I know I said never, but this exposure is okay…

Administration of Flu Vaccine to pediatric patients with egg allergy

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Disclosures

- Will be discussing vaccine trade names along with the generic terminology as these are the most commonly used terminology in practice settings.
- I have no relationship to any vaccine manufacturer.

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Objectives

- Discuss the natural history of egg allergy in children
- Discuss the evidence behind safe administration of vaccines made with egg product
- Discuss alternatives, testing, treatment of reactions and new methods of treating egg allergy in children

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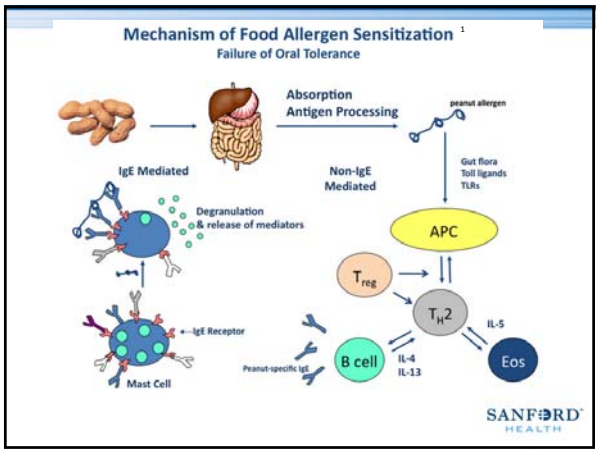

Allergy to Hen's egg

- One of most common food allergy in childhood
  - Along with cow's milk, peanut, tree nuts, fish, shellfish, wheat and soy
- Estimated prevalence 0.5-2.5% of children[2,3]
  - Difficult to obtain true numbers as often self-reported
- Associated with atopy
  - Asthma, atopic dermatitis, additional food allergy

Gallus Gallus Domesticus

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Allergy to Hen's Egg

- Egg allergens[3]
  - Gal d 1 (ovomucoid)
    - Immunodominant protein in egg white
    - Relevant specific IgE in persistent egg allergy
  - Gal d 2 (ovalbumin): heat labile
  - Gal d 3 (ovotransferrin)
  - Gal d 4 (lysozyme)
  - ovomucin
  - Gal d 5 (chicken serum albumin)
    - Major allergen in egg yolk
  - Egg lecithin
    - Used as emulsifier in food production, but likely not in sufficient amounts to trigger allergy

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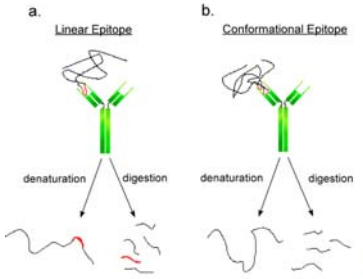
Heat labile epitopes

- Conformational (3D) vs linear epitopes



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Tolerance of extensively cooked egg

- Many egg allergic patient are able to tolerate "Baked" egg, ~70%[13]
  - 350 degrees for 30 minutes
  - Store bought baked products with egg are generally cooked enough to qualify
- Ovalbumin is conformational, heat labile epitope
- Ovomucoid is a linear, heat stable epitope

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Egg allergy

- Usually present in second 6 months of life
- Can be exposed through breast milk
- Most reactions are:
  - Cutaneous
  - Occur within 30 minutes of ingestion
  - GI and/or respiratory symptoms can occur
  - Rare fatalities
    - Peanut and milk much more commonly reported

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Diagnosis

- Clinical history of reaction
- Serum specific IgE to egg white/egg yolk
  - Component testing not commonly used yet
- Skin prick testing to egg white/egg yolk: lab prepared extract
  - Can test to uncooked (raw), cooked, extensively cooked (baked)
- Open challenge
- Double blinded placebo controlled challenge: Gold standard

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Management

- Avoidance
- Anaphylaxis treatment plan
  - Food allergy action plan
  - Epinephrine/Benadryl
- Routine skin prick and serum IgE evaluation
  - Egg white sIgE >2 kU/L is associated with 90% chance of reacting on challenge
  - >6 kU/L is associated with 95% chance of reacting

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Influenza vaccines

- IIV3/IIV4: inactivated influenza vaccine trivalent/quadravalent
  - Afluria, Fluarix, FluLaval, Fluvirin, Fluzone
- LAIV4: Quadrivalent live attenuated influenza vaccine (FluMist)
- RIV3: Trivalent recombinant influenza vaccine (FluBlok)
- ccIIV3: cell culture inactivated influenza vaccine (Flucelvax)

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Current CDC/ACIP recommendations

- Use FluMist (LAIV) for ages 2-8 if available
  - Use IIV if LAIV is not immediately available
- Fluzone (IIV3/4): 6 months and older
- Fluarix (IIV3/4): 3 years and older
- Contraindications:
  - Guillain-Barre syndrome
  - Acute Illness
  - Severe allergy to vaccine component/allergic reaction after previous dose

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Commonly recognized allergens in influenza vaccines

Vaccine	Neomycin	Polymyxin	Gentamicin	Latex (in syringe tip cap)	Ovalbumin	Gelatin
Afluria (IIV)	X	X			X	
Fluarix (IIV)			X		X	
FluBlok (RIV)						
Flucelvax (ccIIV)				X		
Fluvirin (IIV)	X	X			X	
Flulaval (IIV)					X	
Fluzone (IIV)					X	X
FluMist (LAIV)			X		X	X

Adapted from http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu-hcp-info.pdf

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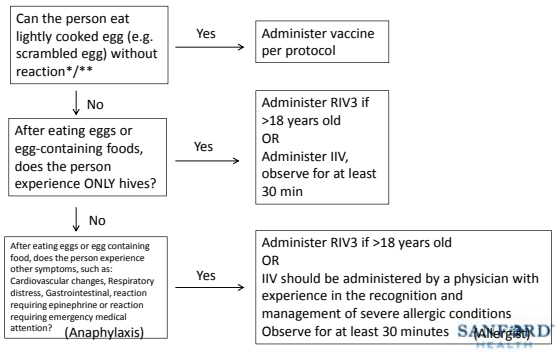
2014-2015 ACIP Egg allergy algorithm



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2014-2015 ACIP Egg allergy algorithm

- * baked egg tolerance does not exclude egg allergy
- ** if suspected egg allergy with no known prior exposure (+ labs, testing): discuss with an allergist or give RIV3 if older than 18 years
- Due to lack of safety data for LAIV with egg allergy, IIV or RIV was recommended rather than LAIV

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ACIP recommendations[5]

- Des Roches et al. 2012[6]
  - 4172 patients
  - 513 with prior severe egg allergic reaction
  - Zero occurrences of anaphylaxis to vaccine
    - Some milder reactions noted in egg allergic patients
- ACIP: "On this basis, some guidance recommends that no additional measures are needed when administering influenza vaccine to egg-allergic persons."

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"However…

  - …occasional cases of anaphylaxis in egg-allergic persons have been reported to VAERS after administration of influenza vaccine."
- Summary:
  - Not allergic: give age appropriate vaccine
  - Only hives:
    - Over 18 yrs: Use RIV3 (FluBlok)
    - Under 18: IIV3/4 and wait 30 min
  - Not sure: let the allergist do it
- 2014-2015 Guidance based on 2012 data and VAERS concerns

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2012 Joint Task Force on Practice Parameters[7]

- Severe egg allergic patients should get single dose under observation
- No skin testing, no graded challenge, no split dose, no component testing
- 2013 update: Kelso JM, et al.[9]
  - Published as a letter to the editor in Annals of Allergy, Asthma and Immunology

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2013 update: Kelso JM, et al.[9]

- Since the publication of 2012 safety data there were no VAERS reported allergic reactions or anaphylaxis
- Greenhawt et al[8]: prospective randomized controlled trial of 143 pts with severe egg allergy: no vaccine related reactions
- Both Des Roches and Greenhawt independently concluded that single dose IIV is safe in any egg allergic patient, "…without requiring administration by an allergist as this poses unnecessary barrier to vaccination."

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2013 Update

- Recommendations:
  - All patients, regardless of egg allergy of any severity should get IIV annually using any age-appropriate IIV dose as a single dose without prior skin testing to the vaccine
  - Egg allergic patients over 18 years can get RIV3 if desired
  - Special precautions such as allergist office or waiting periods are not warranted
  - For IIV: language describing egg allergic patients being at increased risk should be removed from product labeling and guidelines.

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Kelso JM 2014 JACI:IP Editorial[10]

- As of Aug 2014, there were 28 studies on egg allergy and influenza vaccine
  - 4315 combined subjects with egg allergy
  - 656 with anaphylaxis to egg
  - No serious reactions
- Conclusion: Reassuring safety data

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Kelso JM 2014 JACI:IP Editorial[10]

- Egg protein content in all vaccines below the threshold to trigger a reaction even in sensitized people
  - ~10 mg/mL appears to be the threshold to cause rhinitis when egg is taken intranasally in egg allergic children
  - LAIV has <0.24 µg/dose, IIV has <1 µg/dose
  - Oral threshold may be different
- Summary: reiteration that no special precautions are needed for influenza vaccine and egg allergic patients

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LAIV evidence

- Des Roches A, et al. 2014 Clinical Communication[11] (letter in JACI:IP), Prospective cohort study
  - 2-16 year olds
  - 68 egg allergic patients
    - 52 had received IIV3 years prior
  - 55 controls
  - Received LAIV, observed 1 hour, telephone follow up 24 hours later
  - 10% had non-specific adverse reactions
    - None of which needed medical attention or were suggestive of allergic reaction/anaphylaxis
  - 1 control patient with adverse reaction

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LAIV evidence

- Turner PJ et al, JACI:IP 2015; SNIFFLE study[12]
  - UK study, Prospective, multicenter, open-label study
  - 282 egg allergic children, 2-17 years old
  - Majority with asthma
- No systemic reactions
  - 2.8% with mild immediate adverse event within 30 minutes of dose: possible allergic cause
    - 6 rhinitis, 1 localized urticaria, 1 GI discomfort: all mild and self limited
  - No risk factor identified to predict adverse event

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Turner et al (cont.)

- 91 had delayed events after at least 1 dose of LAIV (2-72 hours after dose)
  - 21.2% upper respiratory symptoms
  - 9.4% lower resp. symptoms
    - 4.7% parent reported wheezing
  - 4% eczema flare
  - None needed medical professional treatment
  - Adverse events were not more common in previously diagnosed asthmatics, recurrent wheezers
- Summary: Safety profile regarding systemic reaction is similar between egg allergic and non-allergic pediatric patients
  - Well tolerated in asthmatic children

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Bottom line

- IIV, LAIV are safe in egg allergic children
- No special precautions are needed
- RIV has not been thoroughly studied in children; so don't use off label

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Now… what do we *really* do?

- What do we do to make parents feel safe and confident in our interventions?
  - Referral to allergy
  - Observation with single dose
  - Skin testing
    - If there is no other way to get parents to allow vaccine
    - OR if concerned there was a real anaphylaxis last vaccination and we can determine if a different component caused reaction
  - What to do if false positive on skin testing: such as with eczema?
- If the child has received any prior doses without reaction: ok to give the dose, no precautions needed

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A word on MMR and egg allergy

- None or negligible amount of egg allergen in vaccine
  - Grown on chick embryo fibroblasts
- No special precautions needed
- Gelatin is much more likely suspect than egg in systemic reactions
  - Work up includes skin testing, IgE to vaccine, gelatin, latex
  - If + skin test to a component, can be given in graded amounts

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Treatment of egg allergy

- Oral immunotherapy
  - Not ready for prime time, still research only
  - Food allergy does not behave as predictably aeroallergen therapy
    - Recent OIT trial (DBRPCT) with 31 participants > 4 yo[15]
    - 5 achieved tolerance, all achieved desensitization during trial
    - 1 in placebo group spontaneously became tolerant
  - About 14% of allergists are using OIT, about ½ in an academic/research setting[13]
  - Others using research protocols on their own
  - Are we causing eosinophilic esophagitis with therapy?

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Future directions in egg allergy treatment

- Baked egg introduction
  - 70% of egg reactive children tolerate baked egg[14]
  - Still trying to find skin prick and sIgE levels that will predict which kids will tolerate
- Transdermal patch
  - Contact dermatitis
  - Worsening of eczema
- Combining probiotics, Chinese herbals with OIT and patches

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Conclusions

- IIV3/4 is safe in egg allergic children
- No special precautions needed
- LAIV is likely to be indicated in all children 2-8 years old without regard for atopy
- Opinion: CDC/ACIP will likely never get rid of couching statements due to VAERS
- Any office giving any vaccines should be comfortable in recognition and treatment of systemic reactions

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References

1. Otsu K, Dreskin S. Peanut allergy: An evolving clinical challenge. Discov Med. 2011; 12(65):319-328,.
2. Savage JH, et al. The natural history of egg allergy. J Allergy Clin Immunol 2007;120:1413-7
3. Tey, D and Heine RG, Egg allergy in childhood: an update. Curr Op Allergy Clin Immunol 2009;9:244-250
4. http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu-hcp-info.pdf accessed 3/18/15
5. Grohskopf LA, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)– United States, 2014-2015 influenza season. MMWR 2014;63(32):691-697
6. Des Roches A, et al. Egg-allergic patients can be safely vaccinated against influenza, J Allergy Clin Immunol 2012;1213-6.e.1
7. Kelso JM, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012; 130:25-43
8. Greenhawt MJ, Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy. Ann Allergy Asthma Immunol 2012;109:426-430
9. Kelso JM et al. Update on influenza vaccination of egg allergic patients. Ann Allergy Asthma Immunol 2013;111:298-305
10. Kelso JM. Influenza vaccine and egg allergy: Nearing the end of an evidence-based journey. J Allergy Clin Immunol Pract 2015;3:140-1
11. Des Roches A, et al. Safe Vaccination of patients with egg allergy by using live attenuated influenza vaccine. J Allergy Clin Immunol Pract 2015; 3(1):138-139
12. Turner PJ, et al. Safety of live attenuated influenza vaccine in atopic children with egg allergy. J Allergy Clin Immunol 2015. IN PRESS
13. Leonard S, et al. Baked milk- and egg- containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract 2015;3:13-23
14. Lemon-Mule H, et al. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol 2008;122:977-983.e.1
15. Caminiti L. et al. Oral immunotherapy for egg allergy: a double-blinded placebo controlled trial, with postdesensitization follow-up. J Allergy Clin Immunol Pract 2015; In Press

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