December 2013

General considerations:

• The purpose of this educational material is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

• The content of this educational material does not intend to replace the clinical criteria of the physician.

• If there is any correction or suggestion to improve the quality of this educational material, it should be done directly to the author by e-mail.

• If there is any question or doubt about the content of this educational material, it should be done directly to the author by e-mail.

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December 2013 – content:


- **CD8+ T CELLS PRODUCING IL-3 AND IL-5 IN NON-IGE-MEDIATED EOSINOPHILIC DISEASES** (Stoeckle C, Simon H-U. Allergy 2013; 68: 1622–1625).


- **ILLUSTRATIVE CASES ON INDIVIDUALIZING IMMUNOGLOBULIN THERAPY IN PRIMARY IMMUNODEFICIENCY DISEASE** (Bonagura VR. Ann Allergy Asthma Immunol 2013; 111: S10-13).


• **MANAGING COMORBID COMPLICATIONS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY** (Ballow M. Ann Allergy Asthma Immunol 2013; 111: S6-S9).


• **OPTIMIZING IMMUNOGLOBULIN TREATMENT FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE TO PREVENT PNEUMONIA AND INFECTION INCIDENCE: REVIEW OF THE CURRENT DATA** (Ballow M. Ann Allergy Asthma Immunol 2013; 111: S2-S5).


• **VENTRICULAR FIBRILLATION AFTER ORAL ADMINISTRATION OF AMOXICILLIN AND CLAVULANIC ACID** (Shahar E, Roguin A. Ann Allergy Asthma Immunol 2013; 111: 573-574).


ALLERGY:

  - False-negative diagnosis of drug allergy can lead to severe reactions after exposure.
  - False-positive diagnosis of drug allergy can lead to unnecessary avoidance.
  - Previous studies: (i) 1% of patients with IgE-mediated allergy to penicillin were also reactive to imipenem and meropenem; (ii) 5.5% of patients with T-cell-mediated allergy to β-lactams (mostly penicillins) were also reactive to imipenem/cilastatin.
  - Authors studied 204 subjects (15-79 years old) with demonstrated T-cell-mediated allergy to β-lactams (mainly maculopapular exanthemas to penicillins; 4 cases of toxic epidermal necrolysis) → all subjects tolerated drug challenges to carbapenems (with previous skin testing).
  - Author’s commentaries: (i) carbapenems were tolerated in all subjects with T-cell-mediated hypersensitivity to penicillins (hypothesis: penicillins do not share common side chains with carbapenems); (ii) in patients with delayed allergy to penicillin who need carbapenem therapy, pretreatment skin tests and graded challenges are advisable (at least in subjects who experienced severe reactions).

  - Anaphylaxis: (i) definition: acute severe multisystemic allergic reaction, potentially fatal; (ii) lifetime prevalence: 0.0582%; (iii) incidence: 1/10,000 patient-yr (incidence is increasing; 0-4 yr-old children have higher incidence rates); (iv) mechanisms: release of mediators from mast cells and basophils (mainly IgE-mediated reactions; IgG-mediated mechanisms have been shown in mice); (v) most common culprits: foods, drugs, hymenoptera venom, latex; (vi) factors that influence severity: pathogenic mechanism, allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors; (vii) important comorbidities: atopic dermatitis, asthma, allergic rhinitis, food allergy.
  - Augmentation factors (cofactors) for anaphylaxis (↓ anaphylaxis threshold; appear in up to 30% of anaphylactic episodes; >1 cofactor may be needed to elicit anaphylaxis): (i) physical exercise: most frequent cofactor (e.g. ‘food-dependent exercise-induced anaphylaxis’, which only occur in the presence of exercise; described for wheat, shrimps, meat, pistachio, spinach, etc.; most frequent with hard exercise and high degree of food sensitization; may also occur with minimal exercise [e.g. ironing]); differential diagnosis: cholinergic urticaria, exercise-induced asthma, physical urticaria; (ii) alcohol: relevant factor in up to 15% of anaphylactic episodes; (iii) infections (mild or severe): relevant factor in up to 11% of episodes; may complicate venom or pollen immunotherapy (SIT must be paused or ↓ during infections); (iv) NSAIDs: relevant factor in up to 9% of episodes; (v) other drugs: mast cell-activating drugs (iodinated RCM [most frequently iomeprol and iopromide], muscle relaxants [most frequently suxamethonium], quinolones, opioids), drugs that ↑ bradikinin levels (e.g. ACE inhibitors), drugs that ↓ gastric acid (proton pump inhibitors, H2-receptor blockers [↑ risk of anaphylaxis in patients with oral allergy syndrome due to acid-sensitive allergens]), drugs that block...
counteracting mechanisms during anaphylaxis (β-adrenergic antagonists, ACE inhibitors, angiotensin receptor blockers); (vi) menstruation; (vii) stress.

- **Mechanisms underlying cofactor-induced anaphylaxis:**
  1. ↑ gut permeability (exercise-induced, alcohol-induced, NSAID-induced [e.g. NSAIDs ↓ expression of the tight junction protein claudin-7]) → ↑ allergen bioavailability;
  2. ↓ activation threshold of mast cells and basophils (exercise-induced, NSAID-induced, infection-induced, drug-induced);
  3. ↑ synthesis of leukotrienes (NSAID-induced);
  4. ↓ gastric acid (drug-induced) → ↑ allergen bioavailability;
  5. immune system stimulation (infection-induced): formation of IgG and IgM immune complexes, release of complement anaphylotoxins (C5a is more potent than C3a for mast cell degranulation; mucosal mast cells do not express anaphylotoxin receptors), cell activation through innate immune receptors (e.g. peptidoglycan can induce mast cell degranulation).

- **Approach to a patient with a history of anaphylaxis:**
  1. evaluate all potential triggers (e.g. food, drugs, insect stings, exercise [or food + exercise], temperature changes, menstruation) within 6 hrs before symptom onset (idiopathic anaphylaxis can account for 60% of adult cases);
  2. assess severity by taking a thorough history of all signs and symptoms (place and time of onset, duration, recurrence, response to treatment);
  3. exclude differential diagnosis (e.g. mastocytosis, mast cell activation disorder, carcinoid syndrome, neuroendocrine tumors, drug-induced flush [niacin, nicotine, ACE inhibitors, corticosteroids, cathecolamines], alcohol related flush [alone or in combination with drugs such as disulfiram, griseofulvin or cephalosporins], acute coronary syndrome, pulmonary embolism, postprandial syndromes [ingestion of monosodium glutamate or sulfites, scombroidosis], hereditary angioedema, vocal cord dysfunction syndrome, panic attack, somatoform disorder);
  4. perform proper laboratory tests (serum tryptase, plasma histamine, urinary histamine metabolites, serum PAF, serum PGD2, in vivo and in vitro allergy tests, allergen challenges, tests to exclude differential diagnosis [e.g. imaging studies if suspicion of neuroendocrine tumors, neuropeptide levels if suspicion of carcinoid syndrome, bone marrow biopsy if suspicion of mastocytosis]);
  5. give detailed written indications to prevent and quickly treat further anaphylaxis episodes (e.g. trigger avoidance, use of medical identification, use of autoinjectable epinephrine [2 injections are needed in up to 30% of episodes], quickly assume recumbent position with feet elevated until complete CV recovery, avoidance of some drugs [β-blockers and MAO inhibitors can ↓ epinephrine action; ACE inhibitors can ↓ angiotensin action and ↑ bradykinin levels]).

- **Importance of component-resolved diagnosis (CRD) to assess anaphylaxis risk:**
  1. CRD can help to determine patient’s sensitization on a molecular basis (e.g. specific IgE to Ara h 2 [main peanut allergen]; specific IgE to prolamins or cupins [plant allergens with high anaphylactic potential]; specific IgE to PR-10 proteins or profilins [heat-labile or acid-labile plant allergens with low anaphylactic potential]; specific IgE to ovomucoid [Gal d 1, an egg-white allergen resistant to heat and digestion, associated with persistent and severe allergic reactions]);
  2. CRD can help to define clinical entities (e.g. specific IgE to omega-5-gliadin in patients with wheat-dependent exercise-induced anaphylaxis; specific IgE to galactose-alpha-1,3-galactose in patients with delayed-type immediate allergy to red meat);
  3. CRD can help to identify cross-reactive allergens (e.g. latex-fruit allergy syndrome; mite-cockroach-crustacean allergy syndrome; pork-cat allergy syndrome; allergy to cross-reactive carbohydrate determinants [CCDs] in plants, latex or Hymenoptera venoms; allergy to parvalbumin [a fish panallergen]).
- Specific antibody response to food allergens in non-allergic individuals: high specific IgG, intermediate specific IgM, very low specific IgE.

- Specific antibody response to food allergens in allergic individuals: ↑ production of specific IgE.


  - Authors present a 14-page position paper about asthma and exposure to cleaning products.

  - Work-related asthma (WRA): (i) occupational asthma (OA): asthma caused by exposure to agents in the workplace; can be sensitizer-induced or irritant-induced (‘asthma without latency’, which includes RADS [reactive airway dysfunction syndrome] and ‘not-so-sudden’ irritant-induced asthma); (ii) work-exacerbated asthma (WEA): pre-existing asthma exacerbated in the workplace.

  - Professional and domestic cleaning products (cleaning sprays, bleach, ammonia, disinfectants, mixing products) have been associated with: (i) OA (most cleaning agents have an irritating effect on airways; few agents induce IgE-sensitization [e.g. chloramine-T, enzymes]); (ii) WEA; (iii) respiratory symptoms without asthma.

  - How to prevent and reduce asthma due to cleaning products? (i) substitute cleaning sprays, bleach and ammonia; (ii) minimize use of disinfectants; (iii) avoid mixing products; (iv) avoid aerosolization of products (low-volatility liquid products are less associated with asthma); (v) improve labeling of cleaning products; (vi) use respiratory protection; (vii) educate workers, companies, consumers and general population about the correct use and risk of cleaning products; (ix) promote research in the field (large-scale longitudinal studies); (x) promote collaboration between scientific organizations (e.g. EAACI, WAO) and safety/health agencies (e.g. European Agency for Safety and Health at Work, European Chemicals Agency, Occupational Health and Safety Administration); (xii) reinforce law regulation about chemical hazards.


  - Atopic dermatitis (AD): (i) common chronic skin disease (3% of adults, 20% of children); (ii) impact: ↓ QoL, high costs, ↑ predisposition to skin infections (bacterial, viral) and other allergies (asthma, allergic rhinitis); (iii) pathogenic factors are multiple (genetic, epigenetic, environmental) and result in varied clinical phenotypes; (iv) normal looking, nonlesional skin of AD patients shows invisible inflammation and barrier defect → ‘proactive therapy’ is encouraged (long-term, low-dose intermittent anti-inflammatory therapy to previously affected skin + continuous emollient treatment of unaffected skin).

  - Pathogenic factors for AD: (i) Skin barrier defects: scratching, ↓ synthesis of epidermal barrier proteins (e.g. filaggrin, loricrin, involucrin, cornodesmosin, S100 proteins, desmoglein 1, proteases, antiproteases [e.g. LEKTI], tight junction proteins [e.g. claudin-1]) due to genetic mutations or TH2-cytokine influence (e.g. histamine action) → increased entry of allergens through skin, ↑ susceptibility to skin infections (e.g. eczema herpeticum).
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• **Innate immune dysregulation:** ↑ inflammatory dendritic cells, altered TLR signalling (e.g. TLR2 gene polymorphism), ↓ production of antimicrobial peptides (e.g. cathelicidin, defensins), ↑ keratinocyte production of cytokines that promote a TH2 environment (e.g. TSLP, IL-25, IL-33), ↑ production of neuropeptides (AD is usually associated with stress).

• **Adaptive immune dysregulation** (determined by genetic factors [e.g. polymorphisms in IL4RA, hypomethylation of FcεRIγ8chain-DNA]) and environmental factors [e.g. Staphylococcal superantigens, allergens, low vit D]): ↑ TH2 inflammation (IL-4, IL-13, IL-5, IgE, IL-31 → promote skin barrier dysfunction and pruritus), ↑ TH22 inflammation (promotes acanthosis), altered TH1 responses (predisposition to viral and bacterial infections [e.g. eczema herpeticum]), altered TH17 responses (predisposition to bacterial and fungal infections), ↓ Treg responses.

• **Exaggerated immune responses** to food allergens (e.g. milk, egg), aeroallergens (e.g. house dust mites), microbial molecules (e.g. from S. aureus or Malassezia sp) or self antigens (e.g. human thioredoxin).

• **Abnormal skin colonization by microbes:** S. aureus colonizes the skin in 90% of AD patients (staphylococcal enterotoxins induce polyclonal T-cell and B-cell activation; staphylococcal extracellular vesicles induce inflammation).

• **TH2 responses:** (i) driven by TH2 lymphocytes; (ii) important cytokines: IL-3, IL-4, IL-5, IL-9, IL-13; (iii) pathogenic mechanisms: IgE production, mast cell, basophil and eosinophil activation.

• **TH22 responses:** (i) driven by TH22 lymphocytes; (ii) important cytokine: IL-22; (iii) pathogenic mechanisms: keratinocyte proliferation, diffuse epidermal hyperplasia (acanthosis).

• **Filaggrin:** (i) important protein for the integrity of skin barrier; (ii) expressed by keratinocytes; (iii) not expressed by nasal, bronchial or esophageal epithelium; (iv) main source of pyrrolidone carboxylic acid [PCA] and urocanic acid [UCA] (components of the natural moisturizing factor); (v) loss-of-function FLG gene mutations occur in 30% of AD patients (however, 8% of healthy subjects also carry those mutations); (v) TH2 cytokines ↓ filaggrin synthesis.

• **Desmoglein 1 deficiency** → ↓ epidermal intercellular adhesion → severe dermatitis, multiple allergies, metabolic wasting.

• **Tmem79 (MATT in humans) deficiency** → abnormal lamellar granule secretory system in the epidermis → altered stratum corneum formation → pathogenic factor in atopic dermatitis.

• **Immune effects of vitamin D:** (i) ↑ production of antimicrobial peptides (e.g. LL37, the only human cathelicidin known so far); (ii) improve phagocytosis; (iii) ↓ maturation of dendritic cells; (iv) ↑ Treg differentiation; (v) ↑ TH2 differentiation; (vi) ↓ IgE production (inhibition of activation-induced deaminase?); (vii) controversial effect (protective or aggravating?) on allergic diseases; (viii) synthetic vit D receptor agonists are being developed (immunomodulatory action without hypercalcemic effects).

• **Therapy of AD:** (i) trigger avoidance; (ii) emollients; (iii) topical corticosteroids (advantages: potent antiinflammatory effect, ↑ expression of filaggrin and loricrin; disadvantages: ↓ restoration of stratum corneum, ↓ expression of involucrin and small proline-rich proteins); (iv) topical calcineurin inhibitors (advantages: do not impair skin barrier restoration; disadvantages: less potent antiinflammatory effect compared to corticosteroids); (v) other therapeutic options:
antihistamines (H1R blockers), antimicrobials, omalizumab, immunosuppressants, UV phototherapy, immunotherapy, acupuncture; (vi) research therapies: H4R blockers (↓ pruritus, ↓ skin inflammation), topical PPARα activators, cannabinoids.

• ‘Futuristic’ therapy of AD: determine specific AD phenotypes and endotypes using clinical, laboratory, histologic and genetic biomarkers → individualize therapy.

• Risk factors for allergic contact dermatitis (ACD): (i) atopic dermatitis; (ii) skin barrier defects (eg. filaggrin defects?); (iii) repetitive contact with potential allergens.

• When to suspect ACD? Chronic recurrent or therapy-resistant eczema, even in young children.

• Contact allergens in children: (i) metals: nickel (most common contact allergen), cobalt, chromate; (ii) preservatives, solvents, emulsifiers; (iii) rubber chemicals; (iv) topical drugs (chlorhexidine, neomycin, steroids, emollients, natural remedies); (v) fragrances.

• Where are contact allergens frequently encountered? (i) shoes: potassium dichromate, p-phenylenediamine (PPD), p-tert-butylphenol-formaldehyde (PTBF) resin; (ii) perfumes; (iii) jewelries: nickel; (iv) cosmetics; (v) temporary or permanent tattoos: PPD; (vi) shin guards: rubber chemicals, thiourea derivates; (vii) hair dyes: PPD; (viii) clothing: dyes (often involve thighs), formaldehyde (‘wrinkle resistant’), rubbers; (ix) diapers: ‘Lucky Luke’ dermatitis (sensitization to rubber components → affection of outer buttocks and hips, similar to a cowboy’s gun belt holsters), miliaria-like rash under the stickers; (x) drugs (e.g. topical corticosteroids).

• Products that may contain or cross-react with PPD: hair dyes, azo dyes, tattoos, sulfonamides, p-aminobenzoic acid sunscreens, benzocaine, procaine.

• Diagnosis: patch tests (gold standard) → (i) include all relevant allergens according to the clinical history; (ii) patch tests with topical corticosteroids should be read at ≥7 days; (iii) negative patch test results do not fully exclude ACD.

• Treatment: (i) topical steroids (be careful with sensitization); (ii) emollients (be careful with sensitization); (iii) allergen avoidance (be careful with product’s labeling).

• Prevention: (i) avoid repetitive contact with potential allergens (eg. nickel-containing jewelries, PPD-containing tattoos); (ii) promote laws about product’s manufacturing (eg. nickel content in jewelries); (iii) restore skin barrier in patients with atopic dermatitis; (iv) improve labeling of manufactured products (eg. cosmetics).

• Causes of perioral dermatitis in children: (i) atopic dermatitis; (ii) lip licking; (iii) inhaled steroids; (iv) ACD: sunscreens with a high protection factor, toothpaste, dental fillings, chewing gum.

• Chronic urticaria (CU); (i) definition: recurrent wheals for >6 wks (concomitant angioedema may occur); (ii) lifetime prevalence: up to 20% of the general population; (iii) impact: significant morbidity, ↓ QoL, high socioeconomic impact; (iv) main classification: spontaneous (no clear triggers; 50% of cases are ‘autoimmune’), inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise); spontaneous and inducible urticaria can occur in the same patient; (v) 1st-line treatment: anti-H1 at usual dosing (50% of patients may not respond); (vi) 2nd-line treatment: up to quadruple dose of anti-H1 (50% of patients may not respond → antihistamine-resistant CU); (vii) other reported therapies: mast cell-stabilizing
drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A, sulfasalazine, chloroquine, dapsone, pseudoallergen-free diet, anticholinergic agents, androgens (e.g. stanozolol), selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants; (viii) prognosis: 50% of cases may resolve spontaneously within 1 yr; 75% of cases within 5 yrs.

- ‘Gold standard’ to diagnose autoimmune CU: (i) positive in vivo test showing autoreactivity (e.g. autologous serum skin test); (ii) positive functional bioassay (e.g. basophil activation); (iii) positive immunoassay (e.g. specific IgG antibodies to FcεRIα).

- Pseudoallergens (food additives, vasoactive substances, fruits, vegetables, spices) and NSAIDs may cause CU flares;

- D-dimer may be used as a biomarker for antihistamine-resistant CU (hypothesis: eosinophil infiltration → secretion of tissue factor and VEGF → activation of coagulation cascade → ↑ D-dimer plasma levels).

- Recent reports in drug allergy: (i) selective COX-2 inhibitors (e.g. celecoxib, etoricoxib) may be unsafe in patients with intolerance to paracetamol (urticaria, angioedema); (ii) HHV-6 reactivation occurs in >60% of cases of DRESS syndrome (hypothesis: DRESS syndrome → HMGB-1 is released from damaged skin → HMGB-1 attracts monomyeloid precursors harboring HHV-6 to the skin → HHV-6 infects and replicates in skin-resident CD4+ T cells → HHV-6 reactivation → flaring of symptoms); (iii) published success rates for sulfonamide desensitization in HIV patients or antibiotic desensitization in cystic fibrosis patients reach 80% (slower protocols tend to be more effective than rush protocols); (iv) skin testing with drugs (especially β-lactams) is not risk free; (v) multiple drug hypersensitivities may occur in up to 10% of patients with severe drug hypersensitivity reactions (in these patients, drug-reactive T cells may have a lower threshold for activation); (vi) NOD gene polymorphisms and atopic status were associated with beta-lactam allergy.

- **CD8+ T CELLS PRODUCING IL-3 AND IL-5 IN NON-IGE-MEDIATED EOSINOPHILIC DISEASES** (Stoeckle C, Simon H-U. Allergy 2013; 68: 1622–1625):

  - IL-5, IL-3, GM-CSF (eosinophil hematopoietins): (i) crucial cytokines for eosinophil development, survival and function; (ii) activated CD4+ Th2 cells have been considered as the main source; (iii) CD8+ T cells can be an important source (Tc2 population).

  - Eosinophils: (i) multifunctional effector cells; (ii) normal blood counts: <500 cells/µL (eosinophilia: >500 cells/µL; hypereosinophilia: >1500 cells/µL).

  - Causes of blood eosinophilia: helminthic infections, allergic diseases (e.g. atopic dermatitis, asthma, rhinosinusitis, eosinophilic esophagitis), paraneoplastic eosinophilia, hypereosinophilic syndromes, immune dysregulation.


• **Diagnosis of CRS:** (i) nasal blockage or nasal discharge (anterior or posterior) + facial pain/pressure or hyposmia, (ii) objective clinical, endoscopic or radiologic evidence of sinonasal inflammation (e.g. polyps, mucopurulent discharge, edema).

• **Pathogenesis of CRS:** (i) **Anatomic/structural problems:** nasal septal deviation, nasal valve dysfunction, concha bullosa (enlarged nasal turbinate caused by internal ethmoid air cell), adenoid hyperplasia (mainly in children), nasal choanal narrowing, nasal or sinus mucoceles, scarring from prior nasal or sinus surgery, septal perforations, nasal foreign body, malignancies.

• **(ii) Altered immunity:** altered epithelial barrier (↓ epithelial tight junctions [occludins, claudins, etc], ↑ repairing proteins [psoriasin, calgranulin A and B, SPINK5]); ↓ ciliary clearance (cystic fibrosis, primary ciliary dyskinesia); ↓ antimicrobial peptides (defensins, psoriasin, PLUNC family, lysozyme, lactoferrin); ↓ TLR responses (especially TLR2 and TLR9); ↓ STAT3 function; ↑ immune activation (T-cell responses [TH2, TH17, TH22], IgE, IgA, effector cells [mast cells, eosinophils], autoantibodies, IL-32); immunodeficiencies (eg. agammaglobulinemia); inflammatory diseases (eg. Wegener’s granulomatosis, sarcoidosis, aspirin-exacerbated respiratory disease); ↑ remodeling (TGF-β, MMPs, TIMPs).

• **(iii) Infections (bacteria, fungi, virus, biofilms):** role is not fully defined → antibiotics may help (macrolides and doxycycline have been suggested due to antibacterial and antiinflammatory properties); biofilm destabilizing agents may help; some patients respond to antifungals.

• **(iv) Pollutants and drugs:** cigarette smoke, pollutants, cocaine, topical vasoconstrictors.

• **CRS phenotypes:** (i) CRS with nasal polyps (CRSwNP): 4% of the population, TH2 environment (eosinophilic inflammation), better response to intranasal corticosteroids; (ii) CRS without nasal polyps (CRSsNP): ↑ remodeling (TGF-β, MMP, TIMP, collagen), predominance of neutrophils.

• **Possible CRS endotypes:** (i) fungal-induced endotype (eg. allergic fungal RS); (ii) S. aureus-induced endotype (superantigens favor TH2 milieu; IL-4 and IL-13 ↓ immunity to S aureus); (iii) mucosal barrier defect endotype; (iv) innate immune defect endotype; (v) TH2/IgE eosinophilic endotype; (vi) TH17/neutrophilic endotype; (vii) autoimmune endotype; (viii) drug-induced endotype (eg. AERD); (ix) remodeling endotype.

• **Treatment of CRS:** (i) nasal irrigation/douching; (ii) intranasal and oral corticosteroids; (iii) antibiotics; (iv) surgery; (v) other therapies: antihistamines, LTRA, 5-lipoxygenase inhibitors, allergen immunotherapy, biological agents (monoclonal antibodies, soluble receptors, cytokines), aspirin desensitization, topical and oral antifungals, decongestants, mucolytics (eg. n-acetylcysteine), phototherapy, MTX, protein pump inhibitors, capsaicin, furosemide, vit D, Manuka honey, bromelain, quercetin, undecylenic acid, urtica dioica, massage of the sinus ostia with swabs of botanical essential oils, air purifiers, diets.

• ‘Futuristic’ therapy of CRS: determine specific CRS phenotypes and endotypes using clinical, laboratory, histologic and genetic biomarkers → individualize therapy.

• **Immunoglobulin A (IgA):** (i) 1st-line defence mechanism in mucosas; (ii) main function: neutralization of pathogens and hazardous particles; (iii) origin: mucosal plasma cells produce IgA dimers → epithelial cells transport IgA dimers into mucosal secretions (GI mucosa, urogenital mucosa, respiratory mucosa, tears, saliva, breast milk) using the polymeric immunoglobulin receptor (pIgR).
• Authors show ↓ plgR expression in patients with chronic upper airway diseases (CRSwNP, CRSsNP, allergic rhinitis) → ↓ secretory IgA in nasal secretions, ↑ subepithelial IgA → ↑ susceptibility to respiratory infections, ↑ eosinophilic inflammation.

• Other diseases that may present ↓ local plgR expression: severe COPD, lung cancer, nasopharyngeal cancer.

• EAACI POSITION STATEMENT ON ASTHMA EXACERBATIONS AND SEVERE ASTHMA

  • Authors present a 14-page position paper about asthma exacerbations and severe asthma.

  • Severe asthma: (i) includes untreated asthma, difficult-to-treat asthma and therapy-resistant asthma; (ii) occurs in up to 10% of asthmatics; (iii) impact: high morbidity, significant mortality, high costs; (iv) >80% of patients with difficult-to-treat asthma show poor adherence to therapy.

  • Risk factors for severe asthma: (i) genetic susceptibility (e.g. genetic variants affecting epithelial barrier, innate immunity or adaptive immunity; genetic variants that ↑ asthma risk in one environment may ↓ risk in another environment), (ii) respiratory infections, (iii) comorbidities (e.g. severe nasosinusal disease, obesity, GERD), (iv) pollutants (e.g. smoking, particulate matter), (v) sensitization to fungi (e.g. severe asthma with fungal sensitization).

  • Futuristic approach in asthma/wheezing: use of clinical data and biomarkers to identify specific asthma/wheezing phenotypes and endotypes → give individualized therapy (e.g. leukotriene-induced asthma → give antileukotrienes).

  • A patient with uncontrolled asthma may have: (i) unawareness of disease severity; (ii) a physician who is undertreating or not recognizing the effect of comorbidities; (iii) low adherence to treatment; (iv) treatment-resistant disease; (v) an alternative diagnosis.


  • Authors highlight recent findings in the mechanisms of allergic inflammation with potential therapeutic relevance.

  • Recent findings: (i) the allergic effector unit (interaction between mast cell and eosinophil based on secreted mediators [e.g. leukotrienes] and on ligand-receptor binding [e.g. CD48-2B4]) has a central role in maintaining allergic inflammation; (ii) basophils can promote and amplify allergic inflammation; (iii) PGD2 acts through CRTH2 to recruit eosinophils, basophils and TH2 lymphocytes (CRTH2-antagonists are promising therapies in allergic diseases); (iv) local production of glucocorticoids (GCs) occur in vivo (therapies that promote local GC synthesis can ↑ local GC availability and ↓ systemic side effects); (v) selective GC receptor modulators (SGRMs) can retain the antiinflammatory effects of GC while reducing GC adverse effects; (vi) vitamin D has immunomodulatory functions (↑ epithelial barrier, ↑ synthesis of antimicrobial peptides, ↑ phagocytosis, ↓ activation of dendritic cells, ↑ Treg and TH2 differentiation); (vii) the nuclear protein poly(ADP-ribose) polymerase-1 (PARP-1) promotes allergic inflammation by
inhibiting STAT-6 degradation (PARP-1 inhibitors [e.g. oral olaparib] are promising therapies in allergic diseases); (viii) high-dose intravenous immunoglobulin (target serum IgG levels=2500-3500 mg/dL) has several antiinflammatory mechanisms (anti-idiotypic binding to pathogenic autoantibodies, cell inhibition by FcγRIIb stimulation, ↑ tolerogenic DCs, ↑ Treg differentiation, ↑ death of activated leukocytes [e.g. eosinophil death by antibodies to Siglec-8; neutrophil death by antibodies to Siglec-9], ↓ production of inflammatory molecules [e.g. adhesion molecules], ↑ antimicrobial defense); (ix) SNPs in every TLR gene have been linked to asthma (some SNPs are also linked to atopic dermatitis and atopy); (x) the NLRP3 inflammasome promotes experimental allergic asthma (the NLRP3/IL1 pathway is a potential therapeutic target in allergic diseases); (xi) extracellular ATP from damaged cells ↑ allergic airway inflammation acting through type 2 purinergic receptors (ATP-degrading molecules [e.g. CD39, CD73] and P2 receptor antagonists are potential therapies in allergic diseases); (xii) there are at least two itch sensory fibers (histamine-sensitive C-fibers [responsive to histamine] and mechanically-sensitive C-fibers [responsive to heat and mechanical stimulation]); (xiii) the natriuretic polypeptide b (Nppb) and the gastrin-releasing peptide (GRP) are important itch neurotransmitters (novel therapeutic targets); (xiv) itching substances include histamine, serotonin, leukotrienes, proteases, substance P, IL-31, nerve growth factor (NGF), TLR7 agonists, lysophosphatidic acid, autotoxin; (xv) patients with atopic dermatitis have a lower itch threshold and perceive a prolonged itch duration; (xvi) much of the itch in cold contact urticaria is mediated by the H1-receptor (presumably on the histamine-sensitive C-fiber itch pathway); (xvii) the histamine H4 receptor (H4R) is important for the activation of mast cells, eosinophils, monocytes, dendritic cells and T cells (promising therapeutic target).
ANNALS OF ASTHMA, ALLERGY & IMMUNOLOGY:

  - **Alcohols**: organic compounds characterized as primary (e.g. ethanol), secondary or tertiary based on their chemical structure.
  - **Metabolism of ethanol**: alcohol dehydrogenase (ADH) converts ethanol into acetaldehyde → aldehyde dehydrogenase (ALDH) converts acetaldehyde into acetic acid.
  - **Nonimmunologic reactions to alcohol**: (i) mechanisms: vasodilation, direct mast cell activation, activation of prostaglandin receptors (benefit from NSAIDs?), activation of opioid receptors (benefit from naloxone?); (ii) clinical manifestations: flushing, urticaria, rhinitis, asthma.
  - **Immunologic reactions to alcohol**: (i) mechanisms: specific IgE or T cells against ethanol metabolites (e.g. specific IgE against acetaldehyde-protein conjugates) [specific IgE to an ethanol-protein conjugate has not been reported]; (ii) clinical manifestations: systemic dermatitis (delayed-type reaction?), asthma (acetaldehyde-induced?), anaphylaxis (acetic acid-induced?) [fatal anaphylaxis has been reported].
  - **Risk factors for adverse reactions to alcohol**: female sex, allergic rhinitis, asthma, aspirin-exacerbated respiratory disease, COPD, ALDH polymorphism (↓ metabolism of acetaldehyde → accumulation of acetaldehyde → mast cell degranulation → flushing, tachycardia, nausea), ADH polymorphism, deficiency in diamine oxidase (DAO, an histamine-degrading enzyme; alcohol may accentuate DAO deficiency), interaction with drugs (e.g. griseofulvin, metronidazole, chlorpropamide, disulfiram, topical tacrolimus).
  - **Alcohol beverages** are made using ethanol and non-ethanol components.
  - **Reactions to non-ethanol components in beer**: grains (barley, wheat, hops [including LTPs]), modified grain proteins (by fermentation or germination), brewer's yeast (Saccharomyces cerevisiae), contaminating molds (e.g. Aspergillus niger).
  - **Exercise-dependent alcohol-induced reactions** are related to the ingestion of wheat in beer.
  - **Reactions to non-ethanol components in wine**: grape (including LTP), yeast, preservatives (sulfur dioxide, potassium metabisulfite), contaminants (e.g. contamination with Hymenoptera allergens during grape harvesting).
  - **Reactions to non-ethanol components in distilled liqueurs**: e.g. whisky, vodka; grape, grains, gold (associated with lichen planus), additives, contaminants (e.g. oak in barrels during aging process), preservatives.
  - **Diagnostic approach to patients with adverse reactions to alcohol**: (i) clinical history: clinical manifestations, age of onset (e.g. new onset alcohol-induced flushing should alert for serious disorders such as lymphoma), type of alcoholic beverage, concomitant factors (e.g. drugs, exercise), (ii) skin testing (e.g. patch testing) to ethanol and acetaldehyde in patients with suspected ALDH polymorphism; prick testing in patients with suspected allergy to raw/malted
grains, yeast or grapes); (iii) oral challenge: with the alcoholic beverage or its components (e.g. acetic acid, grains, metabisulfite); (iv) genetic analysis of polymorphisms in alcohol-metabolizing enzymes; (v) other laboratory tests (e.g. tryptase levels to assess mast cell degranulation).

- Treatment of patients with adverse reactions to alcohol: (i) should be individualized; (ii) includes avoidance, prophylactic antihistamines (e.g. for alcohol-induced urticaria or ALDH2-related bronchoconstriction), opioid antagonists (e.g. for alcohol-induced flushing), supplementation with DAO (e.g. for DAO deficiency), desensitization to the culprit component (e.g. allergy to grapes), autoinjectable epinephrine, medical bracelets.

  - Alpha1-antitrypsin (AAT): (i) structure: 52-kDa glycoprotein; (ii) sources: hepatocytes (main source); locally secreted by epithelial cells, alveolar macrophages and neutrophils; (iii) functions: inhibition of proteinases (e.g. trypsin, elastase, cathepsin-G), inhibition of the cytotoxic effects of neutrophil defensins → lung protection from inflammatory damage; (iv) postulated protective levels of serum AAT=11 µmol/L.
  - AAT deficiency (AATD): (i) etiology: genetic mutations in AAT gene; (ii) clinical manifestations: early-onset COPD (may initially present with asthma-like symptoms), liver disease, necrotizing panniculitis (uncommon manifestation); (iii) variable symptomatology (from asymptomatic to severe cases) depending on AAT levels/activity (clinical disease usually occurs when <30% of normal protein levels); (iv) AATD and asthma may coexist (asthma is common in patients with AATD); (v) distinguishing AATD from asthma based on clinical evaluation is not possible (AATD may occur in 3% of patients catalogued as poorly controlled asthma); (vi) AATD is underdiagnosed (mostly due to unawareness and variable clinical expression); (vii) AATD clinical course is aggravated by factors that ↑ lung inflammation (smoking, infections, asthma); (viii) diagnosis of AATD relies on laboratory assays.

- Guidelines recommend screening for AATD in patients with: (i) chronic obstructive lung disease; (ii) asthma and irreversible airflow obstruction; (iii) unexplained liver disease; (iv) necrotizing panniculitis (in adults); (v) siblings affected by AATD.

- When to suspect AATD in patients with asthma? (i) late-onset asthma; (ii) moderate to severe disease; (iii) lack of response to therapy; (iv) irreversible airflow obstruction; (v) progressive lung function deterioration; (vi) lack of improvement after smoking cessation; (vii) negative allergy testing; (viii) normal FENO levels during active symptoms; (ix) predominance of neutrophils rather than eosinophils in bronchial lavage or biopsy; (x) negative methacholine or mannitol challenge results; (xi) hyperinflation on lung images; (xii) concomitant liver disease; (xiii) necrotizing panniculitis; (xiv) family history of emphysema or unexplained cirrhosis.

- Diagnosis of AATD: (i) clinical history; (ii) laboratory testing: AAT serum level, AAT phenotype (by gel electrophoresis); (iii) genetic testing.

- Treatment of AATD (depends on severity): (i) avoidance/control of lung-damaging factors (e.g. smoking, asthma); (ii) augmentation therapy with intravenous AAT; (iii) lung transplantation

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- **Summary statements:**

  - (1) Minimize exposure of susceptible children to dust mite (DM) allergens to ↓ risk of IgE sensitization (although most attempts at primary prevention have been unsuccessful). *(Strong recommendation; A evidence).*

  - (2) Minimize exposure of DM-sensitized children to DM allergens to ↓ risk of developing asthma and possibly rhinitis. *(Strong recommendation; A evidence).*

  - (3) Minimize exposure of DM-sensitized patients with asthma or rhinitis to DM allergens, other relevant allergens and irritants (mite emanations have IgE-independent proinflammatory properties). *(Strong recommendation; B evidence for asthma; C evidence for rhinitis).*

  - (4) Minimize exposure of DM-sensitized children with atopic dermatitis to DM allergens. *(Moderate recommendation; C evidence).*

  - (5) In DM-sensitized crustacean-naive patients, no recommendation can be made regarding crustacean ingestion (although 5-15% of patients who are highly sensitized to DM also are sensitized to crustaceans). *(No recommendation; D evidence).*

  - (6) Evaluate for DM-sensitization in patients who complain of IgE-mediated symptoms after ingestion of grain flour regardless of the presence of wheat-specific IgE. *(Moderate recommendation; C evidence).*

  - (7) Test patients with suspected DM allergy for DM-specific IgE using SPT or *in vitro* testing. *(Strong recommendation; B evidence).*

  - (8) There is no evidence supporting routine measurement of specific IgE to DM components; such measurements may be considered in special cases (e.g. patients with suspected sensitivity to Der p 10 [tropomyosin, also found in cockroach and crustaceans]). *(Weak recommendation; D evidence).*

  - (9) Encourage DM-allergic patients to use a hygrometer to measure home humidity. *(Strong recommendation; D evidence).*

  - (10) Relative humidity (RH) in the home should be permanently kept at 35-50% to ↓ DM growth (mites require RH >65% to prevent water loss and to thrive; if RH >65% for 1.5 hrs/day, as could occur during cooking or bathing, mites can survive; if RH >65% for 3 hrs/day, mites can produce eggs). *(Strong recommendation; B evidence).*

  - (11) Do not recommend acaricides to eliminate DM because of limited efficacy and concerns about risk of chemical agents. *(Moderate recommendation; B evidence).*

  - (12) Physical measures to kill mites (heating, freezing, desiccation) theoretically should be beneficial. *(Weak recommendation; D evidence).*

  - (13) Bedding should be washed weekly to ↓ DM numbers and allergen levels; high temperature is not necessary (risk of burning). *(Strong recommendation; B evidence).*
• (14) When symptoms persist despite efforts to ↓ DM, suggest measurement of DM allergens in settled home dust. (Weak recommendation; D evidence).

• (15) Measurement of airborne DM allergens offers no benefit over their measurement in settled dust and therefore should not be recommended. (Moderate recommendation; C evidence).

• (16) Recommend regular vacuuming using cleaners with HEPA filtration or a central vacuum with adequate filtration or that vents to the outside. (Strong recommendation; B evidence).

• (17) Recommend the use of DM allergen-proof mattress, box spring and pillow encasings. (Strong recommendation; B evidence).

• (18) Discourage subjects with an atopic background to sleep in bunk beds. (Moderate recommendation; B evidence).

• (19) Do not recommend tannic acid to ↓ DM allergens in carpet dust because it is marginally effective. (Moderate recommendation; C evidence).

• (20) HEPA filtration alone is of uncertain benefit, although it can ↓ airborne DM allergens and some irritants. (Weak recommendation; C evidence).

• (21) Recommend a multifaceted approach for DM avoidance (maintaining RH at 35-50%; regular washing of bedding; regular vacuuming with a high-efficiency vacuum; use of mattress and pillow encasings; HEPA filtration if necessary). (Moderate recommendation; A evidence).

• (22) Consider SCIT in DM-allergic patients with rhinitis or mild/moderate asthma. (Strong recommendation; A evidence for asthma; B evidence for rhinitis).

• (23) Consider SCIT for DM-allergic patients with atopic dermatitis (disease might exacerbate initially). (Moderate recommendation; A evidence).

• (24) Patients receiving DM immunotherapy should receive a dose of 7 µg of Der p 1 or 500-2,000 AU per injection to obtain an optimal balance between efficacy and safety. (Strong recommendation; A evidence).

• (25) US DM extracts can be mixed with pollen, grass and animal dander extracts; at maintenance phase, US DM extracts can be mixed with fungal or cockroach extracts when glycerin content is kept at 10%. (Moderate recommendation; LB evidence).

• (26) DM immunotherapy should last 3 to 5 years for optimal benefit. (Moderate recommendation; A evidence).

• (27) Currently there is no FDA-approved SLIT product in the US (although certain SLIT protocols have been safe and effective for DM-allergic patients with rhinitis, mild/moderate asthma and atopic dermatitis [e.g. 4,200 AU containing ~70 µg of Der f 1 given daily]). (Moderate recommendation; A evidence).

**EVALUATION AND MANAGEMENT OF HYPERSENSITIVITY TO PROTON PUMP INHIBITORS**


• Proton pump inhibitors (PPIs): most potent gastric acid-suppressing drugs; usually well tolerated; hypersensitivity reactions (HSR) are rare; anaphylaxis has been reported.
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- **Recommended solutions for SPT:** omeprazole 40 mg/mL, pantoprazole 40 mg/mL, esomeprazole 40 mg/mL, lansoprazole 30 mg/mL, rabeprazole 20 mg/mL.

- **Recommended solutions (non irritant) for IDT:** 1:1000, 1:100 and 1:10 diluted solutions of the concentrations listed above.

- **Oral drug challenges** (increasing doses at 30-min intervals): (i) omeprazole capsule: 5, 10, 20 mg; (ii) lansoprazole capsule: 7.5, 15, 30 mg; (iii) pantoprazole tablet: 5, 10, 20 mg; (iv) rabeprazole tablet: 5, 10, 20 mg; (v) esomeprazole tablet: 5, 10, 20 mg. [Allergy 2013; 68: 1008–1014].

- **Sensitivity, specificity, NPV and PPV of skin tests with PPIs** [Allergy 2013; 68: 1008–1014] = 58.8%, 100%, 70.8%, 100%, respectively.

- Author’s reviewed 39 articles about HSRs to PPIs → (i) 118 cases of immune-mediated HSRs to 5 PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole); (ii) 86% of the HSRs were suspected to be IgE-mediated; (iii) most common clinical manifestations: urticaria (54%), generalized itching (52%), angioedema (38%), hypotension (23%), skin rash other than urticaria (21%), erythema (20%), dyspnea or shortness of breath (20%); (iv) omeprazole was the most frequent culprit PPI (probably due to more time in the market); (v) skin testing showed variable cross-reactivity patterns among PPIs (omeprazole and pantoprazole were more likely to cross-react; lansoprazole and rabeprazole were more likely to cross-react; lansoprazole and dexlansoprazole may cross-react); (vi) authors propose an algorithm for the evaluation and management of patients with a suspected HSR to PPIs.

- **Important points:** (i) skin testing may help in the diagnosis of hypersensitivity to PPIs; (ii) skin testing may help to evaluate cross-reactivity among PPIs; (iii) in patients with suspected allergy to PPIs and negative skin testing, oral drug challenges should be performed after evaluating risk-benefit.

- **Approach to patients with confirmed hypersensitivity to a PPI:** (i) use an alternative gastric acid-suppressing drug (if feasible); (ii) use a non-cross-reacting PPI (if feasible); (iii) consider desensitization with the culprit PPI (if the patient needs the drug obligatorily and there is no absolute contraindication).

**ILLUSTRATIVE CASES ON INDIVIDUALIZING IMMUNOGLOBULIN THERAPY IN PRIMARY IMMUNODEFICIENCY DISEASE** (Bonagura VR. Ann Allergy Asthma Immunol 2013; 111: S108-S13):

- **Uses of intravenous immunoglobulin (IVIG):** replacement therapy in primary and secondary immunodeficiencies; immunomodulatory therapy in autoimmune and inflammatory diseases.

- **Uses of subcutaneous immunoglobulin (SCIG):** replacement therapy in primary immunodeficiencies.

- **Important points:** (i) each patient has a specific ‘biological’ serum IgG level associated with reducing or preventing infection; (ii) in patients who receive replacement therapy with IG, dosing should be individualized to achieve the ‘biological’ serum IgG (instead of trying to achieve a single ‘optimal’ serum IgG level for all patients); (iii) the ‘biological’ serum IgG level in a specific patient must be identified by plotting documented infections vs serum IgG levels over time (these plots help to convince insurance providers about appropriate IG dosing).
• **KETOTIFEN IN THE MANAGEMENT OF CHRONIC URTICARIA: RESURRECTION OF AN OLD DRUG** (Sokol KC, Amar NK, Starkey J, Grant JA. Ann Allergy Asthma Immunol 2013; 111: 433-436):

  - Chronic urticaria (CU): (i) definition: recurrent wheals for >6 wks (concomitant angioedema may occur); (ii) lifetime prevalence: up to 20% of the population; (iii) impact: significant morbidity, ↓ QoL, high costs; (iv) main classification: spontaneous (no clear triggers; 50% of cases are ‘autoimmune’), inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise); spontaneous and inducible urticaria can co-occur; (v) 1st-line treatment: anti-H1 at usual dosing (50% of patients may not respond); (vi) 2nd-line treatment: up to quadruple dose of anti-H1 (50% of patients may not respond → antihistamine-resistant CU); (vii) other reported therapies: mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototheraphy, cyclosporin A, sulfasalazine, chloroquine, dapsone, pseudoallergen-free diet, anticholinergic agents, androgens, selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants; (viii) prognosis: 50% of cases may resolve spontaneously within 1 yr; 75% of cases within 5 yrs.

  - Ketotifen might be an excellent drug to manage CU resistant to conventional therapy → (i) mechanisms of action: ↓ release of mast cell/basophil mediators (e.g. histamine, arachidonic acid metabolites, inflammatory cytokines and chemokines); calcium antagonist activity; ↓ responses to PAF; ↑ sensitivity to β2-agonists; (ii) advantages: oral administration; high bioavailability; rapid onset of action (although it may take up to 6 wks to achieve full prophylactic value); excellent safety profile; low cost; wide use experience in other mast cell-mediated diseases (asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, mastocytosis); (iii) disadvantages: adverse effects (sedation [10-20% of patients], dizziness, CNS stimulation, dry mouth, headache, nausea, weight gain, reversible thrombocytopenia [after concomitant use with glyburide or metformin]); not FDA-approved for CU.

  - Recommended dose: (i) adults and older children: ketotifen 1 mg twice daily; (ii) children from 6 months to 3 yrs old: 0.5 mg twice daily.

• **LATE ELICITATION OF MACULOPAPULAR EXANTHEMAS TO IODINATED CONTRAST MEDIA AFTER FIRST EXPOSURE** (Bircher AJ, Brockow K, Grosber M. Ann Allergy Asthma Immunol 2013; 111: 576-577):

  - Delayed adverse reactions to iodinated contrast media (ICM): (i) time of onset: 1 hr to 1 wk after ICM use; (ii) clinical manifestations: rash, nausea, headache, myalgia, fever; (iii) maculopapular exanthemas are common (likely T-cell mediated, typically 1-2 days after reexposure to ICM).

  - Immune reactions to drugs require a sensitization phase (5 to 10 days) after the 1st encounter with the drug (except in the case of previous exposure to a cross-reactive molecule).

  - Authors report 5 patients who had a delayed maculopapular exanthema 5 to 10 days after the 1st exposure to ICM (hypothesis: sensitization occurred within the 1st days after exposure, reaction occurred because the ICM persisted in the skin for several days) → allergologic tests (1 to 5 months after the reaction): positive skin tests compatible with T-cell mediated allergy.

  - Author’s commentary: (i) for ICM, a 1st single exposure might be sufficient to induce T-cell sensitization and elicitation of a late-onset exanthema; (ii) this pattern of sensitization and rash-elicitation after a single exposure has not been reported with other systemic drugs.

  - **Anaphylaxis**: potentially fatal severe allergic reaction; **1st-line treatment**: injectable epinephrine (at-risk patients are indicated to carry epinephrine autoinjectors).

  - **Limitations of epinephrine autoinjectors**: autoinjector size, low rates of carrying, underuse, parenteral route, incorrect injection technique, misfiring, unintentional injection, availability of only 1 dose, short shelf-life of epinephrine solution (autoinjector should be replaced annually).

  - **Potential advantages of sublingual epinephrine**: (i) convenient administration route (sublingual mucosa is thin and has abundant blood supply → substances can be rapidly absorbed through the epithelium); (ii) noninvasive; (iii) easier to use.

  - **Problems of 1st-generation sublingual epinephrine tablets**: (i) intrinsic bitter taste of epinephrine; (ii) slow dissolution of epinephrine; (iii) high epinephrine dose required for optimal absorption.

  - **Advantages of new-generation rapidly disintegrating sublingual epinephrine tablets (RDSETs)**: (i) citric acid masks bitter taste; (ii) rapid epinephrine absorption (epinephrine disintegrates within 13 seconds and dissolves within 60 seconds); (iii) a 40-mg sublingual dose had similar bioavailability to a 0.3-mg dose of intramuscular epinephrine; (iv) RDSETs are hard enough to resist shipping and handling.

  - Authors show that epinephrine in RDSETs is stable for ≥7 yrs even under suboptimal storage conditions (it is recommended to minimize tablet exposure to oxygen and high temperatures).

  - **Author’s commentary**: RDSETs are ready for phase I studies in human subjects.

• **MANAGING COMORBID COMPLICATIONS IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID)** (Ballow M. Ann Allergy Asthma Immunol 2013; 111: S6-S9):

  - Authors present a review about: (i) the identification of CVID patients (clinical phenotypes and biomarkers); (ii) the treatment of CVID complications.

  - **CVID**: (i) heterogeneous group of immunodeficiencies (diverse etiology and clinical presentation; may involve B or T cell defects; only 15% of cases have confirmed genetic defects); (ii) prevalence: up to 1:25,000 individuals; (iii) clinical characteristics: defective antibody responses; susceptibility to infections, autoimmunity and neoplasms (25% of patients only have infections [better prognosis]; up to 30% of patients develop an autoimmune disease; up to 50% have GI problems; 15% develop granulomatous disease; 15% develop malignancy; 20% develop lymphoproliferation); (iv) it is useful to classify CVID based on severity and prognostic markers for more personalized therapy.

  - Clinical phenotypes and biomarkers that may indicate more severe CVID: poor T-cell function; low TRECs and KRECs; ↓ Treg cells; ↓ switched memory B cells; ↓ CD21+ cells; high serum levels of BAFF and APRIL; genetic markers.

  - **TREC/KREC-based classification of CVID** [J Allergy Clin Immunol 2013; 131: 1437-1440]: (i) correlated well with clinical severity and survival rate in CVID patients; (ii) may differentiate CVID from combined immunodeficiency (CID); (iii) may refine therapy for each CVID patient.
• Phenotype-based classification of CVID [J Allergy Clin Immunol 2012; 130: 1197-1198]: (i) no disease-related complications (‘infections only’); (ii) cytopenias (thrombocytopenia, anemia, neutropenia); (iii) polyclonal lymphoproliferation (granuloma, lymphoid interstitial pneumonitis, persistent unexplained lymphadenopathy); (iv) unexplained persistent enteropathy.

• ↑ IgG trough levels from 500 to 1,000 mg/dL → ↓ pneumonia incidence by 5-fold.


  - Hypersensitivity reactions among hairdressers: (i) occur frequently; (ii) include occupational asthma (OA), occupational rhinitis (OR) and contact urticaria (CU); (iii) major causes: persulfate salts in hair-bleaching products, paraphenylenediamine in hair dyes, rubber latex in gloves.

  - Hydrolyzed wheat protein (HWP): (i) common ingredient in food and cosmetics (e.g. hairdressing products); (ii) hypersensitivity to HWP has been reported (e.g. allergic contact urticaria, wheat-dependent exercise-induced anaphylaxis [WDEIA]).

  - Authors describe 2 hairdressers with hypersensitivity to laurdimonium hydroxypropyl HWP contained in hair sprays → clinical manifestations: OR, CU, OA, WDEIA → allergologic tests with HWP-containing products: positive SPT; urticarial reactions after skin application; positive inhalation or nasal provocation tests.

• OPTIMIZING IMMUNOGLOBULIN TREATMENT FOR PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE TO PREVENT PNEUMONIA AND INFECTION INCIDENCE: REVIEW OF THE CURRENT DATA (Ballow M. Ann Allergy Asthma Immunol 2013; 111: S28-S5):

  - Uses of intravenous immunoglobulin (IVIG): replacement therapy in primary and secondary immunodeficiencies; immunomodulatory therapy in autoimmune and inflammatory diseases.

  - Uses of subcutaneous immunoglobulin (SCIG): replacement therapy in primary immunodeficiencies.

  - Important points: (i) each patient has a specific ‘biological’ serum IgG level associated with reducing or preventing infection; (ii) in patients who receive replacement therapy with IG, dosing should be individualized to achieve the ‘biological’ serum IgG (instead of trying to achieve a single ‘optimal’ serum IgG level for all patients); (iii) ↑ 100-mg/kg IVIG dose → ↑ 121-mg/dL in IgG trough level; (iv) ↑ IgG trough level from 500 to 1,000 mg/dL → ↓ pneumonia incidence by 5-fold; (v) IgG trough level persistently <400 mg/dL is a risk factor for severe infections; (vi) risk factors for pneumonia in CVID patients: ↓ serum IgG and IgA; bronchiectasis and IgA <7 mg/dL; (vii) IgG trough level is not affected by body weight for a given IVIG dosage or interval; (viii) patients with bronchiectasis and CVID complications require higher doses of IVIG; (ix) IVIG and SCIG are therapeutically equivalent; (x) advantages of SCIG: fewer systemic adverse events, improved QoL, more stable serum IgG levels over time; (xi) disadvantages of SCIG: more local infusion site reactions, need of more frequent infusions; (xii) the relationship between SCIG dose and infection rate is not well defined.

• SLEEP IMPAIRMENT AND DAYTIME SLEEPINESS IN PATIENTS WITH ALLERGIC RHINITIS: THE ROLE OF CONGESTION AND INFLAMMATION (Thompson A, Sardana N, Craig TJ. Ann Allergy Asthma Immunol 2013; 111: 446-451):
• **Allergic rhinitis (AR):** IgE-mediated inflammation of the nasal mucosa; (i) **prevalence:** up to 40% of the population; (ii) **impact:** ↓ physical, social, mental and psychological well-being; ↓ QoL; elevated costs; (iii) **clinical manifestations:** rhinorrhea, nasal blockage (most common and bothersome symptom; associated with impaired sleep; occurs when capacitance vessels dilate in the cavernous tissues of the nasal turbinates), sneezing, itching, mouth breathing, snoring, nasal voice, cough, ‘allergic shiners’ (darkened lower eyelids due to chronic congestion), minor epistaxis; (iv) **comorbidities/complications:** conjunctivitis, sinusitis, hyposmia, Eustachian tube dysfunction, middle ear effusion, otitis, ↓ hearing, lymphoid hypertrophy (adenoids, tonsils), pharyngitis, asthma, dental malocclusion, atopic eczema, pollen-food syndrome, sleep disordered breathing (snoring, microarousals, obstructive sleep apnea/hypopnea, chronic nonrestorative sleep), daytime sleepiness, difficulty concentrating, fatigue, impaired school or work performance, systemic inflammation; (v) **diagnosis:** clinical history, anterior rhinoscopy, allergy tests (25% of AR cases are ‘local’ [entopy], which means that specific IgE is not detected by skin or serum tests); (vi) **differential diagnosis** (may coexist with allergic rhinitis): nonallergic rhinitis (infectious, irritant-induced, hormonal, drug-induced, vasomotor, idiopathic), nasal polyps, septal deviation, choanal atresia, stenosis of the piriform aperture, cleft lip, adenoidal hypertrophy, malignancy, leakage of cerebrospinal fluid, GERD, foreign body; (vii) **treatment:** (depends on severity): education about the disease, allergen avoidance, antihistamines (oral, intranasal), corticosteroids (intranasal, oral), antileukotrienes, decongestants (oral, topical), intranasal anticholinergics, saline douches, allergen immunotherapy, omalizumab (if concomitant uncontrolled severe asthma).

• **Mechanisms of sleep impairment in AR:** (i) **breathing obstruction** (↑ number of microarousals and apneic episodes); (ii) ↑ production of inflammatory cytokines (e.g. IL-1β, IL-4, IL-6, IL-10, TNF-α, histamine); (iii) ↓ REM sleep (which provides an important restorative function); (iv) **autonomic disturbance** (cholinergic, adrenergic); (v) use of sedating antihistamines (histamine is important in the CNS for arousal).

• ↑ levels of IL-1β, IL-4 and IL-10 in patients with AR correlated with: (i) ↑ latency to REM sleep; (ii) ↓ time in REM sleep; (iii) ↓ latency to sleep onset.

• **Why AR frequently worsens at night?** (i) high allergen levels in the sleeping place (e.g. house dust mites in bedding); (ii) colder temperature; (iii) normal overnight decline in serum cortisol: (iv) peaking levels of inflammatory cells and mediators in the early morning hours.

• **Therapies for nasal congestion:** (i) intranasal corticosteroids (1st-line therapy); (ii) oral decongestants (moderate efficacy; significant side effects [tachycardia, sexual dysfunction, urinary retention]); (iii) intranasal decongestants (high efficacy; significant side effects [rhinitis medicamentosa or “rebound” congestion]); (iv) antileukotrienes (mild/moderate efficacy; excellent safety profile; effective intervention in young children with large adenoids and sleep disturbance); (v) **antihistamines** (mild efficacy; excellent safety profile); (vi) allergen immunotherapy (more research is needed about its efficacy to ↑ sleep quality in AR patients).


• **Anaphylaxis:** potentially-fatal severe allergic reaction; can be complicated with **acute coronary syndromes** (heart mast cells [located mainly between myocardial fibers, around blood vessels and in the arterial intima] contribute to pathogenesis).
• **Kounis syndrome:** (i) **definition:** coronary vasospasm associated with hypersensitivity reactions; (ii) **triggers:** Hymenoptera venom (can also induce acute coronary syndromes by direct action on the coronary endothelium), drugs, food, latex, snake venom, iodine contrast media; (iii) **types:** type 1 (patients with normal coronary arteries); type 2 (patients with a preexisting atheromatous disease); type 3 (patients with drug-eluting stent thrombosis).

• **Mastocytosis:** (i) **definition:** abnormal mast cell proliferation; (ii) **clinical manifestations:** urticaria pigmentosa (most common skin manifestation), flushing, pruritus, abdominal symptoms, bone lesions, neuropsychiatric symptoms; (iii) in patients with systemic mastocytosis, *anaphylaxis* frequently presents with cardiovascular manifestations and no urticaria or angioedema.

Authors report the case of a 60-yr-old man with systemic mastocytosis (brown macular skin lesions, positive Darier sign; **skin biopsy:** urticaria pigmentosa; **basal serum tryptase level** = 140 ng/mL, **bone marrow biopsy:** extensive mast cell infiltrate, clusters of c-kit-mutated abnormal mast cells) *presenting as type 1 Kounis syndrome* (generalized pruritus, loss of consciousness, hypotension, ischemic changes in the EKG) 15 min after a bee sting → allergy testing: negative skin testing to bee venom; sIgE to honey bee = 0.40 kU/L; sIgE to Api m1 = 0.11 kU/L.

• **Author’s commentary:** patients presenting with Kounis syndrome might have an underlying mastocytosis → measure serum tryptase levels during the reaction and at baseline.

• **VENTRICULAR FIBRILLATION AFTER ORAL ADMINISTRATION OF AMOXICILLIN AND CLAVULANIC ACID** (Shahar E, Roguin A. Ann Allergy Asthma Immunol 2013; 111: 573-574):

• **Anaphylaxis:** acute severe allergic reaction; electrocardiographic changes may occur (ST-segment depression or elevation, T-wave changes, arrhythmias, conduction disturbance).

Authors report the case of a 52-yr-old woman (clinical history: smoking; hypertension; hyperlipidemia; use of statin, low-dose β-blocker and ACE inhibitor) who presented severe anaphylaxis (including ventricular fibrillation) 10 min after using oral amoxicillin/clavulanic acid.
JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:


  - Eosinophilic esophagitis (EoE): immune reaction to food or respiratory allergens in the esophagus (common causal foods in children: milk, egg, soy, wheat, beef, chicken; common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg) → infiltration of eosinophils into esophageal mucosa (usually patchy) → chronic eosinophilic inflammation → esophageal dysfunction (abdominal pain, vomiting, dysphagia, food impaction, heartburn, cough, choking); often misdiagnosed as GERD; frequent association with respiratory and skin allergies.

  - Diagnosis of EoE: (i) clinical history; (ii) esophageal endoscopy and biopsy (positive result: ≥15 eos per high-power field; limitation: 5 biopsies represent only <0.02% of the esophageal surface → false negative results can occur, especially in mild cases); (iii) allergy tests (SPT, in vitro sIgE detection, patch test) with food and respiratory allergens; (iv) food elimination trial followed by reintroduction.

  - Treatment of EoE: (i) diet options: 6-food elimination diet (milk, egg, wheat, soy, fish/seafood, peanut/tree nuts); diet guided by allergy tests; aminoacid formula, (ii) swallowed corticosteroids; (iii) biologic therapies targeting the eosinophil (e.g. anti-IL-5 mAb, anti-IL-5R mAb).

  - Novel strategy to detect EoE-associated inflammation: localize cationic eosinophil granule proteins (e.g. MBP-1) by using anionic heparin radiolabeled with technetium-99m → detection by single photon emission computed tomography (SPECT) imaging.


  - Anaphylaxis: (i) definition: acute severe multisystemic allergic reaction, potentially fatal; (ii) lifetime prevalence: 0.0582%; (iii) incidence: 1/10,000 patient-yr (incidence is increasing; 0-4 yr-old children have higher incidence rates); (iv) mechanisms: release of mediators from mast cells and basophils (mainly IgE-mediated reactions; IgG-mediated mechanisms have been shown in mice); (v) most common culprits: foods, drugs, hymenoptera venom, latex; (vi) factors that influence severity: pathogenic mechanism, allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors; (vii) important comorbidities: atopic dermatitis, asthma, allergic rhinitis, food allergy; (viii) anaphylaxis can present without cutaneous signs (urticaria or angioedema) in >20% of patients.

  - NIAID/FAAN criteria to diagnose anaphylaxis → sensitivity=96.7%, specificity=82.4%.

  - Median times to cardiovascular and/or respiratory collapse during anaphylaxis: (i) 5-10 min for intravenous drugs, (ii) 15 min for field insect stings and intramuscular drugs, (iii) 30 min for food and oral drugs.

  - Allergists/immunologists must know: (i) how to treat acute anaphylaxis (may occur after immunotherapy application, skin testing or food/drug challenges); (ii) how to evaluate and manage a patient with a suspected history of anaphylaxis (confirm diagnosis, determine the etiology, give a treatment plan to prevent and treat further episodes).
• **Platelet-activating factor (PAF):** (i) important mediator of anaphylaxis; (ii) PAF is inactivated by PAF acetylhydrolase (PAF-AH); (iii) low PAF-AH activity might be an independent risk factor for severe anaphylaxis (however, most people experiencing severe anaphylaxis do not have low PAF-AH activity).


  • Ectodermal dysplasia with anhidrosis (EDA): syndromes with abnormal development of ectodermal tissues; characteristics: fine sparse hair, conical or missing teeth, dysplastic nails, hypohidrosis (absence of eccrine sweat glands), periorbital skin wrinkling.

  • Genetic mutations associated to isolated EDA: (i) gene encoding ectodysplasin A; (ii) gene encoding ectodysplasin A receptor; (iii) gene encoding EDARADD (ectodysplasin A receptor–associated death domain containing adaptor protein).

  • Genetic mutations associated to EDA with immune deficiency (EDA-ID): (i) hypomorphic mutations in IKBKG gene (NEMO gene) [X-linked recessive inheritance]; (ii) gain-of-function mutations in NFKBIA gene, which encodes IkBα, the inhibitor of NF-κBα [autosomal dominant inheritance].

  • Mutations in NEMO: (i) ID results from impaired NF-κB activation; (ii) patients present both humoral and cellular ID; (iii) variable clinical presentation, including hyper-IgM syndrome or susceptibility to mycobacteria; (iv) 23% of patients have no EDA; (v) only curative treatment: HSCT (does not correct EDA).

  • Authors report the case of a 5-month-old female with EDA-ID caused by a novel mutation of IkBα → clinical manifestations: ectodermal dysplasia (sparse hair, dry and thin skin, superficial cutaneous venous reticulum, hypohidrosis), severe bacterial and fungal infections (chronic diarrhea, impetigo, osteomyelitis, oral/esophageal candidiasis, bilateral pneumonia, sepsis [S maltophilia, K pneumoniae, C parapsilosis]), respiratory failure, fatal disseminated intravascular coagulation (no response to IVIG; there was no opportunity to perform HSCT) → laboratory: hyper-IgM (IgG=0.3 g/L, IgA=0.05 g/L, IgM=7 g/L), no allohemagglutinins, no antibody response to tetanus toxoid and H influenzae, normal T-cell counts and proliferation, ↑ transitional B cells, ↓ memory B cells, ↓ B-cell survival in vitro, ↓ B-cell response to CpG → genetic analysis: de novo heterozygous mutation in exon 1 of IKBKG gene (c.T110G, p.M37R).


  • Immune tolerance: (i) definition: nonresponsiveness of the adaptive immune system or active Treg response to antigens; (ii) mechanisms: anergy or deletion of reactive lymphocytes, generation of Treg cells.

  • Immune tolerance is essential to prevent: (i) self-destruction; (ii) inflammatory response to beneficial or harmless exogenous molecules (e.g. food, commensal bacteria, allergens).

  • Loss of immune tolerance → allergic or autoimmune disorders.

  • Factors that promote immune tolerance: (i) ↑ tolerogenic microbiota (Lactobacillus sp, Bifidobacterium sp); (ii) ↑ tolerogenic dendritic cells; (iii) ↑ tolerogenic molecules (retinoic acid,
TGF-β, TSLP, indoleamine-2,3-dioxygenase, IL-10, IgG4, IgA); (iv) ↑ T regulatory responses (CD4+CD25+ Tregs, Th3 cells, Tr1 cells, CD8+ Tregs, regulatory B cells); (v) balanced TH1 responses.

- **Populations of cells that have regulatory capacity**: CD4+ Tregs (express several markers, including CD25, Foxp3, CTLA-4 and CD39), CD8+ Tregs, regulatory B cells, regulatory γδ T cells.

- Authors show that: (i) CD39 was a good marker of regulatory γδ T cells in mice; (ii) IL-10 was the pivotal suppressive cytokine of CD39+ γδ T cells.


  - Adenosine deaminase (ADA) deficiency: mutations in the ADA gene (chromosome 20q13.12) → ↑ concentrations of toxic metabolites inside cells → autosomal recessive form of SCID (T-B-NK-) → life-threatening infections, chronic diarrhea, failure to thrive, autoimmunity, neurologic abnormalities.

- Treatment options for ADA-SCID: (i) bone marrow transplant (BMT); (ii) enzyme replacement therapy with pegylated ADA (PEG-ADA); (iii) gene therapy (GT).

- Author show that patients treated for early-onset ADA-SCID (BMT, GT, PEG-ADA) have a high incidence of atopy (↑ IgE level, ↑ TH2 cytokine production, ↑ allergic rhinitis, ↑ asthma).

- Hypothesis: weak T-cell receptor signaling (hypomorphic T-cell function) → ↑ TH2 differentiation, atopy, autoimmunity (Ommen syndrome is an extreme example).

- **HERPESVIRUSES AND THE MICROBIOME** (Dreyfus DH. J Allergy Clin Immunol 2013; 132: 1278-1286):

  - 8 human herpesviruses (HHV): type 1 (HHV1, HSV1, herpes simplex virus 1); type 2 (HHV2, HSV2, herpes simplex virus 2); type 3 (HHV3, VVZ, varicella zoster virus); type 4 (HHV4, EBV, Epstein-Barr virus); type 5 (HHV5, CMV, cytomegalovirus); type 6 (HHV6, human herpes virus 6); type 7 (HHV7, human herpes virus 7); type 8 (HHV8, KSV, Kaposi sarcoma–associated herpesvirus).

  - Burden of HHV: (i) acute infection (e.g. infectious mononucleosis by EBV); (ii) chronic infection (e.g. Kaposi sarcoma by HHV8); (iii) latent/recurrent infection (e.g. labial herpes by HSV1); (iv) infection-related complications (e.g. Burkitt lymphoma by EBV).

  - Abilities of HHV: (i) expression of cytokine-like proteins (e.g. EBV express proinflammatory viral IL-10 [human IL-10 activates B cells and suppress T cells, while viral IL-10 predominantly activates B cells]; CMV and HHV8 express IL-6-like protein); (ii) expression of siRNA and microRNAs, which alter cell activity by targeting mRNA; (iii) modulation of host transcription pathways (e.g. nuclear factor kB); (iv) cause lifelong infection → HHV can be considered as a ‘component of the human microbiome’ (the effects of HHV latent infection on the progression of atopic diseases are not well defined).

  - Relevance of HHV infections in allergy/immunology: (i) atopic patients (TH2-biased immune responses) might have ↑ risk of severe and atypical HHV-related diseases (e.g. patients...
with atopic dermatitis (AD) have ↑ risk of severe skin infections [eczema herpeticum] by HSV1, HSV2 and VZV; elderly patients [mainly atopic subjects] have ↑ risk of VZV reactivation [give the shingles vaccine]; atopic patients might have ↑ risk of cardiovascular inflammation/disease by CMV).

(ii) HHV have pathogenic roles in some allergic processes (e.g. HHV6 and HHV7 can reactivate and cause flares in patients with DRESS syndrome; antibiotic use during acute EBV infection ↑ risk of non-allergic drug exanthema; wild-type VZV infection might ↓ risk of AD [VZV vaccine might ↑ AD risk]).

(iii) HHV infections can be misdiagnosed as skin allergies (e.g. acute EBV or CMV infection can present with a prolonged postviral maculopapular or urticarial rash; HHV6 and HHV7 cause roseola, a nonspecific maculopapular rash.

(iv) Immunodeficiencies (primary or secondary) ↑ risk of HHV infections (e.g. T-cell or NK-cell defects ↑ risk of HHV infections; defects in TLR3 pathway ↑ risk of encephalitis by HSV1; AIDS ↑ risk of HHV8-related Kaposi sarcoma, Castleman disease or chronic shingles [KSV infection can also present as eczema herpeticum]; SAP deficiency ↑ risk of severe EBV infections).

(v) Immunodeficiencies might ↑ risk of infection by HHV-vaccines (e.g. patients with severe T-cell defects must avoid VZV vaccine).

(vi) Immunodeficiencies can contribute to failure of HHV-vaccines (e.g. long-term use of oral steroids in atopic patients can ↓ response to shingles vaccine).

Consider early antiviral therapy (e.g. acyclovir, ganciclovir) in every patient with active HHV infection (antiviral therapy does not appear to prevent generation of subsequent viral immunity).

Consider antiviral vaccines (e.g. shingles vaccine) and prophylaxis (e.g. VZV immune globulin, acyclovir) in every patient with ↑ susceptibility to HHV infections.

• THE EDITORS’ CHOICE (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2013; 132: 1293-1294):

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Risk Score may predict the probability of developing asthma at school age among preschool children with asthma-like symptoms (predictors include: male sex, preterm birth, medium/low parental education, parental asthma, wheezing/dyspnea apart from colds, wheezing frequency, eczema).

IgE-mediated peanut allergy: (i) impact: significant morbidity and mortality, ↓ QoL, high costs; (ii) diagnosis: SPT, serum specific IgE detection, food challenge; (iii) conventional treatment: avoidance (does not prevent accidental exposure), autoinjectable epinephrine, nutritional counseling; (iv) optimal treatment: restore tolerance to allergens (immunotherapy).

Limitations of food immunotherapy: (i) potential lack of efficacy; (ii) frequent allergic reactions during therapy.

Omalizumab can ↑ efficacy and safety of oral desensitization in high-risk peanut-allergic children.
• **Bronchial thermoplasty**: (i) bronchoscopic delivery of **thermal energy** to disrupt airway smooth muscle; (ii) should be considered for patients with **severe persistent asthma** refractory to ICS + LABA (**one-time treatment** can provide long-term asthma control).

• **Hyper-IgE syndrome (HIES) associated with STAT3 gene mutation**: autosomal dominant (AD) inheritance, markedly ↑ serum IgE; recurrent infections (S. aureus abscesses, pneumonia, candidiasis), eczema, coarse facial features, pneumatoceles, delayed shedding of primary teeth, joint hyperextensibility, scoliosis, osteopenia; NIH STAT3 score >40.

• Patients with **AD-HIES** actually have **lower rates of food allergy and anaphylaxis** than patients with similarly high IgE levels but no STAT3 mutations (**hypothesis**: impaired STAT3 signaling reduces mast cell degranulation).

• **Bla g 1** preserves antibody epitopes despite variable fragmentation patterns → **Bla g 1 tertiary structure** facilitated standardization of environmental assays in absolute units.

• **Chronic rhinosinusitis with nasal polyps**: ↑ expression of **SOCS3** (suppressor of cytokine signaling 3) in inflammatory cells in the airway mucosa → ↓ Foxp3 expression → ↓ Foxp3+ Treg cells.

• **Blocking SOCS3 expression/function** is a novel therapeutic target to promote Treg cell activity.