NAEM
National Association of Environmental Medicine

CLINICAL GUIDELINES: ALLERGENS

ABOUT

Allergic disease is increasing in adults and children over the last 3 decades. In 1985, food allergic reactions were estimated to occur in less than 1% of the population and today the prevalence of food allergies in adults and children is estimated to be 8-10% (based on IgE positivity). However, 20% of adults in clinical surveys believe they react allergically to foods, whether they have IgE antibodies to those foods or not. According to the recent epidemiological data, time trend analysis over the last 10 years showed up to a 7-fold increase in hospital admissions for severe food allergic reactions in children in the UK, USA, Italy and Australia. Similar increases in the prevalence of asthma, allergic rhinitis and eczema have also been seen globally.

Attempts to explain the etiology of this significant rise of allergic diseases began in the late 1980s, when building standards changed. This led to increased indoor air allergen exposure as a result of tighter insulation and less air exchange with the outdoor environment. The increased popularity of thick upholstery and carpet was believed to act as a petri dish for dust mites, fungi, and other allergens. This hypothesis was replaced in 1989 with the "hygiene hypothesis" proposed with the underlying assumption that environments devoid of contact with allergens in early

life due to "excessive hygiene" lead to increased risk for developing asthma, hay fever and eczema later on. In 2003, Rook et al. proposed a lack of exposure to non-pathogenic microbes and commensal organisms as an alternative explanation for the increased prevalence of asthma and allergic diseases leading to the "microbial diversity" hypothesis. This theory posits that increases in microbial diversity in the gut mucosa and respiratory tract are crucial in regulating the immune system and allowing for tolerance to multiple exposures that would otherwise initiate an allergic response. Modern life and lack of parasitic infections in the general population of the "developed world" prevents contact with these exposures and thus increases risk for allergic conditions. However, as more research on environmental exposures is published, it appears that exposure to specific toxicants like diesel exhaust particles, phthalates, BPA, pesticides, etc. are also closely correlated with allergic disease.

Allergic reactions can be mediated through 4 identified immune mechanisms:

- Type I or Anaphylactic Response- IgE- eosinophils
    - Mast cell degranulation and histamine release – seen in asthma, dust mite, parasites, food and drug allergy
    - EMR exposure (Electrohypersensitivity)
    - Mold/mycotoxin exposure

Although allergic reactions are classically identified as Type I reactions, research identifies Types II-IV, which are considered delayed-type reactions (DTR), as involved in the etiology of allergic reactions. In DTR the macrophages, basophils, and CD8 T cells are responsible for the symptoms rather than the antibodies.

- Type II or Cytotoxic-Mediated Response - IgG and IgM, complement and macrophages- reactions to cell surface Ag or extracellular matrix protein Ag – seen in autoimmune diseases like -ITP, SLE, and hemolysis drug reactions.
- Type III – Immunocomplex Reactions- IgM and IgG, complement and neutrophils- circulating immune complexes – leads to inflammation, and vasculitis, found in RA, SLE nephritis, Crohn's disease.
- Type IV – Delayed-Type – T cell mediated- starts day 2-3 after contact, Intracellular pathogens and contact antigens –examples are allergic contact dermatitis, dust mites, TB, Mycobacterium, Fungi, HSV, hair dye reactions, and other chemicals, nickel and other metals, poison oak or poison ivy- direct cellular damage seen in granuloma formation, sarcoidosis, TB, leprosy, Schistosomiasis, Crohn's disease, celiac disease, food protein-induced enterocolitis.

EXPOSURE GROUPS

Foods

Reactions to foods can occur as true allergic reactions or what is termed "food intolerance"-defined as an adverse response to a food that is due to the inherent properties of the food (i.e. toxic contaminant, pharmacologic active component such as caffeine, alcohol) or an abnormal response of the host (i.e. lack of enzymes such as lactase in lactose intolerance).
Intolerance can be due to presence of:

- Flavorings
- Tartrazine
- Other food colorings
- Preservatives
- Molds
- Dyes
- Additives
- Pharmacologic agents:
    - Theobromine
    - Alcohol
    - Caffeine
    - Tryptamine
    - Histamine
    - Tyramine
    - Toxic metals
    - Antibiotics
    - Pesticides
    - Food grade glutaminase (added to meat)

Food intolerance reactions tend to be dose-dependent and are not consistently reproduceable. Foods can also cross-react with respiratory allergens. Oral allergy syndrome (OAS) is caused by sensitization to respiratory allergens that are structurally similar to allergens in foods- leading to a cross-reactive immune response. The most common form of OAS develops with sensitization to the major birch pollen allergen, Bet v 1. In patients with this form of OAS, the immune response cross-reacts with allergens in plant-derived food such as:

- Apples
- Nuts
- Carrots
- Celery

This leads to localized itching and swelling of the lips or tongue, caused by IgE-mediated mast cell degranulation.

Food Additives

- Food coloring: tartrazine (FD&C Yellow No. 5 and E102) - the immune system can mount IgE, IgG, or IgA antibody production against food colorants.
- Gum-based food additives:
    - Mastic gum
    - Carrageenan alginates
    - Agars
    - Xantham gum
    - Guar gum
    - Gum tragacanth
    - Locust bean gum (carob bean)
    - β-glucan (made by fungi and yeasts as well as specific pathogenic bacteria) can cross-react with foods based on their protein structure. These antigenic components of gums can cross-react with carbohydrate components in pollen of the olive tree, Japanese cedar, and Bermuda grass and in glycoproteins of celery, potato, tomato, bean, soybean, and pea. Allergenicity of these gums may be significant: a small study of 288 individual serum samples found 15.6%-29.1% positive for IgE elevation to a variety of 7 gums tested. Thirteen percent showed an elevation of IgE to all 7 individual gums. The strongest evidence for cross-reaction was with β-glucan for IgE: kidney bean, shrimp, pea protein, peanut, pineapple rice, corn, lentil, and sesame.
- Microbial Transglutaminase (mTg) A microbially-produced enzyme used widely in the processed food industry: mTg improves gelation and changes emulsification, foaming, viscosity and water-holding capacity. It is considered the “glue of proteins” or “meat glue” improving food palatability, texture and shelf-life. Like human tissue transglutaminase (tTg- used as screening test for celiac disease) mTg can bind to gliadin and facilitate its uptake contributing to celiac disease.
  Microbial Transglutaminase:
    - Enhances intestinal permeability
    - Suppresses mucus and immunological (anti-phagocytic) protective barriers in the gut
    - Stimulates luminal bacterial growth
    - Augments the uptake of gliadin peptide, thus it can imitate tissue transglutaminase. Epidemiological data show a strong correlation between the surges of celiac disease incidence and the consumption of enzymes in the bakeries, mTg being a major one. PMID: 32046248

Air Pollution

Air pollution is strongly associated with asthma onset and exacerbation of asthma, particularly in children with atopy. Components of air pollution related to allergy are:

- Diesel Exhaust Particles (DEP) - DEP are composed of a center core of elemental carbon and adsorbed organic compounds including polycyclic aromatic hydrocarbons (PAHs and nitro-PAHs) and small amounts of sulfate, nitrate, metals, and other trace elements. Diesel exhaust particles contribute almost 60% of airborne traffic pollution and directly stimulate IgE synthesis.
- Ozone, Nitrous Oxide - Results of clinical studies also suggest that exposure to ozone and nitrous oxides may "prime" the eosinophils to activation by inhaled allergens. All of the above pollutants can also bind to pollens and airborne biological allergens, working as carriers and increasing the allergenicity of pollens. PMID: 11453319

Pesticides

- Organophosphate Pesticides
- Carbamates
- Pyrethrins

See Pesticide Clinical Guidelines for more information.

Mold

Mold and mycotoxin exposure are strongly linked to respiratory irritation and inflammation. See Mold Clinical Guidelines for more information.

Metals

Metals, particularly those implanted surgically or through dental procedures can be sensitizing and lead to both dermal, oral, and systemic allergic conditions. See Metal Clinical Guidelines for more information.

Personal Care Products

- Fragrance (phthalates)
- Formaldehyde
- Iodopropynyl butylcarbamate (a preservative)
- Epoxy and (meth)acrylate compounds (nail polish)
- Hair dyes

- Hair bleaches
- Cocamidopropyl betaine and preservative agents in shampoo
- Benzophenones in sunscreen
- Butylene glycol
- Pentylene glycol
- Cocamidopropylbetaine
- Octoxyglycerin
- Methoxy PEG-17
- PEG-22/dodecyl glycol copolymers (skin-conditioning agents).
- Triclosan

See Personal Care Product Clinical Guidelines for more information.

Solvents

- Formaldehyde
- Benzene
- Toluene
- Ethylbenzene
- Xylene

Airborne exposures to the above in nail salon workers were comparable to those measured in studies of oil refinery and auto garage workers.

EXPOSURE SOURCES

See Clinical Guidelines for: Mold, Pesticides, Solvents, Plastics

EHQ

- Had a sudden onset of symptoms (headaches, skin rashes, nausea, fatigue, shortness of breath, etc.) on exposure to fragrance, cigarettes, mold, dust, pollens or other environmental allergens?
- Ever had to leave your residence or job because your environment was making you sick?
- Avoid the detergent isle in a store because it makes you feel ill or have other symptoms?
- Easily get rashes or skin irritation though contact with clothing or body care products?
- Live or work near heavy traffic, airport, gas station, or idling vehicles?
- Use bleach and other chemical cleaners in home or work?

Occupation

- Use chemicals/paints for the following: painting, printing, leatherwork, photo
- Been exposed to interior or exterior paints, stains, finishes, removers
- Been exposed to glues, epoxies, resins, solvents
- Live or work nearby farm or orchard
- Live or work nearby vineyard
- Live or work nearby golf course
- Use pesticides or herbicides used inside your home

Home/workplace or outside on grass or garden

- Have indoor/outdoor animals
- Have animals chemically treated for fleas etc.
- Use antibacterial soap (triclosan)
- Use moth balls
- What percentage of your food is organically grown?
- Be sure to include foods you eat at restaurants
- Dental work including root canals, implants, or bridgework
- Implants (hip, shoulder, etc.) or have had any metal implanted in your body (screws, plates, etc.)
- Do you use personal care products?

Have you ever been or are you currently exposed to the following? (home, work, school, travel, etc.)

- Shampoo/conditioner/body gel
- Toothpaste/mouthwash/dental floss
- Perfume/cologne/scented products
- Hairspray/hair gel/hair dye
- Moisturizer, foundation, eyeshadow, eyeliner, mascara, blush, lipstick, lip gloss, powder
- Sunscreen/sunblock/self-tanners
- Nail polish/nail remover
- Hand soaps/detergents for clothes and dishes/ dryer sheets/bleach/fabric softener
- Plug-in air fresheners/scent sticks/scented candles/room spray/underarm antiperspirants
- Food additives
- Coloring agents
- Liquid and bar soaps
- Green hand sanitizer

- Moisturizers and lotions
- Mouth washes
- Perfumes
- Toothpastes
- Shampoos, conditioners, and other hair products
- Cosmetics such as nail polish, nail polish remover, temporary tattoos, and tanning lotions
- Vitamins
- Antacids
- Cold medications, including cough drops and throat lozenges
- Lotions and creams
- Prescription drugs
- Food Additives
    - Gums (see Exposure Groups above)
    - Trans-Glutaminase (see Exposure Groups above)

EHQ Follow-Up

Evidence for exposure to Mold, Pesticides, Solvents, Plastics, or Personal Care Products may lead to Avoidance or Testing and will be detailed in those specific Clinical Guidelines. Exposure to foods, food additives or contaminants can be followed with guidance on avoidance of specific foods and food additives/contaminants along with testing for allergy/sensitivity (See Testing).

KINETICS

See Clinical Guidelines for: Mold, Pesticides, Solvents, Personal Care Products, Plastics.

Air Pollution

Air pollution particles (diesel exhaust particles) are metabolized directly in the lung and live through Phase II metabolism. The ability to metabolize air pollutants is influenced by single nucleotide polymorphisms and gene deletions, primarily related to glutathione production and recycling.
PMID: 25680669, 27613366, 24215577- For all of the above food allergy symptoms.

HEALTH EFFECTS

Foods

- Atopic dermatitis
- Asthma
- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Dermatitis herpetiformis
- Contact dermatitis
- Food-induced pulmonary hemosiderosis (Heiner's Syndrome)
- Food protein-induced enteropathy syndrome
- Celiac disease
- Pruritus erythema/flushing urticaria
- Angioedema
- Pruritus
- Tearing conjunctival injection
- Periorbital edema
- Pruritus nasal congestion
- Rhinorrhea
- Sneezing
- Hoarseness
- Laryngeal edema
- Cough
- Wheezing
- Dyspnea
- Chest tightness/pain
- Oral pruritus
- Oral angioedema (lips, tongue, or palate)
- Pharyngeal pruritus/tightness
- Colicky abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Tachycardia
- Dizziness
- Loss of consciousness/fainting
- Hypotension
- Metallic taste in mouth
- Uterine cramping/contractions
- Sense of impending doom

- Joint pain
- Migraine
- Blurring of vision
- Ringing in the ears and earaches
- Rhinitis from chronic sinusitis
- Cold and flu symptoms
- Palpitations, arrhythmia
- Nausea, vomiting, diarrhea, and constipation
- Chronic muscle/joint aches and swelling, rheumatoid arthritis, and fibromyalgia
- Unexplained salt/water retention
- Eosinophilic esophagitis
- Proctocolitis
- Enterocolitis

PMID: 25680669, 27613366, 24215577- For all of the above food allergy symptoms.

Food Additives

- Atopic dermatitis, asthma and urticarial attacks. PMID: 25599186

Air Pollution

- Asthmatic bronchitis
- Rhinitis
- Hay fever
- Eczema
- Sensitization to airborne pollens
- Asthma- Atmospheric levels of ozone and nitrous oxides have been linked to increases in respiratory morbidity and in hospital admissions for asthma in children and adults. PMID: 25936911
- Air pollutants cause airway mucosal damage and impair mucociliary clearance, possibly increasing levels of inhaled allergens and promoting airway sensitization. Particulate matter and ozone are also related to oxidative stress that leads to airway inflammation and hyperreactivity.
- Diesel exhaust particle (DEP) combined challenge with an allergen enhances local IgE production 20- to 50-fold in contrast to the 2-3 times increase in allergen-specific immunoglobulin E (IgE) produced with allergen exposure alone.
- Individuals with a GSTM1 gene variant (GSTM1 null) revealed a 3.5-fold higher risk of developing asthma, suggesting a heightened allergic airway response. Those with the most enhanced susceptibility to the adjuvant effects of DEPs were those with both GSTM1-null and GSTP1-Ile/Ile genotypes. Since the

frequency of polymorphisms of GSTM1 AND GSTP1 genes (GSTM1-null genotype or the GSTP1-Ile/Ile genotype) is approximately 40%, protecting those individuals from exposure and improving GST function appears important to the population as a whole.

Pesticides

- Asthma or asthmatic symptoms in adults and children.
- Respiratory dysfunction in the general population.
- In utero and/or early life exposures to environmental OPs may increase risk for childhood asthma.
- Occupational exposures to OP pesticides are associated with decreased lung function, wheezing, and adult-onset asthma. PMID: 24479117, 24881073, 21368619, 24287863

Mold

- Allergic-type rhinitis
- Tearing of eyes
- Metallic taste in mouth
- Sinus congestion
- Nasal drainage
- Increased thirst
- Throat irritation
- Sinusitis
- Rhinitis
- Shortness of breath
- Asthma
- Respiratory tract damage (aflatoxin)
- Hypersensitivity pneumonitis

Personal Care Products

- Contact photo-dermatitis and contact urticaria PMID: 21461388
- Allergic rhinitis-a cohort of 10-year-old Norwegian children were twice as likely to have allergic rhinitis if they were in the highest quartile of triclosan concentration compared to lowest PMID: 23146048

Solvents

- Occupational exposure to formaldehyde is linked to lung damage. PMID: 30933751

- Asthma, hay fever, and chemical odor intolerance were linked to exposure to perfume, pesticide, drying paint, new carpet odor, and car exhaust in a group of patients that had diagnosed allergies and chemical sensitivities. Those with chemical odor intolerance were significantly more likely to report upper and lower respiratory symptoms. PMID: 10416292
- Asthma linked to exposure to natural gas, disinfectants, chlorinated water, room deodorizers, and environmental tobacco smoke. Hay fever linked to exposure to drying paint, and car exhaust. PMID: 10416292

Phthalates

- Higher urine concentrations of monobenzyl phthalate in mothers during pregnancy increased the risk of food allergy in children during the first 2 years of life (odds ratio 4.17). There were no associations with children's urine and allergic symptoms. PMID: 26108074
- Eczema, rhinitis, and asthma in children associated with elevated DEHP levels from PVC- dust exposure from vinyl flooring. PMID: 15471731
- Levels of both high and low molecular weight phthalates (DMP, DEHP, DiBP, and BBzP) in floor dust associated with the prevalence of allergic rhinitis, conjunctivitis, and atopic dermatitis in children. PMID: 24704966

BPA (Bisphenols)

- Asthma in boys associated with 3rd trimester urine levels of BPA in mothers. PMID: 29550712
- Asthma in both sexes correlated with urine levels of BPA at 3,5, 7 years of age and onset asthma at 5-12 years of age. PMID: 23452902
- Asthma in children with higher urine BPA metabolite levels and GSTP1 single nucleotide polymorphism had 4.84-fold higher susceptibility to asthma. PMID: 29411558

ELIMINATION

- See Individual Clinical Guidelines for above Toxicants.
- See Solvent Clinical Guidelines for information about Diesel Exhaust.
- No information is available about elimination pathway of food additives and food colorings.
- Air pollution (diesel exhaust particles) are eliminated in urine and feces, no information is available about elimination through skin or breastmilk.

LAB TESTING

Intradermal Skin Testing

Performed by allergists and environmental medicine providers, this test was the original skin scratch test later modified by Herbert Rinkel MD in 1935 as the Skin Endpoint Titration or SET test and currently called the intradermal dilutional test (IDT). The wheal reaction to injected antigen is staged: "immediate" (within 10-15 min), "late stage" (6-24 hours) or "delayed skin response" (48 hours or later post injection). Reactions are then treated with serial dilutions of the antigen. This immunotherapy technique is used to treat food, chemical, metal, mold, pollen, dust, dander, and fungal allergies/sensitivities in order to de-sensitize the immune system. The process of finding the serial endpoint and treating with that dilution is termed provocation/neutralization testing and treatment. Below is one commonly used list of allergens tested by the IDT.

Training for providers is offered by the American Academy of Environmental Medicine and PAN American Allergy Society (http://aaem.org http://wp.paas.org)

Oral Provocation Testing

Oral provocation tests are considered the most accurate diagnostic test for identifying food allergic reactions in the diagnosis of clinically relevant IgE-associated and non-IgE associated food allergies. These involve placing patients on elimination diets and re-introducing foods or providing an open oral challenge. A double-blind, placebo-controlled food challenge is the standard for antigen identification.

IgG/IgE Antibody Testing

Results from serologic and in vitro tests alone are not sufficient for the diagnosis of IgE-associated food allergies because the presence of allergen-specific IgE is not always associated with symptoms.

Several position papers strongly recommend against testing for food antigen-specific IgG in the diagnosis of food allergy, due to a non-standardization and non-validation of the test methodologies. Exceptions to these recommendations exist, however, with a strong correlation of IgG food antibody positive tests and the etiology and subsequent treatment through avoidance of Crohn's disease, irritable bowel syndrome, and migraine. PMID: 22505375, 22429360, 23216231

TREATMENT OPTIONS

Avoidance
Toxicants

Avoidance of exposure to environmental toxicants can be found in the respective Clinical Guidelines of above individual toxicants.

Food Allergies

Although oral food immunotherapy (timed and measured introduction of the identified allergic food) is becoming a standard of care for pediatric allergies, 10–30% of participants withdraw because of adverse reactions.

Treatment
Probiotics

Multiple human studies have shown that those with food allergies have distinctly altered gut microbiomes when compared to those with no known food allergies. The induction of tolerance to food requires regulatory T cell production and activation, both in the gut and elsewhere and this is initiated via the microbiome. Probiotics have been theorized to be helpful due to their positive influence on the T cell expression and the development of tolerance.

- L. rhamnosus CGMCC 1.3724 used with peanut oral intolerance testing (OIT) in children with peanut allergy. Dosage: 2X 10^{10} colony-forming units (freeze-dried powder) once daily together with peanut OIT (peanut flour, 50% peanut protein. Treatment duration: 18 mos. Outcome: tolerance achieved in 82.1% of patients receiving probiotics and OIT compared with 3.6% of those receiving placebo, the highest rate of tolerance reported for any food immunotherapy treatment evaluated in a randomized controlled study at the time.
- Lactobacillus rhamnosus GG (a minimum of 1.4 x 10^7 CFU/100 mL) improved tolerance to cow's milk in cow's milk allergic infants vs allergic control group as well as improvement in atopy at 3-yr follow-up.

Quercitin

Reduces or inhibits: IL-8 and TNF-α (more effectively than cromolyn sodium), NF-kappaβ activation, IL-6 release. Improves contact dermatitis and photosensitivity - 500 mg qid of water-soluble form. PMID: 224704

Elimination Diet

The elimination diet is considered by the conventional allergists and environmental medicine providers as the most important and relevant long-term management strategy for food allergies. It follows testing with elimination and challenge protocols. The treatment includes the use of immunomodulating and gut-barrier healing nutrients and supplements as well as the elimination of food additives as listed above.

SIT/SLIT

Allergen-specific immunotherapy (SIT) is currently the only allergen-specific and disease-modifying treatment that has demonstrated long-term effects in large clinical trials. SIT is used mainly to treat respiratory allergies, and less frequently to treat food allergies because standardized vaccines are not available. In the case of food allergies, SIT often is performed orally, by administration of the offending food instead of a vaccine.

Sublingual Immunotherapy (SLIT) involves the introduction of very low doses of the triggering antigens. SLIT can also modulate the GI mucosal immune response, with the goal of promoting oral tolerance. SLIT involves the use of a liquid concentrate administered under the tongue.

Provocation/Neutralization

See Lab testing – Intradermal Skin Testing

RESOURCES FOR CLINICIANS

Brostoff J and Challacombe SJ. Food Allergy and Intolerance. Balliere Tindall, England. 1987

Training for intradermal provocation and neutralization testing is offered by the American Academy of Environmental Medicine (aaem.org) and PAN American Allergy Society (http://wp.paas.org)

RESOURCES FOR PATIENTS

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