Food Allergy Literature Review for the Advanced Practice Provider

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TOPICS OF INTEREST

**Medical**
- Prevention
- Diagnosis
- Treatment

**Psychosocial**
- Anxiety
- Bullying
- Covid-19
PREVENTION

A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology

- Consensus statement focusing on early introduction to prevent food allergy
- Emphasizes peanut and egg should be introduced at 4-6 months
- Encourages providers to provide infant food challenges; severe reactions are rare, and OFC can be done safely

David M. Fleischer, MD,†, Edmond S. Chen, MD,‡, Corine Venter, PhD, RD,§, Jonathan M. Spiegel, MD, PhD,¶, Elissa M. Akrami, MD, MPH,†, David Stolos, MD,§, Marion Gruchy, RD,¶, Marcus Shaker, MD, MS,§, and Matthew Shafranow, MD, MBA, MD‡

Aurora, Co; Vancouver, BC, Canada; Philadelphia, PA; Winnipeg, MB, Canada

Columbus, Ohio; New York, NY, and Lebanon, NH

PREVENTION

Early life microbial exposures and allergy risks: opportunities for prevention

- Prenatal and early postnatal environment can affect healthy immune development and allergy risk
- C-section or vaginal delivery may predict possible atopy or metabolic disease in infants
- Pilot study revealed that early bacterial colonization in infants is susceptible to manipulation
- Antibiotic use before and during pregnancy increases risk of asthma
- Antibiotics overall may increase risk for childhood obesity, type 2 diabetes, asthma, and childhood IBD
- Longer duration of breastfeeding is associated with decreased R/O childhood asthma, allergic rhinitis and atopic dermatitis
- Viral infections, such as RSV may predispose to asthma
PREVENTION

No cashew allergy in infants introduced to cashew by age 1 year

- HealthNuts participants in Australia (general population)
- No child who ate cashew by 12 mo. developed cashew allergy
- Data unavailable for dose, frequency or timing of introduction
- Important first study-early introduction of tree nuts seem to be protective

DIAGNOSIS

Ara h 2-specific IgE is superior to whole peanut extract-based serology or skin prick test for diagnosis of peanut allergy in infancy

- Prospective cohort study comparing SPT, PN IgE, Ara h 1-slgE, Ara h 2-slgE, Ara h 3-slgE, and Ara h 8-slgE
- Focused on high-risk infants before PN introduction
- Found that Ara h 2-slgE was superior to PST or peanut-specific-IgE
- Authors suggest Ara h 2-slgE be used to screen for peanut allergy
DIAGNOSIS

Delayed and Severe Reactions to Baked Egg and Baked Milk Challenges

- Retrospective review of 174 OFCs
- Lower respiratory reactions more frequent during BM (37%) vs BE (12%), CM (8%) and PN (12%)
- Epinephrine administered to more BE (44%) and TN (50%) than PN (17%)
- New reaction manifestations ≥ 60 mins after OFC termination in 29% BE & 21% BM
- Consider amended dose-escalation protocols and prolonged observation after BE and BM challenges

Added Diagnostic Value of Peanut Component Testing: A Cross-Sectional Study in Australian Children

- Polysensitization to Ara h1, 2 and 3 was highly predictive of peanut allergy at detectable levels > 0.35 kU/L
- Ara h 8 and 9 were not useful in predicting outcome
DIAGNOSIS

Diagnosis of Sesame Allergy: Analysis of Current Practice and Exploration of Sesame Component 

- Sesame SPT > sesame specific IgE
- Consider sesame OFC in children with sesame SPT ≤ 6 mm
- Ses i 1 promising predictor but needs further study


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Clinical cross-reactivity among mango, pistachio nut, and cashew nut in allergic children


Anaphylaxis and allergy to coconut: An Australian pediatric case series

Pattnaikandavel K, Kaure N, Javvi P, and Ford LS

Oral food challenge outcomes in children under 3 years of age

Eskesen CA, Strofflor WF, Virreal YY, and Pfaller M.

- As many as 20% of patients allergic to cashew or pistachio may tolerate the other nut
- All tolerated mango
- Coconut is a stone fruit, not a tree nut
- Report 9 cases of anaphylaxis to coconut, and 26 cases of less severe IgE-mediated allergy
- Having a tree nut allergy was not associated with increased incidence of coconut allergy
- OFCs were safe in infants and toddlers
  - Cutaneous symptoms most frequent
- No patients required more than 1 dose of epinephrine
TREATMENT

Patient Characteristics and Risk Factors for Home Epinephrine-Treated Reactions During Oral Immunotherapy for Food Allergy

Three-year follow-up of early intervention peanut oral immunotherapy
Legby L, Kinoti Bette A, et al.

Long-term outcomes of peanut immunotherapy in children

- Milk OIT risk factor for epinephrine treated reactions at home and treatment failure
  - Predictors of worse outcome: Asthma, pre-OIT reaction severity, lower threshold dose at entry, and epinephrine-treated reactions during up-dosing
- 27/29 responders (10 completers did not respond) were eating PN
  - 2 no longer eating: 1 with EoE, 1 taste aversion
- F/up of 17 patients enrolled in OIT or SLIT trial
  - 11/17 eating peanut; others avoiding
  - QoL improved in parents but mixed in children

ANXIETY

Development of the Child- and Parent-Rated Scales of Food Allergy Anxiety (SOFAA)
Katherine K. Dahlsgaard, PhD, ABPP,*, Leah K. Wilkey, BA†, Shana D. Stites, PsyD, MS, MA‡, Megan O. Lewis, MSN, CRNP§, and Jonathan M. Spiegel, MD, PhD∥ Philadelphia, Pa.

- There was no accepted condition-specific measure of anxiety for the food allergy population
- Cognitive behavioral therapist and food allergy professionals developed SOFAA as a tool to evaluate
- Reliable way to evaluate anxiety in this population-measured in the child and parent
- 21 question tool is reliable and valid, as is the brief version
BULLYING

Food allergy-related bullying and associated peer dynamics among Black and White children in the FORWARD study

Dannielle Brown, MHS; Olivia Negris, MA; Ruchi Gupta, MD, MPH; Linda Herbert, PhD; Lisa Lemthard, PhD; Alexandra Bozen, BA; Amal Anu’All, MD; Annika Chura, BA; Aamer B. Andy-Nowey, MD; Susan Fox, MMS, PA-C; Mahboobeh Mahdavinia, MD, PhD; Mary Tobin, MD; Adam Robinson, BA; Hemant Sharma, MD, MHS; Amaaziah Coleman, MD; Jaising Jang, BA; Lucy Blavere, PhD; Jamie L. Fiorentin, PhD; Isabel Gallic, BA; Pamela Newmark, BA; Jacqueline A. Pongracic, MD; Andrea A. Papastaso, MD; Christopher Warren, PhD.

- Study evaluated bullying experiences of Black and White children with FA, including associations with peer relationships, anxiety, and school policies
- Surveys were administered to parents of 252 children with physician-diagnosed FA
- The surveys assessed demographics, atopic disease, bullying victimization, and school FA management practices and policies.
- Nearly 20% of school-aged children were bullied for FA with no substantial racial differences
- For children ages 11 years and up, white children reported higher rates of bullying.
- Black children experienced non-FA-related bullying twice as frequently as White children (38.6% vs 17.7%; P = .002).

COVID-19 PANDEMIC AND FOOD ALLERGY

High anxiety and health-related quality of life in families with children with food allergy during coronavirus disease 2019

Jennifer L.P. Proudfiler, PhD, MD; Michael Gelding, MA; Marlee R. Salisbury, BSc; Elisa M. Ahrens, MD, FRCP; Leslie E. Roos, PhD.

- Study evaluated levels of anxiety of mothers of children aged 0 to 8 years with food allergy c/w families of children without FA and the health-related QoL among children with food allergy during the coronavirus disease 2019 pandemic.
- At baseline parents with FA have more anxiety than non-FA parents
- Continued anxiety through the pandemic although some qualitative improvements noted
Questions?

Thank you!

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Anaphylaxis

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AAAAl Mast Cell Disorders Work Group, 8/2019
Proceedings from the Inaugural American Initiative in Mast Cell Diseases (AIM), 4/2021

No Disclosures
Mast Cell Activation Syndrome

- JACI 2019; 144:883-96
- JACI 2021; 147:2043-52
- Definition: Clinical condition with spontaneous and episodic systemic anaphylaxis affecting at least 2 organ systems and resulting from secreted MC mediators.

MAST CELL MEDIATORS/METABOLITES

- Tryptase
- Leukotriene >>>> LTE4/LTD4
- Histamine >>>> N-methylhistamine
- Prostaglandin D2 >>>> 11B-PGF2alpha
- Should be done at baseline and during an acute event
- Two separate times to make the diagnosis.
Symptoms

- Cardio: hypotension, tachycardia, syncope/near syncope
- Derm: urticaria, pruritus, flushing angioedema (eyelids, lips, tongue)
- Resp: wheezing, shortness of breath, inspiratory stridor
- GI: cramps abdominal pain, diarrhea, nausea, and vomiting

Triggers

- Hot water, alcohol, drugs, stress, exercise, hormonal fluctuations, infection, and/or physical stimuli (friction/pressure)
Non-validated Tests

- Lay press and some publications have broadened clinical criteria, but not accurate or validated.
- Chromogranin A
- Histamine (plasma or urine)
- Heparin
- PGD2

Conditions/symptoms not diagnostic of MCAS

- Chronic diarrhea, abdominal pain, flushing (def=episodic)
- Fatigue, fibromyalgia-like pain, dermatographism, chronically ill appearance, edema, rashes, tinnitus, adenopathy, constipation, prostatitis, chronic low back pain, headache, mood disturbances, anxiety, PTSD, weight change, thyroid diseases, polycythemia, anemia, multiple psychiatric and neurologic disorders.
- EDS, POTS (associated with H-alpha-T, not caused by MCAS)
Tryptase, specifically

- In insect stings, peak levels occur 30-90 minutes after onset of anaphylaxis
- 1/2 life= 2 hours
- Optimally, collect at 30 min- 2 hours.
- 4-6 hours okay, then compare to baseline
- Formula for diagnosing systemic anaphylaxis: sAcuteT>(1.2 x sBaselineT) + 2

Treatment

- Mast cell stabilizers
  - Ketotifin
  - Gastrocrom
- Antihistamines
- Anti-leukotrienes
- ASA (may need to be desensitized, is a mast cell degranulator)
- Glucocorticoids (steroids)
- Epinephrine for acute allergic episodes
- Venom immunotherapy for those with venom allergy
- Omalizumab/Xolair
- AVOIDANCE of triggers
Differential Diagnosis

- Benign flushing, familial flushing, endocrine disorders, neuroendocrine tumors (carcinoid), pheochromocytomas, rosacea, medications, reduced alcohol metabolism.

Cutaneous mastocytosis

- Maculopapular CM (urticaria pigmentosa)
  - Adults: maculopapular, small
  - Children: large, irregularly shaped (resolve)
- Diffuse CM (pediatric)
- Mastocytomas (infants)
- Darier’s sign
Maculopapular rash

Pediatric skin presentation
Mastocytoma

AIM’s aim

❖ ECNM, European Competence Network on Mastocytosis—established in 2002, Europe
❖ Multicenter studies on diagnostic criteria for mastocytosis published between 1990-2000, basis for 2001 WHO classification system.
❖ Multicenter registry
❖ Hope to merge registries for more robust data, and diagnostic criteria for subtypes, genetic data, co-morbidities, best practices, etc.
Anaphylaxis

Heritable risk for severe anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1

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No Disclosures
Background: Elevated basal level associated with severe anaphylaxis (i.e. hymenoptra venom). May be clonal mast cell disease or not.

Objective: Determine prevalence and associated impact of tryptase genotypes on anaphylaxis in humans.
HaT

- Methods: Cohorts: SM, venom anaphylaxis, idiopathic anaphylaxis in Italy, Slovenia, and US underwent tryptase genotyping by PCR
- Anaphylaxis severity (Mueller scale) examined.
- Control group of healthy volunteers and non-atopic disease

HaT

- Results: Hereditary alpha-tryptasemia (HaT) caused by increased alpha-tryptase-encoding Tryptase-alpha/beta 1 (TPSAB1)
- Common in healthy individuals (7 of 125, 5.6%)
- Controls with non-atopic disease (21 of 398, 5.3%)
HaT

- Associated with grade IV venom anaphylaxis (relative risk = 2.0; P < 0.5)
- More prevalent in IA (8 of 47, 17%, P = .006)
- More prevalent in SM (10 of 82, 12.2%, P = .03)
  - Among these, HaT associated with increase risk for systemic anaphylaxis (relative risk = 9.5, P = .007)

Conclusion: Risk for severe anaphylaxis in humans is associated with inherited differences in alph-tryptase-encoding copies at TPSAB1

In vitro, PAR2-dependent vascular permeability was induced by pooled mature tryptases but no alpha or beta tryptase homotetramers
HaT

❖ What does this mean for us?
❖ Noted in the general public without disease. Have they not been stung by an insect?
❖ HaT has a commercial genetic test—may help distinguish more severe anaphylaxis in patients
❖ First report of a common heritable genetic risk factor for anaphylaxis.
❖ Should we be screening? (Gene by Gene)
❖ Monoclonal antibody treatment?
❖ Did not look at idiopathic mast cell activation syndrome.

Anaphylaxis

Diagnosis and Management of Patients with the alpha-gal Syndrome

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Alpha-gal

- JACI in Practice 2020; 8:5-23
- Delayed mammalian meat anaphylaxis with positive IgE to the oligosaccharide alpha-gal
Cituximab

- Monoclonal antibody for treatment of head/neck/colon cancers
- 2006: Reactions occurring in southeast US
  - Tina Merritt, MD, Allergist, Fayetteville, AR
  - Dr. Christine Chung et.al., Oncologist, Vanderbilt, TN
  - Pre-existing IgE specific for cituximab targeting galactose-alpha1, 3-galactose on the Fab portion of the mAb.

Alpha-gal

- Prior to 2006, at least 5 patients complaining about allergic reactions eating meat (VA)
- Long delays with minimal IgE skin reactivity to meat
- Compared levels to cituximab patients and they were similar
- 2007: Meeting in KCMO
  - Dr. Barrett Lewis, MD, Allergist, Springfield, MO (FDC)
    - 12 cases, 11 had alpha-gal
Tick bites

- Similar geography of Rocky Mountain Spotted fever
- Strong association of tick bites to sensitization to alpha-gal
- Not to RMSF though
- A americium (lone star tick) don’t usually carry R rickettsia, but carry the related R ambyommatris

Symptoms and diagnosis

- From childhood to adult, but onset classically in adulthood
- Localized hives, chronic pruritus, angioedema, anaphylaxis, abdominal pain/cramping, arthritis, chronic idiopathic/spontaneous urticaria
- 2-6 hours after eating mammalian meat
- sIgE for alpha-gal (>/=2 IU/ml, or >2% of the total IgE)
  - Prick tests unreliable
Treatment

❖ Avoidance of red meat
❖ Epinephrine
❖ Antihistamines

Differential Diagnosis

❖ Cat-pork allergy also present as adults
  ❖ Well-known in Europe, virtually ignored in US.
Pearls of diagnosis

- Tick bites itch for several days/weeks
  - Patients without itchy tick bites typically not affected.
- Chiggers may also be involved
- May not have other atopic disease (allergic rhinitis)
- May not happen every time they eat the meat

Other cross-reactive foods/medications

- Milk
- Gelatin (marshmallows)
- Mammalian fats in other foods, casings
- Not part of primary avoidance, but may avoid if symptoms are noted
RARER

- Gelatin capsules, enzyme replacement (pancreatic), bovine porcine heart valves, antivenom, heparin, magnesium stearate, lactose, etc...
- Alternative medicine approaches?
  - Kinesiology
  - Acupuncture
  - May just be natural history of decreased allergy/sensitization over time.
  - Not recommended

Mechanism of Delay

- Fat tissues, arrival of allergen to peripheral tissues
- Fat in the meat assembled into chylomicrons which enter circulation after 2 hours of ingestion
- Particle size goes from 300 nm to 10-20 nm, may be able to activate mast cells in the skin, gut, arterial walls.
- Hypothesis only
Conclusion

❖ Distinguishing features from other food allergies:
  ❖ Late childhood-adult presentation
  ❖ Only food allergy cause by tick bite
  ❖ Only food allergy caused by a carbohydrate
  ❖ Delayed response and anaphylaxis

Conclusion

❖ 80% improve with avoidance of mammalian meat
❖ 5-20% may need to avoid milk/ gelatin
❖ <1% may need to avoid large number of mammalian derived products
❖ Can be “outgrown” with avoidance of tick bites.
❖ Milk and chronic arterial inflammation has also been noted, but not known what significance this has
Anaphylaxis

Clinical Presentation of alpha-gal allergy among pediatric patients with food allergy in southwest Missouri

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No Disclosures
Importance

❖ Pediatric onset and diagnosis not well studied
❖ Delay in diagnosis
❖ Severe “unknown” anaphylaxis
❖ Avoidance of unnecessary foods due to fear of reaction

Methods

❖ Healthe Analytics by Cerner
❖ Cox health systems (1 million patient population) from Northwest AR to mid MO
Prevalence

❖ Prevalence: 3.31%
❖ 2014-2018: 1298 patients with documented food allergy (0-18 years)
❖ Alpha-gal IgE > 0.35 kU/L
❖ Charts accessed to determine clinical presentation consistent with delayed allergic reaction (3-6 hours)
❖ 42 with alpha-gal
❖ 3 years to 17 years
❖ 57% male

Incidence

❖ 0.87% in 2018
Presenting Symptoms

❖ Urticaria (32 of 41, 78%)
  ❖ Anaphylaxis, angioedema, GI symptoms
❖ ER treatment (13 of 40, 32.5%)
❖ IgE ranged 0.38-67.7 kU/L
❖ History of atopy noted in majority (68.4%)

Conclusions

❖ Compared to Wilson, et.al. J All Cin Immnol Prac 2019, 
❖ Fewer patients with just abdominal pain
❖ Less patients required ER treatment
❖ Similar atopic prevalence
❖ May have diluted numbers due to initial “food allergy” generated list—not known if they were truly IgE mediated
❖ IgE<0.35 has also been noted to have symptoms, which the cut off was 0.35 in this study
Conclusion

❖ In the south and southeast, important cause of food allergy, delayed so may not be diagnosed, and in children, it does occur.
❖ In other areas, remember to get geographic history, recent travel, recent move, etc.

Thank you!!!

❖ Questions to: minh-thu.le@coxhealth.com
Hot topics from the literature

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November 6, 2021

Article #1

• Direct challenges for the evaluation of beta-lactam allergy: evidence and conditions for not performing skin testing
What do we know

- Of those labeled PCN allergic, only 5-10% are truly allergic
- Misdiagnosis leads to use of costly alternatives, treatment failure, hospital acquired infections and prolonged hospitalizations
- Current identification practices include skin testing (ST) and intradermal testing (IDT) followed by drug provocation challenge (DPT) in those ST negative
- Drug provocation challenge (DPT) is the gold standard for diagnosis

Cliff notes version of the article

- Review of previous articles reviewing the use of ST/IDT
- Review of previous articles discussing varied approaches to DPT
- Ways to assess risk
- Algorithm for management of drug hypersensitivity reactions
Assessment of risk

• Risk stratification in the evaluation of beta-lactam allergy according to index reactions adapted from EAACI guidelines

Assessment of risk

• Proposed risk-based pathway for the evaluation of PCN allergy in adults
Management in pediatric patients

- Algorithm for management of drug hypersensitivity reactions in pediatric population

Practical Application

- Benign skin reactions, especially nonimmediate reactions are considered low risk and can move straight to DPT, skipping ST and IDT
- Thorough assessment of risk and accurate description of reaction is of upmost importance
- Improved training of PCP regarding drug allergy is necessary to help in de-labeling of patients
Health disparities and inequities

Health equity is the attainment of the highest level of health which is influenced by social determinants of health (SDOH).

The social factors that impact disparities. Interventions in these areas can impact health.
Allergic Rhinitis

Current knowledge of health disparities in AR
- Allergen sensitization is higher in black children
- AR is higher in Hispanic children with asthma
- Cockroach and mouse allergens are burdens to disease
- Poor QoL is associated with AR in underserved population

Proven interventions
- Treatment with Intranasal corticosteroids for chronic disease improve outcomes
- AIT in low-income patients is associated with reduced health care use and cost savings

Future interventions
- Lower out of pockets for AIT
- Improve access to specialty care in underserved communities
- Culturally sensitive education on disease for patients should be provided
- Increase research studies addressing AR diagnosis, management and outcomes in underserved populations
Asthma

• Current knowledge of health disparities in asthma
  • Asthma prevalence is increasing
  • Morbidity is high in underserved population
  • Racial and ethnic differences in asthma are directly connected to poverty, indoor and outdoor air quality, allergens, suboptimal patient education and poor health care
  • Suboptimal prescribing and/or use of controller therapy in inner-city children

Proven interventions

• School-based awareness and medical management interventions have a positive impact on asthma outcomes
• Environmental control interventions have been implemented to reduce exposure to asthma triggers
• Telemedicine
• Share decision making

Future interventions

• More community programs need to be established
• Increasing specialists that see Medicaid patients and can prescribe biologics
• Address health care system contribution to disparities
• HCP training with cross-cultural education to reduce implicit bias
Atopic Dermatitis

- Current knowledge of health disparities in AD
  - Higher persistence and prevalence in female and black children in urban areas
  - Higher prevalence, severity and impaired QoL among blacks compared with white people
  - Increased risk of Ad is associated with urban setting, health insurance status, smaller family size and single mother households
  - AD presents differently in varying skin colors

Proven Interventions

- Differences in AD in varying racial/ethnic groups and skin color have been reported
- Tele-dermatology is effective in low-resource settings with a multilingual tele-expertise platform increasing access

Future Interventions

- Provide additional training specifically in underserved population
- Improve access to health care
- Implement culturally competent patient education efforts and shared decision making to improve patient trust
Food Allergy

- Current knowledge of health disparities in FA
  - Higher rates of FA-related anaphylaxis and ED visits in lower income and minority populations
  - Race/ethnicity was associated with sensitization to more than 1 food allergen
  - Prevalence of physician diagnosed FA in urban minority children was 3.4%, significantly lower than reported national estimates

Proven Interventions

- Disparities in FA management are documented with Black and Hispanic parents less likely to identify signs of a reaction and the food trigger
- Food insecurity is a risk factor in milk and egg allergy and is associated with lower health literacy
- Underdiagnosis and gaps in management among minority, low-income and rural children exist
- Education of school nurses and stock epinephrine

Future Interventions

- FA education as partnership between allergy specialists with PCP, patient advocacy groups and other stakeholders
- Food Insecurity should be screened and addressed
- FA action plans and epinephrine autoinjectors for all patients
- Culturally sensitive education on disease for patients should be provided
### Practical Applications

- Engage with community organizations to improve access and coordination of care for underserved groups
- Identify barriers within your practice and strategies to address
- Engage staff in implicit bias and cultural competency training
- Screening for SDOH
- Provide culturally sensitive education on disease for patients
- Advocate through medical societies and lay organizations

### Questions

- Email: Jashroba@cmh.edu