Clinical Advances in Allergy, Asthma & Immunology

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Disclosures

• Aerocrine Speaker’s Bureau

• Allergy & Specialists of North Florida

• Florida Allergy, Asthma & Immunology Society Executive Board

• Clay County Medical Society board of directors
Objectives

• Discuss current understanding and risk factors for delayed anaphylaxis to foods
• Review current recommendations regarding egg allergic individuals and their eligibility to receive the flu vaccine
• Review present understanding of distinct asthma phenotypes and how treatment strategies may differ among them
• Discuss the role of emerging asthma biomarkers to differentiate between certain asthma phenotypes
Not an objective

DEATH BY POWERPOINT
Update in Food Allergies
The Alpha-gal Story

- 2006- cetuximab
  - monoclonal mouse/human chimeric epidermal growth factor receptor inhibitor
    - Head/neck, colonrectal cancer

- Unusual amount of severe/fatal hypersensitivity reactions in southern patients after *first* dose-- up to 20% at some centers
Alpha-gal

- Monoclonal Ab bound to an Immunocap revealed existing IgE antibodies to the oligosaccharide residue bound to the Fab portion of the molecule.
- The oligosaccharide = galactose 1,3 alpha-galactose (aka alpha-gal)
Mast cell activation and degranulation:
- Histamine
- Prostaglandins
- Leukotrienes
- Tryptase
- Cytokines

Urticaria and Anaphylaxis
alpha-1,3-galactose (alpha-gal)

- Major blood-group carbohydrate of non-primate mammals
- Common target of IgG antibodies which are present in the serum of immunocompetent individuals
- Unheard of to have IgE antibodies directed at carbohydrate
Questions

• Why were these cases predominately occurring in southern patients?

• How did they become sensitized to alpha-gal in the first place?
“I’m stumped. We’ll have to wait for the autopsy.”
Flash forward to 2009

• Thomas Platt-Mills, MD PhD at UVA

• Studying bizarre cases of delayed anaphylaxis to foods
  o Common history of beef or pork ingested 4-5 hours before onset of spontaneous anaphylaxis
  o All had IgE antibodies to alpha-gal!

• Case solved!
Not exactly…..

- Those with alpha-gal IgE had no other atopic features ("nonallergic")

- Why did those with delayed anaphylaxis to meats have IgE antibodies to alpha-gal when control groups did not?
Why was this happening mainly in the south?

- Reactions to cetuximab and meats were occurring predominantly in southern states (i.e. Virginia, North Carolina, Tennessee, Arkansas, Oklahoma, and Missouri, etc...)

- Geography coincided with the *maximum* prevalence of Rocky Mountain spotted fever.
Geography of RMSF
Delayed food anaphylaxis

• Nearly all of these patients had history of at least one tick bite

• Subsequent studies showed parallel rise in IgG and IgE to alpha-gal after a tick bite.

• Route of immunologic sensitization determines immunologic response
  o Intestinal exposure (ingestion) = tolerance
  o Skin exposure (tick bite) = allergy
(A). Flushing 345 min after 150-g mammalian meat challenge. (B) Systemic urticaria.

Systemic urticaria 225 minutes after challenge with 150g pork sausage

Conclusion

• Delayed anaphylaxis to mammalian meat 4-5 hours after ingestion is rare but is associated with the development of IgE Ab’s directed at galactose 1,3 alpha-galactose

• Novel mechanism of anaphylaxis
  o Carbohydrate, not protein induced

• IgE to galactose 1,3 alpha-galactose now commercially available test
Conclusion

• IgE to alpha-gal can be reassess every 8-12 months

• Sustained avoidance of tick bites results in decrease of alpha-gal specific IgE Ab
  o Some patients can tolerate meats after 1-2 years of tick avoidance*

Update on Influenza Vaccination of Egg Allergic Patients
Flu shot and Egg Allergic Patients: Evolution

- **Absolute contraindication**
- **Relative contraindication**
  - Skin test with vaccine → graded challenge
  - Skin test unnecessary. Graded challenge only
  - Graded challenge unnecessary. Give divided doses (10% then 90%)
  - Divided dose unnecessary. Give single dose
Growing body of evidence showing safety of influenza vaccination in egg allergic individuals.

Consistent with CDC’s Advisory Committee on Immunization Practices recommended that egg-allergic persons receive injectable inactivated influenza vaccine as a **single dose without prior vaccine skin testing** and be observed for 30 minutes.

“Patients with egg allergy should receive influenza vaccinations (TIV) because the risks of vaccinating are outweighed by the risks of not vaccinating.”
Can the person eat lightly cooked egg (e.g., scrambled egg) without reaction?*

**YES**
- Administer vaccine per usual protocol

**NO**
- After eating eggs or egg-containing foods, does the person experience ONLY hives?
  - **YES**
    - Administer TIV
    - Observe for reaction for at least 30 minutes after vaccination
  - **NO**
    - Does the person experience other symptoms such as:
      - Cardiovascular changes (e.g., hypotension)
      - Respiratory distress (e.g., wheezing)
      - Gastrointestinal (e.g., nausea/vomiting)
      - Reaction requiring epinephrine
      - Reaction requiring emergency medical attention
    - **YES**
      - Refer to a physician with expertise in management of allergic conditions for further evaluation
    - **NO**

*Persons with egg allergy might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy.
Since 2012

• Des Roches et al: 4,172 egg allergic patients received 4,729 doses of influenza vaccine with no cases of anaphylaxis, including 513 with severe allergy.

• Greenhawt et al: multicenter, prospective randomized controlled trial and retrospective study: no vaccine-related reactions in an additional 143 patients with severe egg allergy.

• Authors independently concluded risk of an adverse reaction to flu vaccine is exceptionally low for any patient with any severity of egg allergy

Kelso JM. Ann Allergy Asthma Immuno 2013
Since 2012

Two new influenza vaccines not grown in egg embryos have been approved for patients 18 years and older

- **Flucelvax**, (virus propagated in cell culture)
- **Flublok** (produced in an insect cell line)
Joint Summary from AAAAI and ACAAAAI

• ALL patients with egg allergy (including anaphylaxis) should receive flu vaccine annually-- single dose without prior vaccine skin testing.
• Egg-allergic patients 18 years of age and older, either egg based or egg-free vaccine can be used.
• Special precautions regarding medical setting and waiting periods after administration to egg-allergic recipients beyond those recommended for any vaccine are not warranted
• Language describing egg-allergic recipients as being at increased risk or requiring special precautions should be removed from guidelines and product labeling.

Kelso JM. Ann Allergy Asthma Immuno 2013
“Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management.”

- CDC’s Advisory Committee on Immunization Practices
Asthma Update
Asthma Heterogeneity

• Increasingly recognized as a syndrome
• Complex genetic disorder with variable phenotypic expression (endotypes)
  o Th2 dominant atopic /allergic- (IL-4, IL-5, IL-13)- ↑ airway eosinophilia
  o Aspirin exacerbated respiratory disease (AERD)- ↑ cysteinyl leukotriene
  o Allergic broncopulmonary aspergillosis (ABPA)
  o Late onset neutrophilic (TNF-α, IL-1, IL-8)
    • Corticosteroids not helpful, may ↑ neutrophilic inflammation*
  o Exercise/Cold induced (Cross-country skier' Asthma)

• Respiratory epithelial barrier
  o Defects of innate immunity vs immunodysregulation

*Middleton’s Allergy: Principles and Practice. 8th ed. 2014
### Factors Affecting Neutrophilic Asthma

<table>
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<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Endotoxin</td>
</tr>
<tr>
<td>Particulate Matter</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Infections- Viral and Bacterial</td>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td>Diet—high in fats, low in antioxidants</td>
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<td>Occupational exposures</td>
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Th2 Dominant- Atopic Asthma and Exhaled NO$^{1,2}$

- Exhaled NO levels increase during Th2 (allergic) inflammation—often correlates with eosinophilic inflammation.

Exhaled Nitric Oxide

- Biomarker for Th2 endotype (eosinophilic airway inflammation)

- Elevated eNO predicts favorable response to inhaled corticosteroids
## eNO Reference Values

<table>
<thead>
<tr>
<th>Age</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td>Adults and children &gt;12 years</td>
<td>&lt; 25</td>
<td>25-50</td>
<td>&gt;50</td>
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<tr>
<td>Children &lt; 12 years</td>
<td>&lt;20</td>
<td>20-35</td>
<td>&gt;30</td>
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eNO Helps Identify Patients Likely to Respond to Steroid Therapy*

- Predictive accuracy of FeNO to identify steroid response significantly greater than conventional predictor

N=52 patients with undiagnosed respiratory symptoms

eNO As Marker of Allergen Exposure


**Graph:**
- **FeNO (ppb)** on the y-axis.
- **Allergen avoidance** on the x-axis.
- **T0 = before admission to allergen-reduced location in Alps study center (N=20).**
- **T1 = day 15 after placement (N=20).**
- **T2 = 3 months after placement (N=20).**
- **T3 = 14 days after return to sea level (N=10).**

- **Inhaled steroid withdrawal** at T1.
- **P = 0.014** at T0.
- **P = NS** between T0 and T2.
- **P = 0.004** at T3.
Urticaria Update
Big News

• Omalizumab is now FDA approved for treatment of chronic spontaneous histaminergic urticaria refractory to H1 antihistamine therapy.

• First biologic approved for chronic urticaria

• Ages 12 and up.
Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

Allen Kaplan, MD, Dennis Ledford, MD, Mark Ashby, PhD, Janice Canvin, MD, FRCPC, James L. Zazzali, PhD, Edward Conner, MD, Joachim Veith, MD, Nikhil Kamath, MD, Petra Staubach, MD, Thilo Jakob, MD, Robert G. Stirling, MB, FRACP, Piotr Kuna, MD, PhD, William Berger, MD, Marcus Maurer, MD and Karin Rosén, MD, PhD

Journal of Allergy and Clinical Immunology
Volume 132, Issue 1, Pages 101-109 (July 2013)
DOI: 10.1016/j.jaci.2013.05.013
At Week 12, there was a greater improvement in weekly itch score in the omalizumab group, compared with placebo (-8.6 vs. -4.0; P<.001), with sustained benefit at Week 24 (-8.6 vs. -4.0; P<.001)
Take Away Points

• Delayed anaphylaxis to meats can be precipitated by tick bites.
  o Ask about history of tick bite
  o Look for IgE antibodies directed at “alpha-gal”

• History of egg allergy should not preclude individuals from receiving the flu shot.

• Asthma is complex heterogeneous genetic syndrome with variable endotypes
Take Away Points

• Specific identifiable endotypes will determine treatment. One size does not fit all.

• eNO = helpful biomarker for Th2 dominant asthma
  o These respond well to inhaled corticosteroids, neutrophilic predominant asthma does not.

• Omalizumab is option for severe refractory chronic urticaria.
References

3. www.cdc.gov
CAUTION:
Vehicle may be Transporting Political Promises!