Objectives

1. Discuss recently published NIH/NIAID guidelines for the diagnosis and management of food allergy

2. Discuss appropriate food allergy tests for the primary care setting, and when to refer

3. Improve communication with and education of patients who request allergy tests of uncertain efficacy.

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel

- 43 concise recommendations
- Identify gaps in current knowledge
- Provide guidance on points of current controversy

Referrals for food allergies...

- 32 year old woman with a several year history of fatigue, abdominal bloating and cramping, excess gassiness, loose stools. Normal colonoscopy and celiac serology. Requesting food allergy testing, especially for gluten.
- 22 month old boy with an episode of hives, labored breathing, lip swelling after grandmother gave him peanut butter sandwich.
- 56 year old man with 5 episodes of unexplained angioedema / urticaria in past 6 months.
- 24 year old man with 10 year history of solid food dysphagia presents to ER with food impaction while eating a steak burrito. Follow-up EGD reveals eosinophilic esophagitis.
- 24 year old woman with frequent and severe migraines
Definition of food allergy

Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.

IgE-Mediated Food Allergy

- Anaphylaxis
- Acute urticaria
- Angioedema
- Immediate GI hypersensitivity syndrome
- Oral allergy syndrome

Non-IgE Mediated Food Allergy

- Allergic proctocolitis (AP)
- Food protein-induced enterocolitis syndrome (FPIES)
- Food protein-induced enteropathy
- Heiner syndrome

Oral allergy syndrome

Pollen-food allergy syndrome

- Cross reactivity between food protein and pollen protein
- Common symptoms: mouth / throat itch
  - Almost never extends beyond mouth / throat or becomes serious
- Most commonly birch, grass, ragweed pollen
- Most common food proteins:
  - Apple
  - Celery
  - Apricot
  - Cherry
  - Avocado
  - Hazelnut / walnut
  - Carrot
  - Melon

Allergic proctocolitis (AP)

- Healthy infants
- Stools with streaks of blood / mucus
- Milk and soy most common
  - Often present while nursing (maternal diet)
- Systemic symptoms, diarrhea, vomiting, failure to thrive are ABSENT
- Diagnosis: clinical, elimination, challenge
  - Colon eosinophilia
- Outgrown in early childhood (1-3)
Food protein-induced enterocolitis syndrome (FPIES)
- Infants (formula fed)
- Chronic vomiting, diarrhea, failure to thrive, dehydration, stools with blood / mucus
- Repeat challenge can result in dramatic reaction, including shock
- Milk and soy most common
- Rice, oat, wheat, fish, and poultry also reported
- Diagnosis: clinical, elimination, challenge
- Outgrown in early childhood
- Adults – crustacean shellfish

Food protein-induced enteropathy
- Uncommon condition of infants and children
- Syndrome of small bowel injury leading to malabsorption
  - (like celiac disease but less severe)
- Protracted diarrhea within first 9 mo of life
  - 50% have vomiting, failure to thrive, abdominal distension, malabsorption
- Milk most common (soy, wheat, egg)
- Diagnosis: villous injury & crypt hyperplasia on small bowel biopsy
  - Elimination, challenge?
  - Outgrown in early childhood (1-3)

Heiner Syndrome
- Rare
- Infants and young children
- Chronic or recurrent lower respiratory symptoms associated with:
  - Pulmonary infiltrates (pulmonary hemorrhage)
  - Upper respiratory symptoms
  - GI symptoms
  - Failure to thrive
  - Iron-deficiency anemia
- Non-IgE reaction to milk
- Clinical diagnosis, elimination
- Generally not outgrown

Other food allergy syndromes
- Mixed (IgE and non-IgE) Reactions
  - Atopic dermatitis
  - Eosinophilic esophagitis
  - Eosinophilic gastroenteritis
- Cell-mediated
  - Allergic contact dermatitis
  - Garlic: hand dermatitis
  - Mango: perioral dermatitis
  - Chestnut: hand and perianal dermatitis

Food allergy in atopic dermatitis (AD)
- AD and food allergy are highly associated
- 37% of children <5 yrs of age with moderate to severe AD will have IgE-mediated food allergy
- Whether food allergy can exacerbate AD is highly controversial
- Systematic review of 9 RCTs designed to assess dietary exclusions for treatment of AD found little supportive evidence
- Several studies found improvement when egg-allergic children were placed on egg-free diet
- Allergy referral for moderate to severe AD can be very helpful

Role of food allergy in eosinophilic esophagitis (EoE)
- Diagnosed by esophageal biopsy showing >15 eos / hpf
- Children: feeding disorders, vomiting, reflux, abd pain
- Adults: solid food dysphagia, reflux, impaction
- EoE is associated with IgE sensitization to foods
- Precise role of food allergy in EoE is not well defined
- IgE and non-IgE mechanisms may be involved
- Amino-acid based formula resulted in clinical improvement in 160/164 children
- Food allergy should be considered (especially in kids)
  - Skin testing, serum IgE testing, patch testing MAY be helpful
Definition of food allergy

Non-Immune Adverse Food Reactions

- Metabolic
  - Lactose intolerance
  - Fructose intolerance
  - FODMAPs
- Toxic
  - Botulism
  - Scombroid
- Infectious
  - Other
    - "Milk mucus effect"
    - Non-celiac gluten sensitivity

Food allergy?

- 32 year old woman with a several year history of fatigue, abdominal bloating and cramping, excess gassiness, loose stools. Normal colonoscopy and celiac serology. Requesting food allergy testing, especially for gluten.

Lactose intolerance

- Lactase (disaccharidase) deficiency
  - Common
  - Bloating, gas, loose stools, reflux
  - Dietary elimination helpful

Fructose Intolerance

- Monosaccharide found in fruit, increasingly used as sweetener
- Genetic deficiency of "fructose carrier" in small intestine → decreased absorption
  - Abdominal cramping
  - Bloating
  - Excess gassiness
  - Loose stools / diarrhea
- Affects 30-40% of population in Central Europe
- Diagnosed with hydrogen breath test
- Tolerability of foods containing fructose is more related to RELATIVE amounts of fructose and glucose
- Dietary elimination of high fructose foods is helpful
**THE WALL STREET JOURNAL**

*When Everyday Foods Are Hard to Digest*

GI Specialists Suspect Specific Carbohydrates May Cause Painful Symptoms of Irritable Bowel Syndrome

By MELINDA BECK  November 8, 2011

**FODMAPS** = Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols

Examples
- Lactose (dairy)
- Fructose (fruits, sweeteners)
- Fructans (wheat)
- Galactans (legumes)
- Polyols (mannitol, sorbitol)

**FODMAPs**
- IBS symptoms (gas, bloating, constipation, diarrhea)
- Many patients are poor absorbers of FODMAPs
- Widely recognized in Australia, only recently gaining attention in US
- Accumulating evidence that low FODMAP diet is effective treatment of IBS and IBS-like symptom complexes

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**THE WALL STREET JOURNAL**

*Clues to Gluten Sensitivity*

By MELINDA BECK  March 15, 2011

- At least 10% of people report symptoms or conditions that improve with dietary gluten elimination
- Objective evidence of gluten sensitivity in patients with negative evaluation for celiac disease is lacking

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**THE WALL STREET JOURNAL**

*FODMAPs*

**Some foods which contain FODMAPs to eliminate**

- Fruit (apples, pears, berries)
- Vegetables (onions, garlic)
- Dairy (milk, cheese)
- Cereals (wheat, rye)
- Beans (lentils, chickpeas)

**Some foods which are suitable for a low FODMAP diet**

- Fruit (avocado, melon)
- Vegetables (bell peppers, broccoli)
- Dairy (eggs, tofu)
- Cereals (rice, quinoa)

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**THE WALL STREET JOURNAL**

*Non-celiac gluten sensitivity Does it exist?*

- Intestinal biopsy samples of
  - 39 controls (DC)
  - 42 celiac (CD)
  - 26 gluten sensitive (GS)
- Gluten sensitivity may have unique mucosal changes distinguishing from celiac disease and normal controls
  - Altered intestinal permeability
  - Altered intra-epithelial lymphocytes
  - Altered markers of innate immunity
  - Reduced regulatory T-cells
- First evidence of objective differences between non-celiac gluten sensitivity, normal controls, and celiac disease

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*Image sources: The Wall Street Journal*
Most food allergies begin (and end) in childhood

Vast majority of adults with food allergy questions have food intolerances

Prevalence of food allergy

True prevalence difficult to establish
- Included foods
- Definition
- Self-report vs. skin test vs. food challenge

Prevalence appears to be increasing

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel

5 major topic areas
1. Definition, prevalence, epidemiology
2. Natural history
3. Diagnosis
4. Prevention

Natural History of Food Allergy

Generally outgrown Persistent
Milk (80% by age 5) Peanut (<20%)
Egg (66% by age 7) Tree nut (20-30%)
Wheat (65% by age 12) Shellfish (rarely)
Soy (69% by age 10) Fish (rarely)

Serial evaluation and oral food challenge is very important for children and adolescents with food allergies

When should food allergy be suspected?
- Anaphylaxis
- Infants and young children with ...
  - Acute urticaria
  - Moderate to severe atopic dermatitis
  - Eosinophilic esophagitis
  - Enteropathy
  - Allergic proctocolitis
- Adults with eosinophilic esophagitis
When should food allergy be suspected?

- Any combination
- Especially
  - Young children
  - Following ingestion of specific food on more than 1 occasion

Diagnosis of food allergy (IgE)

- Suspicion of food allergy should be confirmed with objective testing
  - 50-90% of presumed food allergies are NOT
  - Risks of over-diagnosis: tremendous negative impact on QoL

- 2 options:
  - Skin prick test (SPT) – generally preferred
  - Allergen-specific serum IgE (sIgE)
    - RAST, ImmunoCAP, others
    - Helpful when skin testing limited by dermatitis, dermatographism, antihistamines

- CAUTION: Positive test alone not sufficient (low PPV)
  - AVOID panels of foods

- Oral food challenge is indicated if history is suspicious and testing is negative

Nonstandardized and unproven procedures

Guideline 13: The EP recommends not using any of the following nonstandardized tests for the routine evaluation of IgE-mediated FA (not validated for use in food allergy)

- Basophil histamine release/activation
- Lymphocyte stimulation
- Facial thermography
- Gastric juice analysis
- Endoscopic allergen provocation
- Hair analysis
- Applied kinesiology
- Provocation neutralization
- Allergen-specific IgG / IgG4
- Cytotoxicity assays (ALCAT)
- Electrodermal test (Vega)
- Mediator release assay (LEAP diet)
Several large commercial laboratories offer IgG testing panels to hundreds of foods. Claims assert that IgG antibodies can identify allergies or intolerances contributing to:

- Fatigue
- Obesity
- Arthritis
- Nasal and sinus problems
- Headache / migraines
- Hyperactivity / ADHD
- Irritable bowel syndrome / Digestive disorders

Used frequently by practitioners of complementary and alternative medicine, as well as by many conventionally-trained / board certified physicians.

**IgG Food Allergy Testing**

**PRO**

- Anecdotal reports
- Published research
- Relatively inexpensive and accessible
- Objective
- Frustration / constraint / limitations associated with conventional treatments

**CON**

- Anecdotal reports
- Poor quality published research
- Cost
- IgG antibodies to foods are normal and may even indicate clinical tolerance
- High rate of false positives
- Risk of over-diagnosis of food allergy, misadjudgments, delayed diagnosis and treatment with standards of care
- Consensus of criticism among allopathic allergy specialty societies
  - EAACI
  - AAAAI
  - NIH
- Not covered by many insurance plans (investigational)

**Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial**

- 150 patients with IBS
- “True” (IgG-based) vs. sham diet
  - YorkTest ELISA
  - 29 different foods
  - 3 months
  - Primary outcome: change in IBS symptoms
  - Careful attention to dietary adherence

**Secondary outcome**

- No significant improvement except in colon symptoms in fully adherent subgroup

**Significant differences in diet**

- Wheat
- Milk

**Question of utility remains**

**Table 7**

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<th>Food</th>
<th>Treatment group</th>
<th>Sham group</th>
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<td>Milk</td>
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<td>8.4</td>
</tr>
<tr>
<td>Other</td>
<td>8.2</td>
<td>8.1</td>
</tr>
</tbody>
</table>

**Primary outcome**

- 10% greater reduction in symptom score

**Secondary outcome**

- No significant improvement in adherent subgroup

**Significant differences in diet**

- Wheat
- Milk

**Question of utility remains**
So why do so many people report benefits from IgG testing?

IgG Food Allergy Testing
Possible confounding variables
- Placebo effect
- Food intolerances
  - Lactose
  - Non-celiac gluten sensitivity
  - FODMAP
  - Others
- Natural history of symptom complex or illness

IgG Food Allergy Testing
THE BOTTOM LINE…
- Value of IgG testing to foods is uncertain (at best)
- Consensus among food allergy experts world-wide is that evidence of benefit is lacking
- Elevated IgG levels to foods are NOT consistent with current accepted definitions of food allergy (normal!!!)
- Conventional diagnostic and therapeutic considerations for symptoms should be discussed (exhausted?)
- Cost / lack of insurance coverage
- Testing and time-limited dietary elimination could be considered

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5 major topic areas
1. Definition, prevalence, epidemiology
2. Natural history
3. Diagnosis
4. Prevention (and management)

Prevention of food allergy
- Recommended:
  - Exclusive breast feeding for first 4-6 months
  - Hydrolyzed cow’s milk formula for high risk infants
  - Parent or sibling with hx of eczema, asthma, allergic rhinitis, or food allergy
- NOT recommended:
  - Maternal dietary restriction during pregnancy / lactation
  - Substituting soy milk formula for cow’s milk formula
  - Delay of introduction of potentially allergenic foods beyond 4-6 months
  - Delay of introduction of solid foods

Avoidance vs. early introduction
- 1995 (Zeiger)
  - Avoidance of allergenic foods during last trimester and infancy DID NOT reduce risk of developing food allergy
- 2000 AAP Committee on Nutrition
  - Delay introduction of foods in high risk infants
- 2008 AAP Committee on Nutrition
  - No evidence that delayed introduction reduces risk of developing food allergy

LEAP
Learning Early About Peanut Allergy
www.leapstudy.co.uk
- Does eating peanuts during infancy INCREASE OR DECREASE risk of developing peanut allergy?
- UK study of 640 children, 4-11
  - Randomized to avoidance vs. consumption
  - Outcome: development of peanut allergy at 5 yrs of age
- 2013
Prevention of food allergy reactions
- Avoidance of allergen
- Consider testing infants at high risk
- Food labeling and food allergy
  - FALCPA requires labeling of top 8 allergens
  - Precautionary labeling is voluntary
    "may contain..."
    "this product was prepared in a facility that also
    prepares products containing..."
  - Allergen content may be as high as 10%
  - EP recommends avoidance of precautionary labeled foods

Vaccination and egg allergy
- Several vaccines are grown in chick embryos
- MMR / MMRV / Imovax (rabies) are SAFE
- Yellow fever NOT RECOMMENDED
- Influenza
  - "insufficient evidence to recommend administering" to egg allergic patients
  - ACIP, AAP, and vaccine manufacturers do not recommend vaccination in egg allergic pts

Infuenza vaccination and egg allergy
- Risks of vaccinating egg-allergic patients with influenza vaccine FAR OUTWEIGH risks of not vaccinating
  - Even in patients with history of anaphylaxis
  - Skin testing with vaccine NOT helpful
  - Influenza vaccine can be administered as a single dose
  - Allergy evaluation is recommended
  - Administer in setting capable of treating anaphylaxis and observe for 30 minutes
  - Injectable TIV should be used

Emerging treatment options for IgE mediated food allergy
- Anti-IgE therapy
- Oral Immunotherapy
- Traditional chinese medicine (FAHF-2)

Anti-IgE therapy for food allergy
Omalizumab and Talizumab
- Effect of anti-IgE therapy in patients with peanut allergy.
  - 34 patients, 12-60 yrs old, RDBPCT
  - Increased sensitivity threshold from to ½ peanut to 9 peanuts
  - Stopped prematurely
  - 44% treated vs. 20% placebo increased sensitivity
- Take home:
  - Anti-IgE therapy reduces sensitivity to accidental ingestion, but does not eliminate allergy
  - Very expensive
  - Does not induce tolerance (cure)
Immunotherapy for food allergy

Peanut Oral Immunotherapy Trial (Duke / Univ Arkansas)

- Immunotherapy for treatment of food allergy is NOT recommended
- 29 peanut allergic children
- 3 phases of treatment
  - Initial day: 0.1 mg → 50 mg; doubling every 30 min
  - Build up: 50 mg → 300 mg; increase by 25 mg every 2 wks
  - Maintenance: 300 mg for 4-22 months
- Oral challenge
  - 300, 600, 1200, 1800 mg every 30 min

Immunotherapy for food allergy

Peanut Oral Immunotherapy Trial (Duke / Univ Arkansas)

- Initial escalation reaction rate: 93%
  - 79% upper airway
  - 68% abdominal
  - 61% skin
  - Most were mild

- Buildup reaction rate: 46%
  - 29% respiratory
  - 24% skin
  - 6% abdominal
  - None severe

- Maintenance reaction rate: 3.5%
  - Upper respiratory and skin symptoms most common

- 27 of 29 patients completed full challenge
  - Mild symptoms
  - 1 stopped due to parental anxiety
  - 1 stopped due to mild urticaria / vomiting

- Symptoms occur with 15-25% of doses
  - Mostly mild, oropharyngeal, occur during "initial escalation"
  - Low rate during buildup and maintenance
  - Moderate to severe reactions <1% of doses
  - Systemic reactions can occur at previously tolerated doses of allergen (exercise, viral illness, menses)

- OIT appears safe, effective, but still investigational

IgG Food Allergy Testing

- Peanut IgE levels decrease
- Peanut IgG and IgG4 antibodies INCREASE
Food Allergy Herbal Formula (FAHF)

- Herbal formula used for centuries in traditional Chinese medicine
- 11 traditional Chinese medicinal herbs
- FAHF-2 has shown equal effectiveness and enhanced safety in animal models of peanut anaphylaxis
- Safe in phase 1 trials
- Phase 2 clinical trial is ongoing (June 2012)
  - 68 subjects, age 12-45 yrs, with peanut, tree nut, fish, or shellfish allergy
  - 10 tablets TID x 6 months
  - Outcome: response to oral food challenge

An approach to the evaluation of adverse food reactions

**IgE-mediated allergy?**

- Acute urticaria, angioedema, anaphylaxis, EoE
- Child with mod-sev eczema
  - Allergy referral OR serum specific IgE testing
  - If POSITIVE:
    - Avoidance
    - Epipen (if indicated)
    - Reassess
- Oral allergy syndrome
  - Allergy referral

**Non-IgE-mediated allergy?**

- Celiac disease → serology
  - If positive → small bowel biopsy
  - If negative → depends on clinical suspicion
- Child with symptoms of:
  - Allergic proctocolitis
  - Food protein-induced enterocolitis or enteropathy
  - Pulmonary hemosiderosis
  - Empiric elimination of dairy, consider soy, egg, wheat OR allergy referral
- Allergic contact dermatitis to foods?

An approach to the evaluation of adverse food reactions

- IBS / IBS-like
  - Bloating, gassiness, nausea, loose stools
- Migraine
- Fibromyalgia
- Fatigue
- GERD
- Postnasal drip / phlegm exacerbated by milk
- Nasal congestion exacerbated by wine or beer
- Chinese restaurant syndrome (MSG)
- Food poisoning
- Positive test on IgG food allergy testing

- NOT due to food allergy
- IgE and IgG testing NOT likely to be helpful or supported by current evidence
- Primary focus should be on conventional evaluation and treatment of symptoms or condition
- Dietary changes / lifestyle modification may be helpful
  - Time limited empiric elimination?
  - Food and symptom diary?
Summary

- Most adverse food reactions in adults do not have an immune mechanism
- Most food allergies begin (and end) in childhood
- IgE testing to foods is the only validated test for diagnosing food allergies
  - BUT ...
    - Has significant limitations
    - Low positive predictive value
- Oral food challenge is a very important tool
- IgG testing has not been validated as a tool for evaluating adverse reactions to foods and is of questionable validity

THANK YOU