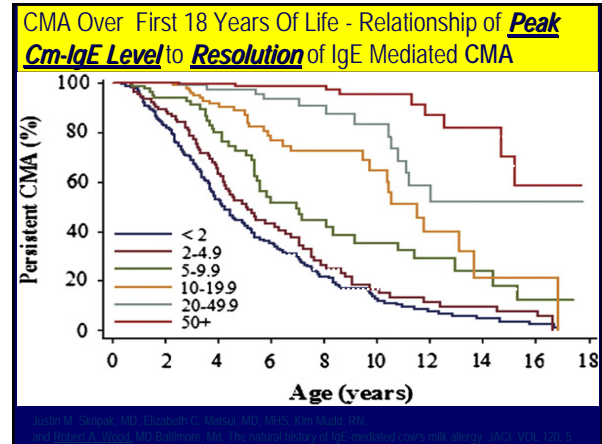
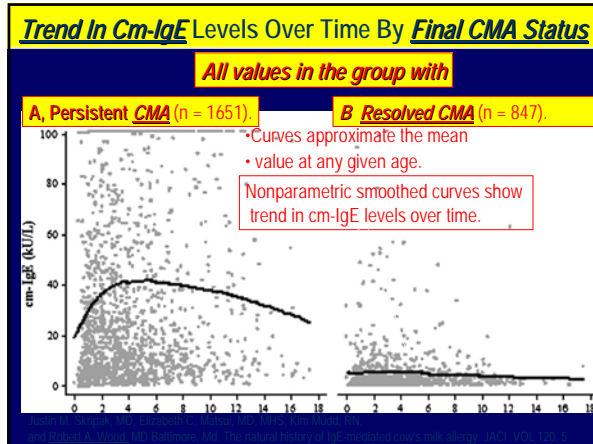
Criteria / Definition of Clinical Tolerance

Definition # 2 of Tolerance Is Arguably The Most Accurate.

- Tolerance defined as
 - passing a challenge or
 - having a cm-IgE <3 kU/L and
 - no reactions over the previous year

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5





Results **Natural History Cow Milk Allergy -(CMA)**

Rates of resolution were
 19% by age 4 years
 42% by age 8 years
 64% by age 12 years &
 79% by 16 years.

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Predictors Of Prognosis CMA

Higher Peak cm-IgE levels

- Persistent allergy patients had higher cm-IgE levels in the first 2 years of life than those who developed tolerance
 - Median **19.0** kU/L vs **1.8** kU/L; P < .001),
 - Difference was maintained up through age 18 years

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Predictors Of Prognosis CMA

Trends in IgE levels also differed:

- Persistent allergy
 - Increasing levels over the first 3 to 4 years of life followed by a plateau and then
 - Gradual decrease up to age 18 years
- Resolved allergy
 - Decrease over first 1 to 2 years of life after which cm-IgE levels stable

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Predictors Of Developing Oral Tolerance

- Peak cm-IgE levels
- Trends of cm Serum IgE
- Asthma
- Allergic Rhinitis &
- History Of Being Fed Formula

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Contradictions To Past Studies

- Previous Data**
 - " 75% of children with IgE-mediated milk allergy were tolerant by the age of 3 years."
 - Most often quoted
 - CMA is unlikely to be lost if it has persisted into their school-age years.
- This study**
 - Findings in marked contrast
 - A positive finding is that patients did continue to achieve tolerance well into adolescence.
 - Clearly indicates that there is no age at which outgrowing CMA is impossible

Things Change

Largest cohort of children with milk allergy ever

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Conclusion **Natural History Cow Milk Allergy -(CMA)**

- Largest cohort of children with milk allergy ever
- Prognosis for the resolution of IgE-mediated CMA significantly worse than previously reported.
- Sensitivity persists into school age and beyond in the majority of this studies patients
- Cm-IgE is highly predictive of outcome and should be used in counseling patients on prognosis.

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

Clinical Implications **Natural History Cow Milk Allergy -(CMA)**

- When counseling families regarding expected clinical course consider
 - The increasing potential for persistence of CMA, along with
 - Cow milk-IgE level's effect on prognosis

Justin M. Skripak, MD, Elizabeth C. Matsui, MD, MHS, Kim Mudd, RN, and Robert A. Wood, MD Baltimore, Md. The natural history of IgE-mediated cow's milk allergy. JACI. VOL 120, 5

From Yesterday To Tomorrow

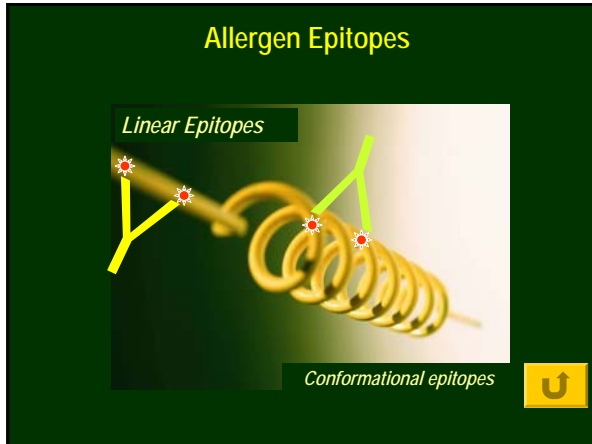
We are at the crossroads of yesterday and tomorrow

Epitopes

Natural History

Conformational Epitopes Linear Epitopes

IgE binding to epitopes



The Nature Of Epitopes Important

The major cow's milk allergen contains

- **Linear epitopes** composed of a linear array of amino acids *in a row*;
 - Resistant to heating and G-I enzymatic action
 - *Pt will likely react* to milk in heated form (e.g., in baked goods).
 - Young children reactive to linear epitopes will be more likely to *continue* to have milk allergy past age 4-5 years
- **Conformational epitopes** in which the amino acids are connected in a **three dimensional arrangement**.
 - Generally not resistant to these effects.
 - Will likely not react to milk in baked goods
 - Young children reactive to conformational epitopes will be less likely to continue to have milk allergy past age 4-5 years

Yesterday

- The trouble with research is that it tells you what people were thinking about yesterday, not tomorrow. It's like driving a car using a rearview mirror.
 - Bernard Loomis, toy manufacturing executive
 - *ATtribution: International Herald Tribune 9 Oct 85*
 - *SUBJECTS: The World: Business: Executives*

So we need research telling us what is going to happen tomorrow

So we need research telling us what is going to happen tomorrow

- Research resolves riddles rhymes

Tests For IgE Binding To Specific Epitopes

- Considerable interest in
 - Characterizing *not just* the food allergens but also their *key IgE-binding epitopes*
 - Developing *clinical lab assays for detecting IgE antibodies against these epitopes*.
 - *"Qualitative differences in epitope diversity may provide prognostic information"*
 - Sampson AAAAI 2005

Natural History

Dependent on food protein

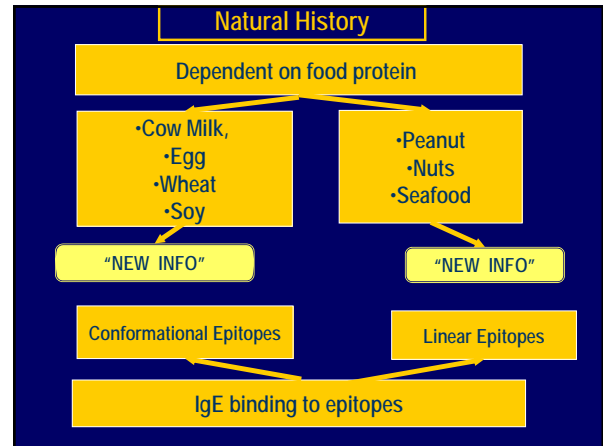
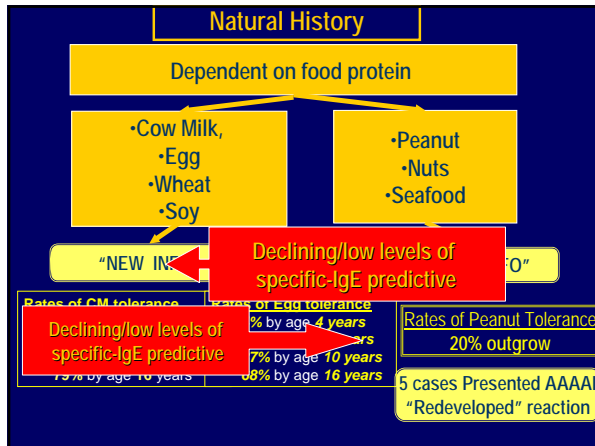
•Cow Milk,
•Egg
•Wheat
•Soy

•Peanut
•Nuts
•Seafood

"NEW INFO"

Rates of CM tolerance	Rates of Egg tolerance	Rates of Peanut Tolerance
19% by age 4 years	4% by age 4 years	20% outgrow
42% by age 8 years	12% by age 6 years	
64% by age 12 years	37% by age 10 years	
79% by age 16 years	68% by age 16 years	

5 cases Presented AAAAI "Redeveloped" reaction



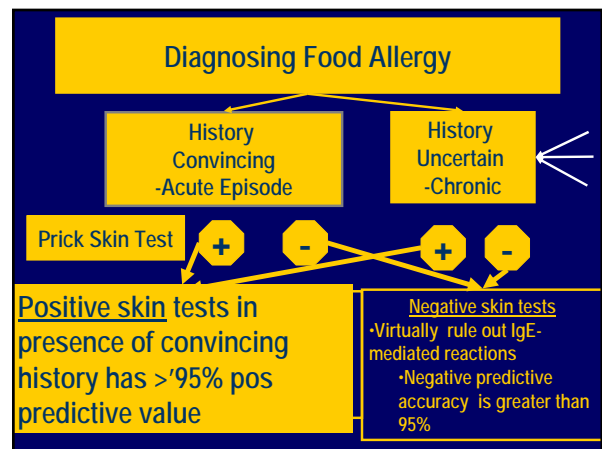
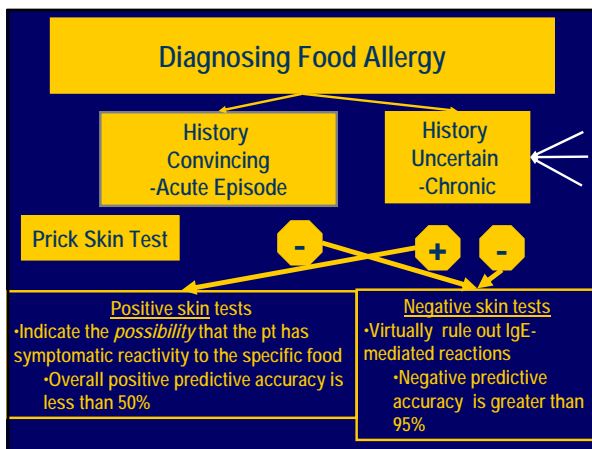
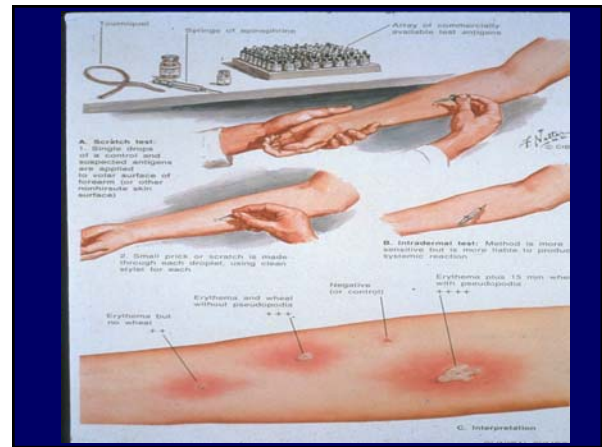
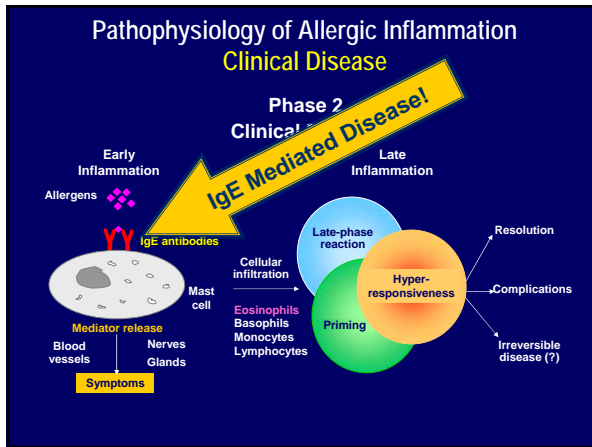
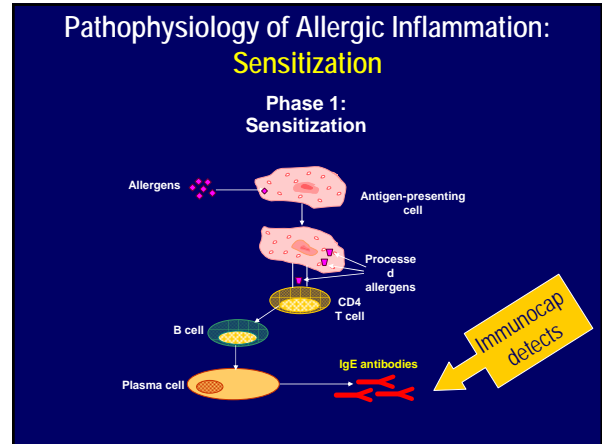
Documentation of the allergic foods /culprit allergens in the individual patient

- Diagnosis Of Adverse Food Reactions**
- Begins with the
 - Medical history and
 - Physical examination
 - Based upon information derived from these initial steps various **laboratory studies** may be ordered

- Few Foods Account For 90 % Of Reactions**
- Any food may cause an allergic reaction
- Age Dependent Reactions To Foods**
- Infants/Young Children
 - Cows milk
 - Hen egg
 - Peanuts
 - Fish
 - Soybeans
 - Tree nuts
 - Wheat
 - Adults
 - Peanuts
 - Tree nuts
 - Fish
 - Crustacea
 - Mollusk
 - Fruits/vegetables
- (Sampson Ann Rev Nutr 1996)

- Medical History**
- To establish/ determine the likelihood that food-allergic reaction occurred and to
 - To construct an appropriate challenge at a later date
 - Requires the following information:
 - (1) The food presumed to have provoked the reaction
 - (2) The quantity of the suspected food ingested
 - (3) The length of time between ingestion and development of symptoms
 - (4) Whether similar symptoms developed on other occasions when the food was eaten
 - (5) Whether other factors (e.g., exercise or alcohol ingestion) are necessary, and
 - (6) How long since the last reaction to the food occurred

So what is
IgE Mediated Disease?



Diagnosing Food Allergy

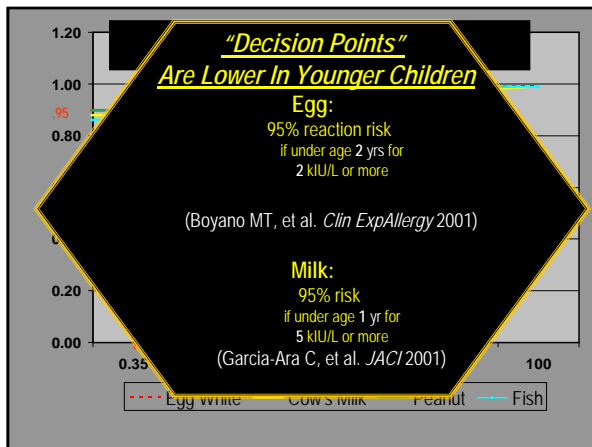
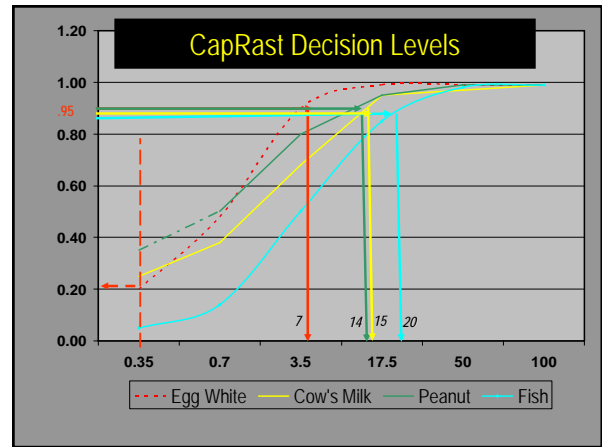
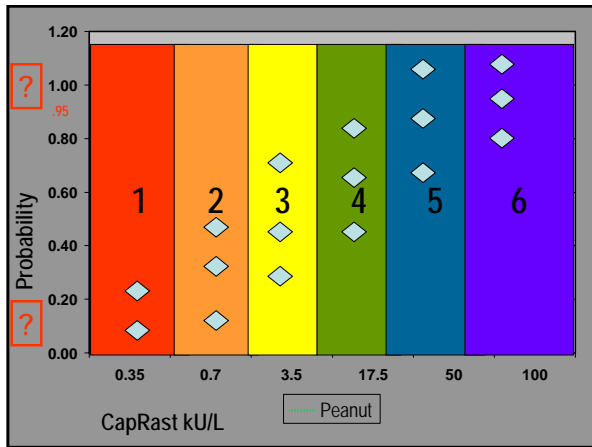
Skin Tests can remain positive when tolerance already developed.
 There is a *lag behind* Cap Rast tests in evaluating those who have outgrown FA

<p>Positive skin tests in presence of convincing history has >95% pos predictive value</p>	<p>Negative skin tests -Virtually rule out IgE-mediated reactions -Negative predictive accuracy is greater than 95%</p>
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Diagnosing Food Allergy

Skin Tests can remain positive when tolerance already developed.
 There is a *lag behind* Cap Rast tests in evaluating those who have outgrown FA

<p>Positive skin tests in presence of convincing history has >95% pos predictive value</p>	<p>Negative skin tests -Virtually rule out IgE-mediated reactions -Negative predictive accuracy is greater than 95%</p>
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As Avoidance is Stressful

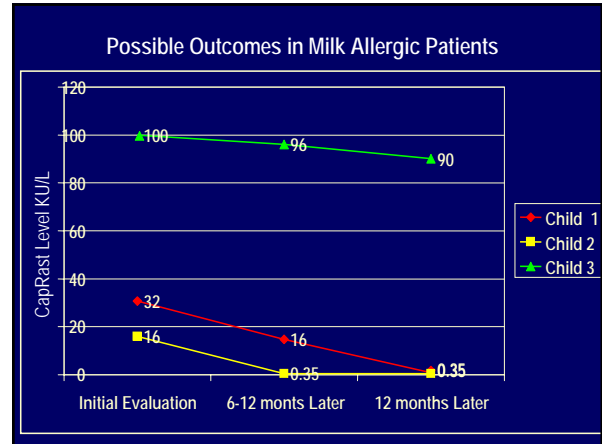
- Multiple food allergy in given child
- Multiple sources of food allergen
- Multiple venues including school
- Multiple members of school team with
- Multiple responsibilities
- Multiple children in family/ other family members

As Natural History Dictates Child Will Outgrow Clinical Reactivity

Allergist should re-evaluate

The Doctor May Not Always Know

Not from Allergy and Asthma Specialists, PA



Decision Points Under MD Supervision or at Home?

- *Food challenges should be performed with **physician supervision**, regardless of food-specific IgE value.
 - In patients with a **strongly suggestive history** of an IgE-mediated food allergic reaction,
- Food challenge can be performed at **home unless there is a compelling history of reactivity**
 - If the food-specific IgE level is **less than 0.35 kU/L AND**
 - Prick skin test is **negative**,

Utility of food-specific IgE concentrations in predicting symptomatic food allergy. JACI 2001;107:891-6. High likelihood of reaction

The Relationship Of Allergen-Specific IgE Levels And Oral Food Challenge Outcome

- Challenges were performed **when:**
- Oral tolerance was suspected
- Food-specific IgE level
 - was **less than 0.35 kU/L** or
 - approached **one fourth** of the previously established 95% PPV for milk, egg, and peanut or
 - one fourth the 50% and 75% PPVs established for soy and wheat, respectively.

⊘ Medically closely supervised challenges. Don't try this at home!!

Perry, TT. ; Wood, R.A. et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. JACI 114(1) July 2004 p 144-149

The Relationship Of Allergen-Specific IgE Levels And Oral Food Challenge Outcome

- **Most patients had clear history** of reacting to the suspect food
- Some diagnosed solely on the basis of
 - positive skin test or
 - food-specific IgE levels
- Others had a less clear history of reaction
 - such as a worsening of AD with exposure to that food.

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Perry, TT. ; Wood, R.A. et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. JACI 114(1) July 2004 p 144-149

The Relationship Of Allergen-Specific IgE Levels And Oral Food Challenge Outcome

- **Results:**
- **Challenges Passed**
 - Milk 45%
 - Egg 57% for
 - Peanut 59%
 - Wheat 67%
 - Soy 72%

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Perry, TT. ; Wood, R.A. et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. JACI 114(1) July 2004 p 144-149

Relationship Allergen-Specific IgE Levels And Oral Food Challenge Outcome

- Although it is *reasonable to consider different cutoff levels depending on the*
 - particular food and
 - clinical situation
- Authors *recommend challenges* when there is approximately:
 - 50% likelihood FC will be passed on basis of the available data.
- Proved very useful when considering the
 - Risk, expense, and time that each challenge entails and
- Well accepted by patients and families.

⊘ Medically closely supervised challenges. Don't try this at home!!

Perry, TT, Wood, R A, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. JACI 114(1) July 2004 p 144-149

For Children With Possible Allergy To Egg, Milk Or Peanut, When Is It Reasonable To Offer A Food Challenge?

- If prior history of reaction**
 - milk <2 kIU/L,
 - egg < 2 kIU/L, and
 - peanut <2 kIU/L
- Without prior history of reaction**
 - milk 5 kIU/L,
 - egg 5 kIU/L, and
 - peanut 5 kIU/L

Based upon study of referred children, Median age 4.8 yrs, 77% multiple food allergy, Challenged when serum food-specific IgE was about 25% of "decision point" values or <0.35 kIU/L.

⊘ Medically closely supervised challenges. Don't try this at home!!

The Relationship Of Allergen-Specific IgE Levels And Oral Food Challenge Outcome

- Conclusions:
- Allergen-specific IgE concentrations to
 - milk, egg, and peanut and,
 - to a lesser extent, wheat and soy serve as
- Useful predictors of challenge outcome and
- Should be considered when selecting patients for oral challenge to these foods.

⊘ Medically closely supervised challenges. Don't try this at home!!

Perry, TT, Wood, R A, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. JACI 114(1) July 2004 p 144-149

Case Histories: Sorting Out Those With Loss of Clinical Reactivity

Sorting Out Those With Loss of Clinical Reactivity

Convincing History Egg Anaph 3-Acute Episodes	Avoided egg	Subsequent history of Tolerance to inadvertent Egg product consumption
Prick Skin Test +	+	+
Cap Rast		-
Allergist supervised Egg white challenge in ER		
Tolerated 3 egg whites over 3 hours		
Include egg white in diet		

Sorting Out Those With Loss of Clinical Reactivity

Convincing history Peanut & egg anaph 1-acute episode to each	Avoided Peanut & egg	Parents sought check Whether tolerant to Egg product
Prick Skin Test +	+	+
Cap Rast		-
Allergist supervised Egg white challenge in ER		
Reacted with hives within 1 hour. Reaction treated		
Avoid egg white in diet		

Change

Change is not made without inconvenience,
even from worse to better.

- Richard Hooker (1554–1600),
– British theologian. Quoted in Samuel Johnson

Natural History



• Teach him something of natural history,
and you place in his hands a catalogue of those which are worth turning round.

- Thomas Henry Huxley (1825–95)
• British biologist and educator.

Treatment: Follow-Up

- **Re-evaluate for tolerance periodically**
- **Interval and decision** to re-challenge:
 - Type of food allergy
 - Severity of previous symptoms
 - Degree to which family is *coping with avoidance*
- **Ancillary testing**
 - Skin prick test/ CAPRAST may remain positive
 - Reduced concentration food specific-IgE encouraging
- Challenge under appropriate circumstances.

Do not challenge in school cafeteria

Allergist's Approach



- Consider referral to Allergist
- Determination of culprit allergen
 - History, Skin testing and CapRast
- Education of Patient & Family
 - Avoidance of allergen
 - Medical alert
 - Recognition & Management of Reaction
 - **Reintroduction of allergen when indicated**

Allergy Evaluation Aims for Comprehensive Care

Allan Stillerman, MD

The Practice



Allergy & Asthma Specialists, P.A.

Minneapolis- Medical Arts Bldg

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