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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January 2013 – content:


- **PSYCHOSOCIAL FACTORS AND CHRONIC SPONTANEOUS URTICARIA (CSU): A SYSTEMATIC REVIEW** (Ben-Shoshan M, Blinderman I, Raz A. Allergy 2013; 68: 131–141).


- **ANTILIPID AGENTS MAY PROVIDE ALLERGY PROTECTION** (Rosenberg LJ. Ann Allergy Asthma Immunol 2013; 110: 1).


- **TREATING PATIENTS WITH MULTIPLE DRUG ALLERGIES** (Khan DA. Ann Allergy Asthma Immunol 2013; 110: 2-6).


- **ADVANCES IN ALLERGIC SKIN DISEASE, ANAPHYLAXIS, AND HYPERSENSITIVITY REACTIONS TO FOODS, DRUGS, AND INSECTS IN 2012** (Sicherer SH, Leung DYM. J Allergy Clin Immunol 2013; 131: 55-66).

- **ADVANCES IN PEDIATRIC ASTHMA IN 2012: MOVING TOWARD ASTHMA PREVENTION** (Szeffler SJ. J Allergy Clin Immunol 2013; 131: 36-46).
• **ALLERGY TO SULFONAMIDES** (Schnyder B, Pichler WJ. J Allergy Clin Immunol 2013; 131: 256-257).
• **CAN WE PRODUCE TRUE TOLERANCE IN PATIENTS WITH FOOD ALLERGY?** (Berin MC, Mayer Ll. J Allergy Clin Immunol 2013; 131: 14-22).
• **SUCCESSFUL DESENSITIZATION TO ROSUVASTATIN IN A PATIENT WITH A HISTORY OF ANAPHYLAXIS TO MULTIPLE STATINS** (Khan FS, Stewart DK, Brunzell JD, Natrajan KM, Castells MC, Henderson WR, Ayars AG. J Allergy Clin Immunol 2013; 131: 234-236).
• **THE CHANGING CARE FOR PATIENTS WITH FOOD ALLERGY** (Jones SM, Wesley Burks A. J Allergy Clin Immunol 2013; 131: 3-11).
**ALLERGY:**

  - Authors asked a questionnaire to 25,610 individuals to determine risk factors for insomnia → risk factors for insomnia: uncontrolled asthma, nasal congestion, smoking and obesity.

  - The efficacy of single-allergen immunotherapy in polysensitized subjects is controversial.
  - Authors analyzed data from 6 RCT (1871 individuals) comparing the efficacy and safety of Grazax (Phleum pratense) in mono- and polysensitized subjects with allergic rhinoconjunctivitis with or without asthma → reduction in the mean total combined symptom/medication score within the immunotherapy group was similar in mono- and polysensitized subjects (28% and 26%, respectively); the safety profile was good.
  - There was no difference in efficacy and safety of single-allergen grass immunotherapy between mono- and polysensitized subjects.

  - Authors investigated whether maternal and cord blood vit D levels are associated with atopy in early infancy → Results: 1) high correlation between maternal and cord blood vit D levels; 2) higher maternal vit D levels increased children’s risk for food allergy within the first 2 years; 3) cord blood vit D levels were negatively correlated with Treg cell numbers.
  - This study shows that high vit D levels in pregnancy and at birth may contribute to a higher risk for food allergy → more controversy about the benefit of vit D for allergy prevention.

  - Tolerance by the immune system is important to prevent: 1) autodestruction; 2) excessive inflammatory response to beneficial or innocuous exogenous molecules.
  - The normal response to allergens and self-antigens is tolerance (absence of response or active regulatory response). Loss of tolerance → allergic or autoimmune disorders.
  - Treg cells (natural or induced) are main inductors of tolerance → ↑ production of IL-10, TGF-β, IgG4 and IgA; ↓ Th2 inflammation; suppress dendritic cells (DCs), mast cells and eosinophils.
Factors that influence allergenicity: allergen structure (repetitive motifs, aggregates, grade of glycation, binding to heat-resistant ligands), amount of allergen, transepithelial allergen delivery, activation of epithelial cells, local immune response.

DCs are crucial to induce T effector or T reg cells. CCL18 induces tolerogenic DCs. In allergic subjects, DCs bind less CCL18 than they do in healthy individuals.

Central tolerance occurs in the thymus, where self-antigen reactive T cells are deleted or differentiate into Treg cells. However, central tolerance is often incomplete → peripheral tolerance mechanisms are needed.

Peripheral tolerance: 1) Extrinsic mechanisms: Treg cells, tolerogenic APCs, suppressive cytokines (IL-10, TGF-β). 2) Intrinsic mechanisms: T-cell anergy, apoptosis. Both extrinsic and intrinsic mechanisms are interrelated.

IL-4 → IL-4R → STAT6 → GATA3 → binds FOXP3 promoter → inhibits FOXP3 expression → reduction of Treg cells.

PBMCs of children with active asthma produce elevated levels of IL-4 and IL-13 after HDM stimulation. When asthma is in remission, PBMCs produce more IL-10 after stimulation.

TIM-1 (T cell/transmembrane immunoglobulin and mucin-1) is a costimulatory molecule expressed in Th2 cells of patients with allergic diseases. TIM-4 is the natural ligand of TIM-1. TIM-1 polymorphisms are associated with atopic diseases. Specific immunotherapy may disrupt the interaction of TIM-1/TIM-4 → suppression of Th2 responses.

Activation of airway epithelial cells → TSLP production → TSLP stimulates CD11c+ DCs to produce CCL17 and CCL22 → attraction of Th2 cells.

TSLP polymorphisms are associated with asthma. Increased expression of TSLP is observed in patients with severe asthma.

Th17 cells are involved in neutrophilic asthma.

TGF-β alone → Treg cell differentiation. IL-4 alone → Th2 cell differentiation. TGF-β + IL-4 → Th9 cell differentiation (lower FOXP3 expression and lower Th2-type cytokine production, but enhanced IL-9 secretion). In Th9-commited cells, IL-4-activated STAT6 stimulates IRF4, which induces IL-9 production. It is unknown whether Th9 cells are different from Th2 cells or whether Th2 cells can transform into Th9 cells during allergic inflammation.

T-reg cells can suppress mast cell degranulation through cell–cell contact (OX40–OX40 ligand interaction; production of cAMP by Treg cells).

Treg cells aggregate around DCs to downregulate the expression of CD80/86 on DCs in a CTLA-4- and LFA-1-dependent manner → inhibition of DC maturation.

Children allergic to cow’s milk who became tolerant had an increased number of circulating CD4+ CD25+ Treg cells compared with children who still had a clinically active allergy.

Naturally, common food and aeroallergens do not stimulate tonsil T cells. Depletion of FOXP3+ Treg cells in tonsil tissue leads to allergen-induced proliferation of tonsil T cells.
• **Bee venom repeated exposure** during bee-keeping season → Th1 and Th2 cell responses switch to T reg response (IL-10-secreting Tr1 cells). At the end of the bee-keeping season, the peripheral T-cell response returns to baseline level within 2–3 months.

• Binding of IgE to FceRI on DCs and monocytes and to FceRII on B cells enhances the uptake of allergen by APCs.

• High levels of IgG4 are associated with tolerance induction and improvement of allergic symptoms. Nonallergic beekeepers have a 1000 times higher specific IgG4/IgE ratio as compared to allergic individuals.

• **Allergen-specific immunotherapy** → early decrease of degranulation activity in basophils and mast cells; decrease of Th1 and Th2 responses; induction of Treg cell response; increase in IgG4 levels; early increase followed by a late decrease in IgE levels.

• **Antiallergic cytokines:** IL-10, TGF-β, IL-35.

• iT(R)35 cells are a specific subtype of Treg cells induced by IL-35; they mediate suppressive functions only through IL-35 (↓ allergen-induced airway inflammation; ↓ IgE production).

• **PSYCHOSOCIAL FACTORS AND CHRONIC SPONTANEOUS URTICARIA (CSU): A SYSTEMATIC REVIEW** (Ben-Shoshan M, Blinderman I, Raz A. Allergy 2013; 68: 131–141):

  • CSU: high economic burden; low quality of life; low physical and school performance; more absence to work than any other allergic disease; spontaneous remission occur in only 30–55% of cases within 5 years; causal role of infections and psychological components is controversial.

  • Authors present a systematic review to explore the association between CSU and psychosocial factors → psychosocial factors had a prevalence of 46.09% in patients with CSU → psychotherapeutic strategies may be beneficial, even if psychological symptoms develop subsequent to CSU and have no part in its pathogenesis.

  • **Neural mediators** (CRF, NGF, NT, SP, VIP, PACAP) can activate mast cells.

  • A case study reported a young women with CSU whose symptoms resolved after self-talk and relaxation techniques.

  • Although **IgE sensitization** is higher in CSU patients than in the global population, CSU generally does not constitute an expression of an IgE-mediated allergy.


  • **Airway epithelial cells** are the first to encounter aeroallergens.

  • **Pathogenesis of allergy in the airway mucosa:** 1) Contact of the allergens with the epithelium (including allergen modifications, such as spore or pollen germination) → disruption of epithelial tight junctions by allergen proteases (pollutants, virus and genetic defects contribute to epithelial disruption); activation of epithelial cells by signalling through TLR and PAR → entry of the allergens through the disrupted epithelium; transcytosis of the allergen through epithelial cells via a caveolae-mediated mechanism; secretion of TSLP, IL-25 and IL-33 by epithelial...
cells. 2) Activation of dendritic cells by cytokines (TSLP, IL-25 and IL-33) and PRR-mediated signalling → expression of OX-40L; secretion of CCL17 and CCL22. 3) Attraction of T cells, antigen presentation to T cells in MHC-II molecules → differentiation into Th2 cells. 4) Innate lymphoid cell activation by TSLP, IL-25 and IL-33 → secretion of IL-4, IL-5, IL-13 → induction of Th2 responses. 5) Signalling to B cells from Th2 cells and Th2-inducing environment → CSR to IgE. 6) Attraction and activation of effector allergy cells (mast cells, eosinophils, basophils).

• Some allergens from HDM, cockroach, fungi and pollen are cysteine, serine or aspartic proteases. Proteolytic allergens disrupt epithelial airway tight junctions, activate epithelial cells through PAR, and down-regulate mucosal antiproteases (α1-antitrypsin inhibitor, lung surfactant proteins A and D, elastase-specific inhibitors, secretory leukocyte protease inhibitors).

• Netherton’s syndrome: severe disruption in the skin integrity linked to mutations in SPINK5, a gene encoding a protease inhibitor.

• Cigarette smoke reduces airway epithelial barrier function → more than threefold increase in allergen penetration → increased sensitization and allergic inflammation.

• Influenza and RSV have cytotoxic effects on bronchial epithelium. HRV disrupt tight junctions.

• Dysfunctional filagrin → impaired skin barrier function in AD. Epithelial disruptions are also seen in asthma, chronic rhinosinusitis with nasal polyposis and Crohn’s disease.

• Some inflammatory genes are constantly activated in allergic individuals. Failure to down-regulate these genes may be more important than their initial activation.


• 3 characteristic phenotypes of atopic dermatitis (AD): non-IgE-associated AD, IgE-associated AD and autoimmune AD. It is important to define the AD phenotype in childhood because atopic sensitization is associated with subsequent wheezing and asthma.

• AD remission is more frequent among patients with the IgE-associated form.

• In the natural history of AD, the first clinical phase without IgE sensitization switches rapidly to the IgE-associated form during the first months of life in most cases.
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

  - **High serum tryptase**: allergic reactions (urticaria, angioedema, anaphylaxis), mast cell disorders (mastocytosis, mast cell leukemia), myeloid malignancies, myelodysplastic syndromes.
  - **Case report**: 54-year-old woman with recurrent angioedema and high serum tryptase → allergic cause was suspected. Final diagnosis: **acquired C1-inh deficiency** (recurrent angioedema, no family history, no ACEI intake, low C4, low C1-inh level and function, low C1q) caused by a **B-cell lymphoma** (splenomegaly, B-cell monoclonality). The high tryptase was incidental. Treatment of lymphoma resolved angioedema attacks and normalized complement markers.

• **ANAPHYLAXIS TO QUINOA** (Hong J, Convers K, Reeves N, Temprano J. Ann Allergy Asthma Immunol 2013; 110: 60–61):
  - **Quinoa** (*Chenopodium quinoa* Willd.): plant from the Andean region of Bolivia and Peru; it is actually a fruit and has been called a pseudo-cereal; protein content: 13.8-16.5%.
  - **Case report**: 29-year-old woman with anaphylaxis after ingesting quinoa. Diagnosis was confirmed by skin prick test with a prepared quinoa extract.

• **ANTILIPID AGENTS MAY PROVIDE ALLERGY PROTECTION** (Rosenberg LJ. Ann Allergy Asthma Immunol 2013; 110: 1):
  - Recent articles show that **statins** have immunomodulatory actions → benefit for asthma.
  - However, we must consider the **side effects** of statins. The risk-benefit of using statins to treat CV diseases is not the same as to treat or prevent asthma, even more if we have potentially safer therapies (allergen immunotherapy, ICS, ICS/LABA, anti-leukotrienes, anti-IgE).

  - **VIT**: best therapy for **hymenoptera venom anaphylaxis**; it provides protection in 90% of patients.
  - **Standard VIT**: maintenance dose is given every 4 to 6 weeks; it may have adherence problems.
  - **Extended maintenance dose (EMD)**: given every 3 to 4 months; similar effectiveness and safety as the conventional regimen. Advantages: more convenience, less cost.

• **FIXED DRUG ERUPTION (FDE) DUE TO AMOXICILLIN AND QUINOLONES** (Ponce Guevara LV, Laffond Yges E, Gracia Bara MT, González Ruiz AM, Moreno Rodilla E. Ann Allergy Asthma Immunol 2013; 110: 61-62):
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- **FDE:** drug-induced dermatosis that recurs at fixed sites. FDE to >1 chemically unrelated drugs is rare; lesions may appear on identical or separate areas.

- Case report: 73-year-old man with FDE due to amoxicillin and quinolones (ciprofloxacin, moxifloxacin, and levofloxacin).

- **Patch tests to diagnose FDE?**
  - **Advantages:** simple and safe.
  - **Disadvantages:** low sensitivity.
  - **Considerations:** a) patch tests should be performed at the sites of previous lesions; b) they should be performed ≥2 weeks after resolution of the lesions; 3) conditions that favor false-negative results: sensitization to drug metabolites and not to the original drug, low drug concentrations in the patch, limited penetration properties of the drug.

- **Oral challenge:** most reliable method for establishing the causative drug in FDE.

  - **Type VI mucopolysaccharidosis (MPS):** mutations in the gene encoding arylsulfatase B.
  - **Therapy:** weekly recombinant human arylsulfatase B (galsulfase); infusion reactions: 16%.
  - Authors report a rapid desensitization protocol for IgE-mediated allergy to galsulfase.
  - **Diagnosis** of galsulfase allergy: positive intradermal test to 1:10 diluted (0.1 mg/mL) galsulfase.
  - IgE-mediated allergy has also been described to enzyme therapy given for MPS I and MPS II.

  - T cells from allergic people recognize allergen-derived peptides (epitopes) which are presented in HLA molecules. These epitopes have been largely undefined.
  - The diversity of asthma phenotypes may be related to different epitope-specific responses.
  - Authors show: a) that allergen-specific T-cell responses are highly heterogeneous; b) that allergen-derived epitopes can often bind to multiple HLA class II molecules; c) a method to characterize allergen-derived epitopes recognized by T cells.
  - The Immune Epitope Database is a NIAID-sponsored resource that catalogs the immune epitopes associated with infectious diseases, autoimmunity, transplantation, and allergy.
  - **Plasticity of TH subsets:** a) a subset of TH2 cells from allergic individuals can produce TH17 and TH2 cytokines; b) TH17 cells can become dual IL-4/IL-17-producing cells; c) TH1 polarizing stimuli can induce TH2 cells to produce IFN-γ; d) TH1 cells autoregulate by producing IL-10.

- **TREATING PATIENTS WITH MULTIPLE DRUG ALLERGIES** (Khan DA. Ann Allergy Asthma Immunol 2013; 110: 2-6):
  - Authors present a clinical vignette of a 71-year-old woman with a history of isolated throat symptoms (throat itching, throat tightness, dysphonia) within minutes after receiving different classes of antibiotics (ciprofloxacin, meropenem, cephalaxin, “sulfa”, tetracycline,
clarithromycin). Because of isolated throat symptoms, a diagnosis of vocal cord dysfunction (VCD) was suspected. Fiberoptic rhinolaryngoscopy during a positive drug challenge to ciprofloxacin confirmed VCD. Throat relaxation techniques resolved her symptoms within 5 minutes; then she completed ciprofloxacin therapy uneventfully.

- Isolated throat symptoms to multiple medications → suspect drug-induced VCD → perform drug challenge with confirmation via direct laryngoscopy.

- Drug-induced laryngeal edema due to many non-cross-reactive medications of different chemical structure would be extremely rare.

- The term multiple drug allergy is controversial because: 1) usually it is not confirmed by skin testing or drug challenges; 2) there is no clear immunologic explanation.

- A better term to describe patients with reactions to multiple drugs is multiple drug intolerance syndrome (MDIS): reactions to ≥3 unrelated drugs; anxiety is usually associated.

- Even patients with suspicion of multiple medication allergies can typically be effectively managed through a combination of a detailed history, skin testing and graded challenges. Patients are extremely grateful for this service that is unique to Allergy specialty but underused.

- Skin testing to diagnose immediate drug allergy has low negative predictive value (NPV). Main exception: penicillin (NPV: 97%); however, a confirmatory penicillin challenge is recommended.

- Many experts do not recommend skin testing with non-penicillin antibiotics, with the exception of a history of anaphylaxis, where anecdotally it may be helpful.

- Skin testing and in vitro tests to diagnose drug allergy have low NPV → a drug challenge is usually required.

- Reasons for false-negative drug challenges: inadequate dose, inadequate duration of drug challenge, missing cofactors (infection? exercise? stress? comedication?).

- It is important to differentiate between drug challenge (do not modify immune or non-immune response to a given drug) and drug desensitization (induction of drug tolerance).

- For patients with purely subjective symptoms or “multiple drug allergies”, the challenge should be single-blind, placebo-controlled, to exclude reactions to placebo.

- Testing for sulfonamide allergy should be done cautiously because of the propensity to cause severe cutaneous adverse reactions.

- Patients with cephalosporin allergy appear to tolerate other β-lactams, such as carbapenems and aztreonam, in >95% of cases. Cross-reactions: ceftazidime-aztreonam.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

**JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:**

- **ADVANCES IN ADULT ASTHMA DIAGNOSIS AND TREATMENT IN 2012: POTENTIAL THERAPEUTICS AND GENE-ENVIRONMENT INTERACTIONS** (Apter AJ. J Allergy Clin Immunol 2013; 131: 47-54):
  - Only 57% of asthma cases among atopic subjects were due to atopy → 43% of atopic patients with asthma will not benefit from treatment aimed at atopy control.
  - Heterogeneity of ventilation in small-airways is correlated with poor asthma control.
  - Allergic asthma → blunted innate response to LPS → susceptibility to bacterial infections.
  - BAFF polymorphisms → increased BAFF levels → higher innate and adaptive immune responsiveness to viruses → asthma exacerbations.
  - Caspase-1 activation may link airway viral infection and asthma exacerbation.
  - Filaggrin gene null mutations → susceptibility to asthma and smoke-induced bronchoconstriction.
  - IL-32 expression increases when asthma control is improved → IL-32 is a potential biomarker and predictor of treatment response.
  - Vit D deficiency has been linked with asthma development and severity.
  - Airway smooth muscle cells insensitivity to corticosteroids in patients with severe asthma correlates with p38 MAPK levels → a p38-MAPK inhibitor might have therapeutic benefit.
  - Activin A promotes TH9 activity; IL-9 promotes allergic response → inhibitors of activin A or IL-9 are therapeutic targets in patients with allergic asthma.
  - TLR3 stimulation in airway epithelial cells → release of thymic stromal lymphopoietin (TSLP), which promotes asthma → TSLP it is a therapeutic target.
  - MMP-12 has excessive activity in patients with COPD and asthma → a MMP-12 blocker is a potential therapeutic target for severe asthma, particularly in smokers.
  - CD8+ cells (but not CD4+ cells) of patients with severe asthma upregulated mRNAs of chitinase 3 protein 1 and arginase, which are possible potential therapeutic targets.
  - Serum periostin levels correlate with airway hypereosinophilia and IL-13 activity. Lebrikizumab (anti-IL-13) is a potential therapy for asthma.
  - Next generation of asthma therapeutics: ICSs with fewer systemic and local side effects; once-daily β-agonists; long-acting muscarinic antagonists (eg, tiotropium); IL-5 blocking mAbs (mepolizumab and reslizumab); vitamin D.
  - The transcriptome is the set of all mRNA molecules.
  - Ambient air pollution → epigenetic modifications, alteration of the innate immune response → increase in allergic diseases.
  - Climate changes influence plant and microorganism biology → effect in allergen exposure.

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• ↑ exposure to bacterial endotoxins, β-glucans, and muramic acid correlates with ↓ risk of allergy and asthma in both rural and urban populations.

• Elite swimmers had ↑ airway hyperresponsiveness to methacholine and exercise-induced bronchospasm. Limiting exposure to chlorine and pool chemicals is advisable.

• Why the course of asthma is so variable (remitting and relapsing in some patients, resolving for others, never remitting in others)? It remains unexplained.

• HIV-infected patients may have increased prevalence of asthma.

• Outcomes for asthma research: symptoms, exacerbations, composite scores, quality of life, lung physiology, biomarkers, health care utilization and costs.

• Discontinuing LABA in adults with asthma controlled by ICS/LABA was associated with a decrease in asthma control.

• No association was found between omalizumab treatment and risk of malignancy.

• No association was found between montelukast and birth defects or cardiovascular disease.

• ADVANCES IN ALLERGIC SKIN DISEASE, ANAPHYLAXIS, AND HYPERSENSITIVITY REACTIONS TO FOODS, DRUGS, AND INSECTS IN 2012 (Sicherer SH, Leung DYM. J Allergy Clin Immunol 2013; 131: 55-66):

• In a recent study, milk (2.23%), peanut (1.77%), and tree nuts (1.73%) were the most common allergens in children; shellfish (1.91%), fruits (1.61%), and vegetables (1.29%) were the most common allergens in adults.

• Risk factors for food allergy: route and timing of exposure to food allergens; skin barrier defects; Filaggrin gene loss-of-function mutations; vit D deficiency; dietary fat; low antioxidants; obesity; infections; exposure to triclosan.

• MicroRNAs profile can be useful to diagnose and monitor activity of eosinophilic esophagitis.

• Mainstays of therapy for EoE: diet and swallowed inhaled steroids. New promising therapy: reslizumab (anti-IL-5). Elemental diet has better results than an empiric 6-food elimination diet or removal of positive foods on skin testing.

• Food protein–induced enterocolitis syndrome (FPIES): non–IgE-mediated delayed food allergy; vomiting, dehydration, hypotension; generally affects infants and young children.

• Food allergens can interact directly with dendritic cells to induce TH2 skewing.

• Allergen has to be absorbed to induce symptoms → immunotherapies that induce systemic IgG can suppress local and systemic food-induced allergic reactions.

• STAT6 and LRP1 polymorphisms were associated with food sensitization. STAT6 has been associated with food allergy, asthma, and EoE.

• Delayed anaphylaxis to meats is associated with IgE reactivity to galactose-α-1,3-galactose after tick bites → carbohydrate determinants can be responsible for severe allergic reactions.
• An egg white–specific IgE level of 2.5 kUA/L had a negative predictive value of 0.89, and a level of 10 kUA/L had a positive predictive value of 0.60 for a positive OFC to baked egg.

• Sensitization to Ara h 2 may predict better the result of OFC to peanut. Presumably many persons only sensitized to Ara h 8, a birch-related protein, can consume heated peanut.

• Oral food challenge (OFC) is the primary way to diagnose or exclude food allergy. Barriers: risk, lack of time, poor reimbursement, lack of staff, lack of office space. 70% of the 670 members of the AAAAI performed ≤5 OFCs each month.

• A patient with a negative OFC result may react on subsequent ingestion of the food, raising the question of whether the gradual feeding during the OFC creates a brief desensitized state for some patients → a complete OFC may need to include a full food ration on a subsequent day.

• Oral and sublingual immunotherapy are promising therapies for patients with food allergy. Unmet issues: Is tolerance long lasting? Is the therapy safe? Who will benefit most?

• Egg allergic children who tolerate baked egg are 14.6 times more likely to develop tolerance to unheated egg compared to those who do not tolerate baked egg.

• Options to improve food immunotherapy: use of digested proteins, addition of omalizumab, addition of probiotics.

• Platelet-activating factor (PAF): potent mediator of anaphylaxis; levels correlate with severity (unlike tryptase or histamine). Epinephrine down-regulates the PAF axis.

• Obesity did not increase epinephrine need during anaphylaxis.

• For some epinephrine autoinjectors, it might require more force to activate the trainer than the live device.

• Risk factors for severe anaphylaxis in patients with Hymenoptera venom allergy: high baseline tryptase levels; absence of urticaria or angioedema during anaphylaxis; <5 min from sting to symptom onset; older age.

• Component-resolved IgE testing and basophil activation test may clarify the diagnosis of allergy to stinging insects.

• Regarding venom immunotherapy, the ultrarush initiation regimen increased risks and the lower maintenance dose reduced them; the effect on treatment efficacy is not well defined.

• The endogenous peptide-loaded HLAB*1502 molecule presented carbamazepine to cytotoxic T cells without the involvement of intracellular drug metabolism or antigen processing.

• Isolated urticaria after egg ingestion → trivalent influenza vaccine can be given as a single dose with a 30-minute observation; equipment to manage anaphylaxis must be available. Anaphylaxis to egg → referral to an allergist for essentially the same approach.

• Atopic dermatitis (AD): skin barrier defect, microbial colonization, autoreactivity → early TH2 response (acute phase) followed by TH1 and TH22 response (chronic phase).

• TH2 response contributes to skin barrier defect and ↑ levels of IL-31 (enhances pruritus, affects keratinocyte differentiation). TH22 response (IL-22) decreases epidermal differentiation.
• Polymorphisms in ANO3, MUC15 and IL10 have been associated with AD.
• TSLP release from keratinocytes in AD → effects on dendritic cells → early TH2 cell activation.
• New approaches for AD: probiotic or bacterial lysate therapy early in the course of illness; immunotherapy to primary allergens; phototherapy.
• Thyroid autoimmunity → activation of complement by the complement controller domain of thyroperoxidase → chronic urticaria.

• ADVANCES IN PEDIATRIC ASTHMA IN 2012: MOVING TOWARD ASTHMA PREVENTION (Szefler SJ. J Allergy Clin Immunol 2013; 131: 36-46):
  • Periostin levels correlate with airway eosinophilia; it is a potential biomarker in asthma.
  • Epigenetic mechanisms must be considered in the pathophysiology of asthma.
  • Decreased vit D level is associated with lower lung function, poor asthma control, increased medication use and more asthma exacerbations.
  • Vit D supplementation might improve corticosteroid sensitivity and asthma control in children.
  • Children with asthma → more expression of TGF-β, VEGF and periostin in airway cells.
  • Lung function can be used to predict hospitalizations, emergency department visits, and need for oral corticosteroid therapy in asthmatic children.
  • Asthmatic children (irrespective of their atopic status) and atopic children without asthma have deficient interferon responses to HRV infection. It correlates with increased FceRI expression on plasmacytoid dendritic cells.
  • Deficit in lung function in childhood can persist into adulthood → risk for COPD?
  • Children with asthma at 7 years old have lung function deficits and increased bronchial responsiveness as neonates. Research into the origins of asthma should consider early life before and after birth.
  • FENO, bronchial hyperresponsiveness and asthma risk increase with multiple sensitizations to different allergen groups.
  • Anti-IgE therapy has the potential to reduce severe asthma exacerbations.
  • Concerns remain regarding the adverse effects of ICSs on growth. One controversial strategy is to use ICSs on an intermittent basis when symptoms occur.
  • Uncontrolled asthma and recent exacerbations predict future asthma exacerbations.
  • Smoking should be stopped during pregnancy to prevent and improve asthma.
  • Atopic infants should be protected against respiratory irritants, molds and overweight.
  • Minimizing exposure to air pollution might reduce asthma exacerbations.
  • There is concern regarding the potential of acetaminophen to increase asthma risk.
• **TSLP** is increased in some patients with severe asthma → anti-TSLP is a potential therapy.

• Some variations in IL4A gene in asthmatic children enhance response to anti-IL-4α therapy.

• An IL-6 receptor SNP may increase risk for severe asthma.

• High P2X7 function is associated with enhanced leukocyte recruitment to the airways, asthma risk and severity.

• 50% of children with severe RSV-induced bronchiolitis have a subsequent asthma diagnosis. Associated risk factors: increased CCL5 (previously known as RANTES) levels in nasal epithelia; allergic sensitization by age 3 years.

• **ALLERGY TO SULFONAMIDES** (Schnyder B, Pichler WJ. J Allergy Clin Immunol 2013; 131: 256-257):

  • Authors present a clinical vignette of a 48-year-old man with DRESS syndrome (fever, rash, eosinophilia, lymphadenopathy, hepatitis, facial swelling) due to sulfasalazine. Lymphocyte transformation test (LTT) revealed a strong proliferation of the patient’s lymphocytes to sulfapyridine and sulfamethoxazole [SMX] (stimulation index >30; normal value <2).

  • **Sulfonamides**: drugs carrying the SO2-NH2 group. Antibacterial sulfonamides (sulfadoxine, SMX and sulfapyridine), which are derivatives of sulfanilamides, are of allergenic relevance. Two sulfanilamides (amprenavir and fosamprenavir) are used as protease inhibitors in HIV therapy; they induce rashes in 25% of patients.

  • Patients with allergy to sulfanilamides might cross-react with other sulfanilamides but not with sulfonamides in general (non-sulfanilamide drugs: glibenclamide, furosemide, celecoxib) → the term “sulfa allergy” is therefore misleading.

  • **Sulfasalazine** is split in the GI tract into 5-aminosalicylic acid and sulfapyridine → patients with allergy to sulfanilamides should never take sulfasalazine, and vice versa.

  • **Hypersensitivity reactions to sulfanilamides**: 2% of population; more frequent in HIV-infected individuals; they can be IgE-mediated (rare), IgG-mediated (rare; mainly hemolytic anemia) and T cell–mediated (most frequent; mainly rashes; occasionally severe delayed reactions).

  • Two mechanisms of hypersensitivity to SMX: A) **Hapten mechanism**: SMX is metabolized intrahepatically to SMX-NHOH, and then to SMX-NO → SMX-NO binds to cysteines in soluble and cell-bound proteins → innate immunity activation; IgE– or T cell–mediated responses. B) **Pharmacologic interaction with immune receptor (p-i) mechanism**: SMX directly binds to TCR and stimulates T cells without prior metabolism or binding to a protein.

  • **DRESS syndrome**: not all patients have eosinophilia; recurrent symptoms long after having stopped the causative drug are common, often related to reactivation of herpesviruses (HHV6, EBV, CMV) or intake of other drugs (different “innocuous” drugs, such as acetaminophen, can cause flare-up reactions as long as activated lymphocytes remain in the circulation; permanent allergy to more drugs can occasionally develop); allergy workup (skin and in vitro tests; low sensitivity; good specificity) is recommended 1 to 6 months after the reaction.

  • **Patch tests** (10% in dimethyl sulfoxide or petrolatum) have very low risk, but have lower sensitivity compared to **intradermal tests** (late reading). LTT measures drug-induced
proliferation of patient’s PBMCs during a 6-day culture; it seems to be more sensitive; it allows testing compounds in vitro, which are not available for in vivo tests.

- **SMX** at a concentration of 80 mg/mL has been shown to be nonirritating in intradermal tests.


  - **Soy allergy**: it has been described sIgE to >15 soybean proteins; diagnostic workup includes SPT, IgE detection assays, elimination diet and OFC; no screening test has 100% NPV or PPV.

  - **Pillow stuffing** can contain polyester, feathers, down or soy-based materials. Authors report 4 patients with anaphylaxis caused by hidden soybean allergens in pillows. All patients had purchased a viscoelastic pillow before symptom onset. SPT was positive to soybean oil, but not to conventional soybean extract (perhaps due to the localization of oleosins in oil bodies, which are underrepresented or denatured in most diagnostic extracts of seeds and nuts). Microarray-based IgE detection assay (ISAC) was positive to β-conglycinin (nGly m 5).

  - **Component-resolved diagnosis** and microarray technology might be useful in patients with food allergies or anaphylaxis caused by hidden allergens.


  - **Oral mite anaphylaxis (OMA)**: severe immediate allergic symptoms after eating foods made with mite-contaminated wheat flour; more prevalent in tropical environments (high temperature and relative humidity); most frequent causing food are pancakes (“pancake syndrome”); most patients are atopic adolescents and young adults, it can occur in children; thermoresistant allergens may be involved in pathogenesis; 2 deaths have been reported; OMA is frequently confused with allergy to wheat; a variety of this syndrome can occur during physical exercise (dust mite ingestion–associated exercise-induced anaphylaxis).

  - **Herranz (1963)** reported a 56-year-old man who died after eating a pap made with milk and wheat flour. Autopsy revealed intense bowel irritation and disseminated granulomas. Tyroglyphus farinae mites were present in stools and gut.

  - **Mites causing OMA** include **domestic mites** (Dermatophagoides pteronyssinus, D farinae and Blomia tropicalis) and **storage mites** (S medanensis, Aleuroglyphus ovatus, Lepidoglyphus destructor, Tyrophagus putrescentiae, Tyrographus entomaphagus and Blomia freemani).

  - **Risk factors for OMA**: atopic disease; sensitization to mites; NSAID hypersensitivity; ingestion of foods containing wheat flour; ingestion of >1 mg of mite allergen (>500 mites per gram of flour).

  - **OMA should be suspected** in patients with acute symptoms during or immediately after eating foods prepared with wheat flour or other products that could be contaminated with mites.

  - **Diagnostic criteria for OMA**: 1. allergic symptoms occurring after eating foods prepared with wheat flour; 2. previous history of rhinitis, asthma, atopic eczema or food allergy; 3. demonstration of mite-specific IgE in vivo or in vitro; 4. positive skin test response induced by an extract of the incriminated flour; 5. negative skin test response to commercial wheat extract.
and to an extract of uncontaminated flour; 6. tolerance to other foods made with uncontaminated wheat flour; 7. microscopic identification of mites in the suspected flour; 8. detection of mite allergens in the flour by immunoassay; 9. aspirin/NSAID hypersensitivity.

- How to prevent OMA? Store the flour in sealed plastic or glass containers in the refrigerator; improve air quality through air purifiers; decrease intradomiciliary humidity; clean and disinfect furniture and floors; use acaricides.

- Immunotherapy can benefit patients with OMA?


- A recent RCT phase II trial shows positive results with omalizumab for the management of allergic and nonallergic patients with nasal polyps and asthma → omalizumab might be an option to treat patients with recalcitrant CRSwNP, regardless of atopy or asthma status.

- Why omalizumab was efficacious in “nonallergic” patients? Hypothesis: “nonallergic” patients might only have local, and not systemic, IgE production (entopy) → omalizumab neutralizes locally-produced IgE in the polyp tissue and possibly in the lower respiratory tissues as well.

- Anaphylaxis to omalizumab: 0.2% → administration should be done in a health care setting.

- Anti–IL-5 antibodies for CRSwNP induce polyp shrinkage in 50% of the patients.

- Siglec-8 is only expressed by human eosinophils, mast cells and basophils → potential target for the management of allergic disorders by neutralizing all 3 cell types.

**CAN WE PRODUCE TRUE TOLERANCE IN PATIENTS WITH FOOD ALLERGY?** (Berin MC, Mayer LL. J Allergy Clin Immunol 2013; 131: 14-22):

- Tolerance: nonresponsiveness of the adaptive immune system or active Treg cell response to antigens.

- Mechanisms of tolerance: anergy or deletion of reactive lymphocytes; generation of Treg cells.

- Anergy: nonresponsiveness of the T cells without having suppressive or tolerogenic activity.

- Immediate food allergy → TH2-response and specific IgE antibodies to food allergens.

- Mechanisms of central tolerance: removal of self-reactive lymphocytes in the thymus and bone marrow; generation of FoxP3+ natural T reg cells.

- Thymic medullary epithelial cells can express antigens from other parts of the body through AIRE gene → maturing T cells which react against self antigens are deleted or turn into T regs.

- Mutations in AIRE → autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED).

- Mutation in FoxP3 → lack of T reg cells → immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX).
• **Mechanisms of peripheral tolerance:** anergy or deletion of inappropriate-reactive lymphocytes in the periphery; generation of induced Tregs. It depends on: a) environment where antigen presentation occurs; b) presence or absence of costimulatory molecules in antigen presenting cells; c) activation of the innate immune system by microbial signals (pathogen-associated molecular patterns, PAMPs) or damage signals (DAMPs).

• Antigen presentation in the gastrointestinal tract promotes Treg response, leading to tolerance. Feeding of antigen can prevent asthma, food allergy and anaphylaxis in experimental models. The respiratory tract and the oral mucosa are also tolerogenic.

• **Gastrointestinal tract:** high constitutive levels of IL-10 and retinoic acid.

• In the gastrointestinal tract, CD103+ dendritic cells acquire antigen through intestinal goblet cells and migrate to the mesenteric lymph nodes, where they induce gut-homing Treg cells (CCR9+, α4β7+) and gut-homing IgA-secreting B cells through mechanisms dependent on TGF-β, retinoic acid, indoleamine 2,3-deoxygenase (IDO) and the cosignaling molecule 4-1BB.

• TGF-β is necessary for induction of tolerance in oral mucosa. Role of IL-10? Conflicting data.

• Treg cells, even in adults, are necessary for maintenance of self-tolerance. They can affect other T cells acting through a common antigen-presenting cell.

• CTLA-4 is constitutively expressed by Treg cells and is upregulated in activated T cells.

• The paradigm of T cell deletion at a high antigen dose and Treg induction at a low antigen dose might not always hold true.

• Surgical ablation of the mesenteric lymph nodes abolishes oral tolerance; Peyer patches have been shown to be dispensable for tolerance.

• **Adjuvants** (eg. cholera toxin, staphylococcal enterotoxin B) must be used to elicit allergic sensitization through the GI tract. Oral administration of cholera toxin → migration of CD103+ DCs from lamina propria to draining lymph nodes, expressing the costimulatory molecule OX40L → TH2 generation from naive T cells.

• How can we **restore tolerance** in individuals with food allergy? Administering the causative food allergens in a tolerogenic environment (**food immunotherapy**). IgE production is especially susceptible to oral tolerance.

• Higher doses and longer duration of food immunotherapy can generate sustained tolerance.

• A recent study showed that 25% of children with **egg allergy** can achieve tolerance after a 2-year period of oral immunotherapy (**OIT**).

• **Proposed effects of OIT:** increase of food-specific IgG4 and IgA; reduction in basophil and mast cell reactivity; induction of Treg cell response.

• Studies are needed to establish: a) whether baseline clinical tolerance to foods in healthy subjects is associated with a food-specific Treg response; b) whether acquired clinical tolerance is primarily due to an induction of Treg response, a waning of allergic sensitization, or both.

• Signalling by **SIGNR1** (specific ICAM3 grabbing nonintegrin-related 1) on dendritic cells can favour the induction of IL-10–producing Treg cells.
• Methods to enhance efficacy of food IT: new routes (eg. epicutaneous); use of adjuvants to promote Treg response (eg. mannosylation, TLR ligands); coupling food allergens with syngeneic spleen cells (antigens from apoptotic cells can function as tolerogenic adjuvants).

• EARLY-LIFE ENVIRONMENTAL DETERMINANTS OF ALLERGIC DISEASES AND THE WIDER PANDEMIC OF INFLAMMATORY NONCOMMUNICABLE DISEASES (NCDs) (Prescott SL. J Allergy Clin Immunol 2013; 131: 23-30):
  • Allergies (30-40% of the world’s population) are the most common NCDs.
  • Chronic low-grade inflammation is a common feature of virtually all NCDs. Several NCDs (obesity, addictive behaviour) are linked to TLR-4 activation. Positive metabolic effects of exercise are partially mediated through downregulation of TLR4.
  • Risk factors associated with NCDs: modern diet (low intake of fiber, fruit and vegetables; high intake of saturated fat), sedentary indoor lifestyle, vit D insufficiency, environmental pollutants (smoke, gaseous and particulate pollutants), certain infections, stress.
  • Diseases associated with vit D insufficiency (decreased sunlight exposure): hypertension, type 2 diabetes, type 1 diabetes, multiple sclerosis, bone disease, breast and hematological cancers, susceptibility to infection, food allergy and asthma.
  • Gut microbiota and ω-3 PUFA–rich fish oils have antiinflammatory properties and promote gut epithelial integrity → potential tools to prevent and treat inflammatory diseases (allergy, obesity, cardiovascular and metabolic disease, behavior disorders?).
  • Soluble fiber (prebiotic carbohydrate) is a major substrate for beneficial gut microbiota, mainly bifidobacteria; its fermentation products (short-chain fatty acids) have anti-inflammatory effects and promote integrity of intestinal epithelial cells (proliferation and differentiation).
  • Research is ongoing to determine the effect of probiotics in pregnancy and postnatal period for allergy prevention.

• EPINEPHRINE (ADRENALINE) ABSORPTION FROM NEW-GENERATION, TASTE-MASKED SUBLINGUAL TABLETS: A PRECLINICAL STUDY (Rachid O, Rawas-Qalaji MM, Simons FER, Simons KJ. J Allergy Clin Immunol 2013; 131: 236-238):
  • Epinephrine autoinjectors are essential to manage patients with a history of anaphylaxis. Problems: autoinjector size, parenteral route, incorrect injection technique, misfiring, unintentional injection, availability of only one dose, short shelf-life of the epinephrine solution.
  • Sublingual mucosa is thin and has abundant blood supply → rapid absorption of medication through the epithelium into the interstitial fluid by passive diffusion according to Fick’s law.
  • Sublingual epinephrine is an excellent option. Epinephrine bitartrate is a hydrophilic drug with a low molecular weight → high dose is needed to create the concentration gradient for diffusion.
  • Authors show (in rabbits) that sublingual epinephrine is rapidly absorbed in the first 20 min. It enters the systemic circulation through the sublingual veins, bypassing the gastrointestinal tract and hepatic first-pass metabolism.
The new-generation sublingual epinephrine tablets have similar bioavailability to epinephrine injected intramuscularly in the thigh, and are ready for phase I studies in human subjects.

Problems of first-generation sublingual epinephrine tablets: epinephrine had intrinsic bitter taste, epinephrine dissolution was slow.

New-generation epinephrine sublingual tablets: citric acid masks bitter taste; epinephrine disintegrates within 13 seconds and dissolves within 60 seconds.

Regardless of the route of epinephrine administration, 2 peaks in plasma concentrations are noted: 1) the first peak corresponds to rapid epinephrine absorption, followed by vasoconstriction at the site of administration; 2) the second and higher peak corresponds to subsequent vasodilation and epinephrine absorption.

SUCCESSFUL DESENSITIZATION TO ROSUVASTATIN IN A PATIENT WITH A HISTORY OF ANAPHYLAXIS TO MULTIPLE STATINS (Khan FS, Stewart DK, Brunzell JD, Natrajan KM, Castells MC, Henderson WR, Ayars AG. J Allergy Clin Immunol 2013; 131: 234-236):

- Adverse reactions to statins: myositis, urticarial vasculitis, DRESS, SJS/TEN.
- Case report: 37-year-old man with significant premature coronary artery disease caused by familial combined hyperlipidemia; anaphylaxis to multiple statins (atorvastatin, simvastatin).
- Successful rapid oral desensitization to rosuvastatin was performed. Metoprolol was held for 72 hours before the procedure in the case epinephrine was needed; H1 blockers were held to prevent masking of an early IgE-mediated reaction; pretreatment consisted of montelukast and zileuton for 48 hours before the procedure; aspirin, ranitidine and ondansetron were given on the morning of the desensitization.
- Rosuvastatin is more potent and has fewer side effects than atorvastatin.

THE CHANGING CARE FOR PATIENTS WITH FOOD ALLERGY (Jones SM, Wesley Burks A. J Allergy Clin Immunol 2013; 131: 3-11):

- More than 170 different foods have been reported to cause allergic reactions.
- Component-resolved diagnosis may be useful to diagnose food allergy.
- Auvi-Q (Sanofi, Bridgewater, NJ): new FDA-approved epinephrine autoinjector; it has audio and visual indications for each step of the injection process.
- Desensitization refers to a transient induction of unresponsiveness to allergens. Tolerance refers to a long-lasting induction of unresponsiveness that persists after treatment is stopped.
- Oral immunotherapy (OIT) is the more effective among emerging therapies for food allergy.
- Pretreatment with omalizumab before and during OIT reduced side effects and the time to reach maintenance dosing in a pilot study of 11 patients with milk allergy.
- The Food Allergy & Anaphylaxis Network (FAAN) and the Food Allergy Initiative (FAI) were started by parents of children with food allergy. These 2 organizations have recently announced their merger as Food Allergy Research & Education (FARE; www.foodallergy.org).
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

- Educational materials about food avoidance in allergic patients can be found in www.foodallergy.org and www.cofargroup.org.
- A multimedia course is available at www.AllergyReady.com to understand: (1) basic facts about food allergy, (2) how to avoid food allergens, (3) how to recognize an allergic reaction, and (4) how to establish an emergency protocol.