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.

Juan Carlos Aldave Becerra, MD
Allergy and Clinical Immunology
Hospital Nacional Edgardo Rebagliati Martins, Lima-Peru
jucapul_84@hotmail.com

Juan Félix Aldave Pita, MD
Medical Director
March 2014 – content:


- **PREVALENCE OF ATOPY, EOSINOPHILIA, AND IgE ELEVATION IN IgG4-RELATED DISEASE** (Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Allergy 2014; 69: 269–272).

- **SERUM BASAL TRYPTASE MAY BE A GOOD MARKER FOR PREDICTING THE RISK OF ANAPHYLAXIS IN CHILDREN WITH FOOD ALLERGY** (Sahiner UM, Yavuz ST, Buyuktiyaki B, Cakmakci O, Yilmaz EA, Tuncer A, Sackesen C. Allergy 2014; 69: 265–268).

- **VITAMIN D AS AN ADJUNCT TO SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY IN ASTHMATIC CHILDREN SENSITIZED TO HOUSE DUST MITE** (Baris S, Kiykim A, Ozen A, Tulunay A, Karakoc-Aydiner E, Barlan IB. Allergy 2014; 69: 246–253).


- **EFFECT OF MATERNAL ω3 FATTY ACID SUPPLEMENTATION ON INFANT ALLERGY** (Ciaccio CE, Girdhar M. Ann Allergy Asthma Immunol 2014; 112: 191-194).

- **EXERCISE-INDUCED DYSPNEA: MORE THAN VOCAL CORD DYSFUNCTION OR LARYNGOMALACIA** (Weinberger M. Ann Allergy Asthma Immunol 2014; 112: 270-271).


- **INTRAVENOUS β AGONISTS AND SEVERE PEDIATRIC ASTHMA EXACERBATION: TIME FOR A CLOSER LOOK AT TERBUTALINE?** (Kantor DB, Phipatanakul W. Ann Allergy Asthma Immunol 2014; 112: 187).

- **LONG-TERM FOLLOW-UP OF IgE-MEDIATED FOOD ALLERGY: DETERMINING PERSISTENCE VERSUS CLINICAL TOLERANCE** (Burks AW, Land MH. Ann Allergy Asthma Immunol 2014; 112: 200-206).

- **LYMPHOPENIA INDUCED BY ETANERCEPT** (Pepper AN, Talreja N, Cowan GM, Glaum MC, Lockey RF. Ann Allergy Asthma Immunol 2014; 112: 262-263).
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.

- **RADIOCONTRAST-INDUCED IODIDE SIALADENOPATHY AND NEUTROPHILIC DERMATOSIS** (Fok JS, Ramachandran T, Berce M, Smith WB. Ann Allergy Asthma Immunol 2014; 112: 262-263).
- **T-CELL BIOLOGY IN IMMUNOTHERAPY** (Steinke JW, Lawrence MG. Ann Allergy Asthma Immunol 2014; 112: 195-199).
- **ADVANCES IN PEDIATRIC ASTHMA IN 2013: COORDINATING ASTHMA CARE** (Szefler SJ. J Allergy Clin Immunol 2014; 133: 654-61).
- **PENICILLIN ALLERGY AS A PUBLIC HEALTH MEASURE** (Solensky R. J Allergy Clin Immunol 2014; 133: 797-798).
- **ONE EDITORS’ CHOICE** (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2014; 133: 662-663).


ALLERGY:


  - **Food allergy (FA):** (i) IgE-mediated: urticaria, angioedema, bronchospasm, GI symptoms, anaphylaxis; (ii) non-IgE-mediated: enterocolitis, proctocolitis, Heiner syndrome, celiac disease, contact dermatitis; (iii) IgE- and cell-mediated: atopic dermatitis, eosinophilic GI diseases.

  - **IgE-mediated FA:** (i) ↑ prevalence worldwide (6% of children, 4% of adults); (ii) impact: mortality risk, ↓ QoL, costs; (iii) >170 foods have been reported to cause allergic reactions; (iv) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soy, seafood; (v) diagnosis: specific IgE detection by skin prick test (SPT) or in vitro testing (sIgE, CRD), basophil activation test, food challenge (DBPCFC is the gold standard); (vi) conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling, follow up to confirm spontaneous development of tolerance (especially in egg, milk, wheat and soy allergy), ingestion of extensively heated egg or milk products in children who tolerate them (this may accelerate resolution of egg and milk allergy, respectively); (vii) optimal treatment: restore tolerance (immunotherapy).

  - Authors performed a systematic review to summarize evidence about the management of FA → (i) 84 studies were included (2/3 had high risk of bias); (ii) meta-analysis was not feasible due to heterogeneity; (iii) acute management of FA: anti-H1 may be beneficial in non-life threatening reactions (weak evidence); (iv) long-term management of FA: mast cell stabilizers may ↓ FA symptoms (weak evidence); extensively hydrolyzed and amino acid-based formulas can be beneficial in infants with cow’s milk allergy (moderate evidence); probiotics have not proved helpful; food immunotherapy can modify disease; (v) more evidence is needed.

  - **Author’s commentary:** the best management strategy for FA likely depends on the patient’s age, the culprit food, the type and severity of FA, and the response to previous therapies.


  - Authors review the contribution of pharmacogenetics and transcriptomics to the understanding of hypersensitivity drug reactions (HDRs).

  - **Adverse drug reaction (ADR):** “any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment” (WHO).

  - **HDRs:** (i) 6–10% of all ADRs; (ii) impact: significant morbidity, mortality risk, ↓ QoL, costs; (iii) almost any drug can cause HDRs; (iv) HDRs can be immune- or non-immune mediated; (v) immune-mediated HDRs can be immediate (IgE-mediated) or delayed (antibody- or cell-mediated); (vi) diagnosis: clinical history, allergologic tests (in vivo and in vitro), drug challenges; (vii) therapy: avoidance of the culprit drug(s), use of alternative drugs, drug desensitization, preparation for an unexpected HDR.
Futuristic approach in allergic diseases (including HDRs): use of clinical, laboratory, imaging, histologic and genetic markers to identify specific genotypes/endotypes/phenotypes → give individualized therapy (optimize efficacy and safety).

Goals of pharmacogenetics: (i) to identify specific alleles that can predict efficacy and safety of a drug (e.g. HLA-B*57:01 ↑ risk of abacavir hypersensitivity; HLA-B*58:01 ↑ risk of allopurinol-induced SJS/TEN/DRESS; HLA-B*15:02 ↑ risk of carbamazepine-induced SJS/TEN; HLA-B*57:01 ↑ risk of flucoxacilline-induced liver injury; variants of FceRIβ, STAT6, IL-4, IL-13, IL-4RA and TNFα may ↑ risk of penicillin allergy); (ii) to define personalized therapies based on the patient’s genetic profile.

Transcriptomics: (i) definition: the quantitative study of all genes expressed in a given biological state; (ii) importance: allows investigation of HDR mechanisms by analyzing gene expression in different hypersensitivity entities (e.g. SJS/TEN, DRESS, anaphylaxis, etc).


Allergens: (i) molecules that can cause and trigger allergic diseases; (ii) allergenic structures can be found in every species; (iii) estimated allergen repertoire: ~5000 different structures; (iv) current allergen list (WHO/IUIS Allergen Nomenclature Subcommittee - www.allergen.org): 753 molecules; (v) most major allergens from mites, animal dander, pollens, insects and foods have been cloned.

Fungi: (i) ~100,000 reported species; (ii) important source of allergenic molecules (enzymes, toxins, cell wall components); (iii) officially-approved fungal allergens include 105 iso-allergens and variants from 25 fungal species of the Ascomycota and Basidiomycota phyla; (iv) many more fungal allergens are described in the literature (e.g. Aspergillus fumigatus can produce ≥81 different IgE-binding proteins) (v) fungal extracts are not standardized, although dozens of commercial products exist (reasons: differences in source materials and manufacturing procedures, lack of accepted potency assays, vast number of allergic fungal species); (vi) fungal allergens have been largely neglected in molecular allergology; (vii) the 1st recombinant fungal allergens (Alt a 1, Asp f 1 to 4) immobilized in ImmunoCAPs are now commercially available.

Allergy to fungi: (i) exaggerated immune responses to fungal molecules → excessive inflammation; (ii) mechanisms: IgE-mediated, IgG-mediated, cell-mediated; (iii) ~80 mould genera have been shown to induce IgE-mediated allergies (e.g. Alternaria, Aspergillus, Cladosporium, Candida, Penicillium, Clavularia, Malassezia); (iv) cross-reactivity between homologous fungal allergens has been demonstrated (and even between distant species such as Candida boidii and A. fumigatus).

General difficulties to diagnose fungal allergy: (i) most patients sensitized to fungi are not aware of the source of exposure; (ii) fungal extracts for skin tests are not standardized; (iii) in vitro tests may not be enough accurate; (iv) fungal extracts contain cross-reactive carbohydrate determinants (often clinically irrelevant).

Treatment of fungal allergy includes allergen avoidance (often not feasible due to ubiquitous location of fungi), antifungal drugs (e.g. itraconazole), antiinflammatory therapy (e.g. oral or inhaled corticosteroids) and specific immunotherapy.
Diseases where fungal allergy plays an important role: (i) allergic bronchopulmonary mycosis (ABPM), such as allergic bronchopulmonary aspergillosis (ABPA), (ii) allergic asthma (especially severe asthma with fungal sensitization [SAFS]); (iii) allergic rhinosinusitis (especially allergic fungal rhinosinusitis [AFRS]); (iv) atopic dermatitis; (v) extrinsic allergic alveolitis (occupational exposure to thermophilic actinomycetes).

ABPA: (i) hypersensitivity to Aspergillus fumigatus in the lower airways; (ii) affects up to 2.5% of adults with severe asthma (patients with severe asthma should be screened for ABPA); (iii) predisposing conditions: severe asthma, cystic fibrosis, hyper-IgE syndrome, chronic granulomatous disease, family history of ABPA; (iv) complications: uncontrolled asthma, recurrent pneumonias, bronchiectasis, lung fibrosis, ↓ lung function, respiratory failure; (v) differential diagnosis: ABPM, SAFS, cystic fibrosis, bronchopulmonary infections.

When to suspect ABPA? (i) severe asthma with expectoration of mucous plugs; (ii) pulmonary infiltrates (especially in upper or middle lobe); (iii) perihilar mucous plugging; (iv) lobar or lung collapse; (v) central bronchiectasis (inner 2/3 of lung fields); (vi) blood eosinophils ≥8%; (vii) total IgE >417 kU/L (while not receiving systemic corticosteroids); (viii) positive skin tests (SPT, IDR) to A. fumigatus; (ix) ↑ specific IgE and IgG (precipitating antibodies) to A. fumigatus; (x) A. fumigatus in sputum culture; (xi) suggestive histology (allergic mucin, fungal hyphae, bronchi with mucoid impaction, bronchocentric granulomatosis); (xii) major improvement with systemic corticosteroids (↓ infiltrates, ↓ total IgE); (xiii) concurrent AFRS.

Difficulties to diagnose ABPA: (i) no pathognomonic test exists (skin tests appear highly sensitive, in vitro tests [specific IgE and IgG to A. fumigatus] appear highly specific); (ii) pulmonary infiltrates and bronchiectasis can be relatively silent.

Frequent diagnostic mistakes in ABPA: (i) to exclude ABPA when antibodies to A. fumigatus are not detected; (ii) to exclude ABPA when skin testing to A. fumigatus is negative; (iii) to exclude ABPA when total IgE is <417 kU/L (IgE may ↓ during remission stage or corticosteroid use); (iv) to exclude ABPA when bronchiectasis are not present (seropositive ABPA).

ABPM: (i) syndrome similar to ABPA, but caused by other fungi (e.g. Candida, Penicillium, Curvularia species); (ii) less frequent than ABPA.

SAFS: (i) this term describes patients with severe persistent asthma, fungal sensitization and good response to antifungal treatment; (ii) diagnostic criteria are not defined.

AFRS: (i) 5-10% of cases of chronic rhinosinusitis (CRS); (ii) mainly caused by Aspergillus sp (other causal fungi: Bipolaris, Exserohilum, Curvularia, Alternaria); (iii) more frequent in humid and warm regions; (iv) pathophysiology: entry of fungal spores in the sinuses → fungal growth → IgE production to fungal allergens → eosinophil attraction and activation → tissue inflammation and damage; (v) typical presentation: immunocompetent atopic young adult or adolescent with severe CRS and nasal polyps; (vi) diagnosis: CRS with nasal polyps (frequently unilateral), peripheral eosinophilia, ↑ total IgE, ↑ specific IgE to Aspergillus sp (skin or in vitro testing), eosinophilic mucous plugs with fungal hyphae (‘allergic mucin’); (vii) complications: inflammation/erosion/compression of contiguous structures (e.g. bone, orbits, brain), secondary bacterial infections; (viii) management: team approach (allergist, ORL, neurologist, etc.), functional endoscopic sinus surgery (removal of the fungi and secretions), steroids for ≥3 months (intranasal and systemic), antifungal drugs, fungal immunotherapy.
Diagnostic criteria for AFRS (Bent and Kuhn, 1994): (i) nasal polyposis; (ii) presence of ‘allergic mucin’ (eosinophil-rich thick secretions with Charcot-Leyden crystals and fungal elements) without fungal invasion of the paranasal tissues; (iii) CT findings suggestive of CRS; (iv) fungi detection by histology or culture; (v) positive specific IgE to fungal allergens.

Atopic dermatitis (AD): (i) common chronic skin disease (3% of adults, 20% of children); (ii) impact: ↓ QoL, high costs, ↑ predisposition to skin infections and other allergies (~1/3 of AD patients develop asthma, ~2/3 develop allergic rhinitis); (iii) multiple pathogenic factors: ↓ skin barrier, immune dysregulation, sensitization to foods, microbial molecules or self antigens.

Malassezia sympodialis: (i) skin colonizing yeast (colonization occurs immediately after birth); (ii) may cause IgE-mediated sensitization in AD patients (favoring factors: ↓ skin barrier, immune dysregulation), contributing to AD chronicity; (iii) cross-reactivity reactions between M. sympodialis allergens and human proteins can occur (e.g. Mal a s 11 and human manganese-dependent superoxide dismutase; Mal a s 13 and human thioredoxin).


- Approaches in cancer immunotherapy (only i, ii and iii are currently practically relevant in public health): (i) vaccination against tumorigenic viruses; (ii) passive immunotherapy with monoclonal antibodies; (iii) activation of antitumor immunity via blockade of immune checkpoints; (iv) vaccination with tumor cells or tumor-associated antigens (TAAs); (v) in vitro ‘pulsing’ of antigen-presenting cells; (vi) selection/cloning of NK cells and cytotoxic T cells targeting TAAs.

- Passive immunotherapy with monoclonal antibodies (mAbs) against cancer: (i) mAbs directed specifically against TAAs; (ii) all FDA-approved mAbs comprise the IgG class (IgG1, IgG2, IgG3), although other classes have been proposed (IgM, IgA, IgE); (iii) effector mechanisms of IgG mAbs: inhibition of proliferation signals, activation of NK cells, phagocytes and complement system (antibody-dependent cell-mediated cytotoxicity [ADCC], antibody-dependent cell-mediated phagocytosis [ADCP]); (iv) some IgG mAbs have been coupled with cytotoxic molecules to ↑ killing of cancer cells; (v) some IgG mAbs have been modified (e.g. site-directed mutagenesis or altered glycosylation) to ↑ binding to activating Fcγ receptors and ↑ cytotoxicity.

- Examples of IgG mAbs against cancer: (i) anti-HER-2 mAbs to treat metastatic breast cancer overexpressing HER-2 (human epidermal growth factor receptor-2); (ii) anti-EGFR mAbs to treat metastatic colon cancer overexpressing EGFR (epidermal growth factor receptor); (iii) anti-CD20 mAbs to treat B-cell non-Hodgkin’s lymphoma; (iv) anti-CTLA-4 mAbs (ipilimumab) to treat advanced metastatic melanoma; (v) anti-PD-1 (programmed death-1) mAbs (nivolumab, lambrolizumab) to treat advanced metastatic melanoma.

- Genetic factors that may affect the efficacy of mAbs regarding ADCC: (i) polymorphisms in FcγR genes; (ii) copy number variations in FcγR genes; (iii) epigenetic modifications of FcγR genes; (iv) posttranslational glycosylation of constant regions in the heavy chains of mAbs.

- IgE: (i) important role in defense against some parasitic infections; (ii) its production is dysregulated in allergic diseases; (iii) may have high tumoricidal efficacy; (iv) effector mechanisms: activation of mast cells, eosinophils and basophils.

- Arguments that favor the use of IgE mAbs in cancer immunotherapy: (i) there is an inverse association between atopic diseases and some neoplasms (e.g. pancreatic cancer, glioma,
childhood leukemia); (ii) IgE can activate effector cells (eosinophils, monocytes and basophils) with a high inflammatory, cytotoxic and/or phagocytic potential upon binding to IgE receptors (FccRI seem to mediate cytotoxicity, FcεRII [C23] seem to mediate phagocytosis); (iii) IgE can restimulate the immune system via facilitated antigen uptake and presentation; (iv) affinity of IgE to Fcc receptors is higher than IgG to Fcγ receptors; (v) humans and dogs have a highly comparable IgE biology → canine cancer models can be useful to predict the therapeutic potential of IgE mAbs in human cancer.

- Arguments against the use of IgE mAbs in cancer immunotherapy: (i) mast cells can promote angiogenesis and tumor development; (ii) mast cell and basophil activation can lead to anaphylactic reactions.


  - Anaphylaxis: (i) definition: acute, severe, life-threatening systemic hypersensitivity reaction; (ii) lifetime prevalence: 0.05-2%; (iii) incidence: 1/10,000 patient-yr (incidence is increasing); (iv) 0-4 yr-old children have higher incidence rates; (v) mechanisms: release of mediators from mast cells and basophils (mainly IgE-mediated reactions; IgG-mediated mechanisms have been shown in mice); (vi) most common culprits: foods, drugs, hymenoptera venom, latex; (vii) factors that influence severity: pathogenic mechanism, allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors; (viii) augmentation cofactors: exercise, alcohol, infections, NSAIDs, drugs, menses, stress; (ix) anaphylaxis can present without cutaneous signs (urticaria or angioedema) in >20% of patients; (x) 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 IV drugs, (ii) 15 min for field insect stings and IM drugs, (iii) 30 min for food and oral drugs.

  - Allergists/immunologists must know: (i) how to treat acute anaphylaxis (it 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).

  - Authors performed a systematic review (55 studies) to establish the effectiveness of interventions to manage anaphylaxis → key recommendations: (i) epinephrine is the drug of first choice to manage anaphylaxis, via intramuscular route into the anterolateral portion of the midthigh (middle of vastus lateralis muscle); (ii) failure or delay in epinephrine administration can ↑ death risk; (iii) anaphylaxis management plans may ↓ severity of subsequent reactions; (iv) venom immunotherapy can ↓ anaphylaxis risk and ↑ QoL in patients with severe venom allergy; (v) prophylactic epinephrine can ↓ severe reactions after anti-snake venom administration; (vi) more research is needed.

- PREVALENCE OF ATOPY, EOSINOPHILIA, AND IgE ELEVATION IN IgG4-RELATED DISEASE (Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Allergy 2014; 69: 269–272):
• **IgG4:** (i) 5% of total IgG; (ii) antiinflammatory properties (negligible binding to C1q; exchangeable heavy chains ["Fab arm exchange"] that prevents cross-linking of antigen; higher affinity toward inhibitory FcγRIIb than to activatory FcγRIIa and FcγRIIIa).

• **IgG4 autoantibodies** are pathogenic in some autoimmune disorders (e.g. pemphigus vulgaris: IgG4 to desmoglein; idiopathic membranous glomerulonephritis: IgG4 to PLA2 receptor).

• **IgG4-related disease (RD):** (i) multi-organ fibroinflammatory disease (tumefactive lesions rich in T cells and IgG4-positive plasma cells); (ii) unclear pathogenesis (TH2 cells may have a pathogenic role); (iii) can affect almost every organ; (iv) usually affects middle-aged to elderly men; (v) common clinical manifestations: autoimmune pancreatitis, sialadenitis, orbital disease (typically affecting lacrimal gland), allergic diseases, eosinophilia, ↑ serum IgE; (vi) 30% of patients have normal serum IgG4 concentrations; (vii) histology: diffuse lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, ↑ eosinophils; (viii) treatment: corticosteroids, immunosuppressants, rituximab.

• Authors evaluated the prevalence of atopy, peripheral blood eosinophilia (PBE) and ↑ IgE in 70 patients (24–82 yrs old) with biopsy-proven IgG4-RD → (i) 43 patients (61%) had ↑ serum IgG4 levels; (ii) 22 patients (31%) were atopic (similar prevalence of atopy to the US general population); (iii) ~20% of nonatopic subjects had PBE and ↑ IgE (hypothesis: processes inherent to IgG4-RD itself may contribute to PBE and ↑ IgE); (iv) there was a positive correlation between serum IgG4 levels and both serum IgE and eosinophil counts.

• **SERUM BASAL TRYPTASE MAY BE A GOOD MARKER FOR PREDICTING THE RISK OF ANAPHYLAXIS IN CHILDREN WITH FOOD ALLERGY** (Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A, Sackesen C. Allergy 2014; 69: 265–268):

  • Serum basal tryptase (sBT): (i) marker of mast cell activity and burden; (ii) marker of anaphylaxis; (iii) sBT>11.4 ng/mL is a risk factor for hymenoptera venom-induced anaphylaxis (sBT might be a marker of an underlying clonal disease).

  • Authors evaluated the value of sBT to predict the risk of anaphylaxis in children with food allergy (FA) → (i) sBT level was significantly associated with the risk of moderate to severe anaphylaxis in children with FA [OR: 1.3]; (ii) sBT levels >5.7 and 14.5 ng/mL were associated with 50% and 90% predicted probabilities, respectively, of moderate to severe anaphylaxis; (iii) children with tree nut or peanut allergy, compared to children with milk or egg allergy, had significantly higher levels of sBT and more severe anaphylaxis episodes.

• **VITAMIN D AS AN ADJUNCT TO SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY IN ASTHMATIC CHILDREN SENSITIZED TO HOUSE DUST MITE** (Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A, Sackesen C. Allergy 2014; 69: 265–268):

  • Vit D effects on the immune system: (i) ↑ skin barrier function; (ii) ↑ production of antimicrobial peptides (β-defensins, cathelicidin); (iii) ↑ phagocytic activity of macrophages; (iv) ↓ maturation of dendritic cells; (v) ↓ differentiation of TH1 and TH17 cells; (vi) ↑ differentiation of Treg cells; (vii) ↓ function of B-lymphocytes; (viii) ↓ production of IgE; (ix) ↑ IL-10 production by mast cells.

  • Hypovitaminosis D has been associated (frequently but not uniformly) with ↑ occurrence or severity of allergy (allergic sensitization, recurrent wheezing, asthma, allergic rhinitis, food allergy, atopic dermatitis).
• Exposure to aeroallergens (e.g. house dust mites [HDM]) in genetically susceptible subjects → specific TH2 responses to aeroallergens → IgE-mediated allergic respiratory diseases.

• Allergen immunotherapy: (i) only treatment that can change the natural history of IgE-mediated allergies; (ii) method: administration of the specific allergen progressively to induce tolerance; (iii) mechanisms: ↑ Treg cells, ↑ specific IgG1 and IgG4, ↓ specific IgE, ↓ reactivity of mast cells and basophils; (iv) routes: subcutaneous (SCIT), sublingual, intralymphatic, epicutaneous.

• Authors studied 55 children with asthma and HDM sensitization to evaluate the beneficial effect of vit D as an adjunct to SCIT → (i) 58% of children had ↓ serum vit D levels; (ii) vit D levels correlated negatively with the number of asthma attacks; (iii) SCIT and [SCIT + vit D] gave better results than pharmacotherapy alone at the end of 1 yr; (iv) vit D might be beneficial as an adjunct to SCIT in asthmatic children sensitized to HDM (more research is warranted).
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

  
  Acquired angioedema with C1-INH deficiency (ACID): (i) recurrent episodes of bradykinin-mediated angioedema due to C1-INH consumption; (ii) pathophysiology: lymphoproliferative disease, autoimmune disease, MGUS (monoclonal gammopathy of unknown significance) → autoantibody production → activation of the classical complement pathway → consumption of C1q, C1-inh and C4 → ↑ activity of FXII and kallikrein → ↑ production of bradykinin → ACID; (iii) usually presents after 40 yrs of age; (iv) clinical manifestations: recurrent swelling of subcutaneous tissues (face, hands, arms, legs, buttocks, genitals), abdominal organs (stomach, gut, bladder) or upper airways (larynx), unresponsive to antihistamine or corticosteroids.

  Authors report 3 patients with ACID, lymphoproliferative disease and antibody deficiency → (i) Patient 1: 29-yr-old woman with ALPS due to FAS gene mutation; acute lymphoblastic leukemia with remission after chemotherapy; hypersplenism that required splenectomy; autoimmune hemolysis; immunodeficiency (recurrent respiratory infections; ↓ IgG levels; ↓ antibody responses) that required IVIG; ACID (swelling of left hand and arm; ↓ C4, C1q and C1-INH levels) treated with tranexamic acid prophylaxis and C1-INH during attacks. (ii) Patient 2: 55-yr-old woman with ACID (recurrent cutaneous swelling and abdominal pain; ↓ C4, C1q and C1-INH levels) requiring tranexamic acid; hemolytic anemia that required splenectomy; low-grade B-lymphoplasmacytic lymphoma; immunodeficiency (2 episodes of S pneumoniae sepsis; ↓ IgG and IgA levels; ↓ antibody responses to pneumococcal vaccines) that required IVIG. (iii) Patient 3: 47-yr-old man with ACID (recurrent facial and hand swelling; ↓ C4, C1q and C1-INH levels) treated with tranexamic acid prophylaxis and icatibant or C1-INH during attacks; MGUS; mild immunodeficiency (↓ IgG and IgM levels; ↓ antibody response to pneumococcal vaccines).

  Author’s commentary: ACID patients should be monitored for lymphoproliferative disease and antibody deficiency.

- EFFECT OF MATERNAL ω3 FATTY ACID SUPPLEMENTATION ON INFANT ALLERGY (Ciaccio CE, Girdhar M. Ann Allergy Asthma Immunol 2014; 112: 191-194):

  Allergic diseases have dramatically increased (probably due to environmental and lifestyle factors; unlikely due to a genetic cause) → proposals to stop this trend: (i) ↓ allergen exposure (e.g. house dust mites); (ii) ↑ allergen exposure at early age (e.g. food); (iii) promote 1st contacts with allergens in a more ‘tolerogenic environment’ (e.g. use of probiotics, prebiotics, vit A, vit D, breastfeeding, ω3 fatty acids); (iv) restore tolerance to allergens (e.g. immunotherapy).

  ω3 polyunsaturated fatty acids (n-3 PUFAs): (i) cognitive and cardiac benefits; (ii) ↑ “antiinflammatory” gut microbiome; (iii) ↓ IgE synthesis (e.g. α-linolenic acid from green leaves).

  n-6 PUFAs: (i) found in grains (e.g. corn); (ii) convert into arachidonic acid (precursor of PGE2 and LTB4); (iii) most Americans eat 25 times more n-6 PUFAs than n-3 PUFAs (e.g. beef is no longer considered a n-3 PUFA-rich food because cows are now corn-fed rather than grass-fed).

  Supplementation with the n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during pregnancy can ↓ risk of atopic diseases, particularly food allergy and eczema.
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.

- **Important remarks:** (i) if n-3 PUFA supplementation is immunomodulatory, the required doses are likely greater than the doses studied to enhance developmental outcomes and the current commercially available doses; (ii) n-3 PUFA supplementation is likely to be cost-effective.

- **More evidence is required to:** (i) determine the appropriate dosing, timing and duration of n-3 PUFA supplementation; (ii) reveal its effect on asthma and allergic rhinitis; (iii) demonstrate if a diet high in green leafy vegetables, fish and grass-fed beef can ↓ the atopic epidemic.

- **EXERCISE-INDUCED DYSPNEA: MORE THAN VOCAL CORD DYSFUNCTION OR LARYNGOMALACIA** (Weinberger M. Ann Allergy Asthma Immunol 2014; 112: 270-271):
  - Authors discuss about the most proper way to approach the patient with exercise-induced dyspnea → differential diagnosis: exercise-induced bronchospasm, exercise-induced vocal cord dysfunction, exercise-induced laryngomalacia, cardiac disease, primary hyperventilation, restrictive physiology, lactic acidosis → monitored exercise challenge (cardiac and respiratory function, blood pH and PCO2, laryngeal motion) can help to establish the correct diagnosis.

- **Options to treat exercise-induced VCD:** speech therapy, prophylactic ipratropium.

- **Options to treat exercise-induced laryngomalacia:** speech therapy, laser laryngoplasty.

  - Antigenic hypothesis: immune-stimulating conditions (e.g. allergies) → ↑ cell proliferation and stimulation → ↑ random mutations in dividing cells → ↑ cancer risk.
  - Immune surveillance hypothesis: immune-stimulating conditions (e.g. allergies) → ↑ immune system activity and surveillance → ↓ cancer risk.

- Authors examined the association between self-reported history of allergic diseases and lung cancer occurrence using data from a case-control study → asthma, eczema and hay fever were inversely associated with lung cancer.

- **INTRAVENOUS β AGONISTS AND SEVERE PEDIATRIC ASTHMA EXACERBATION: TIME FOR A CLOSER LOOK AT TERBUTALINE?** (Kantor DB, Phipatanakul W. Ann Allergy Asthma Immunol 2014; 112: 187):
  - Acute exacerbations: (i) main cause of morbidity and mortality in patients with asthma; (ii) inhaled β2-agonists are the mainstay of emergency asthma management.
  - Intravenous β2-agonists (terbutaline): (i) can improve severe asthma exacerbations refractory to inhaled bronchodilators; (ii) early initiation may prevent progression to respiratory failure; (iii) presumed advantage: ability to access smooth muscle receptors on obstructed distal airways not accessible to aerosolized drugs; (iv) prospective trials evaluating the benefit of intravenous terbutaline in acute asthma are needed.

- **LONG-TERM FOLLOW-UP OF IgE-MEDIATED FOOD ALLERGY: DETERMINING PERSISTENCE VERSUS CLINICAL TOLERANCE** (Burks AW, Land MH. Ann Allergy Asthma Immunol 2014; 112: 200-206):
• IgE-mediated FA: (i) increasing prevalence worldwide (3-8% of the population); (ii) impact: ↓ QoL, high costs, mortality risk; (iii) >170 foods have been reported to cause allergic reactions; (iv) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soybeans, seafood; (v) diagnosis: specific IgE detection by skin prick test (SPT) or in vitro testing (sIgE, CRD), basophil activation test, oral food challenge (OFC); (vi) conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling; (vii) optimal treatment: restore tolerance by exposing patients to gradually increasing doses of allergen (immunotherapy).

Follow-up to evaluate spontaneous resolution of IgE-mediated FA: (i) follow-up should be individualized; (ii) milk, egg, soy and wheat allergy are likely to resolve → reevaluate yearly; (iii) peanut, tree nut, fish and shellfish allergy are not likely to resolve → reevaluate every 2-3 yrs; (iv) OFC: best test to evaluate the resolution or persistence of FA; (v) skin and in vitro testing can variably predict OFC results.

Factors that influence the decision to perform an OFC: (i) natural history of the FA (e.g. fish allergy is not likely to resolve while milk allergy is usually outgrown); (ii) nutritional value of the culprit food; (iii) specific culprit allergen (e.g. ovomucoid allergy is more persistent than ovalbumin allergy; casein is more stable than whey; Ara h 1, 2, 3 and 9 are heat-stable); (iv) time and severity of previous allergic reactions; (v) patient’s age, comorbidities, sociocultural factors and interest in consuming the food; (vi) results of allergy testing; (vii) capability of avoiding the culprit food; (viii) tolerance to baked food (in cases of egg or milk allergy).

Allergy testing to predict FA resolution: (i) no single test can be used alone to predict tolerance; (ii) in the initial diagnosis of FA, SPTs have low sensitivity compared with OFCs; (iii) in patients with confirmed FA, SPTs and sIgE have high sensitivity and NPV with regard to OFC outcomes; (iv) decision points of allergy testing are food-specific (e.g. a milk-specific IgE level ≤5 kUA/L predicts a 90% chance of tolerating heated milk).

LYMPHOPENIA INDUCED BY ETANERCEPT (Pepper AN, Talreja N, Cowan GM, Glaum MC, Lockey RF. Ann Allergy Asthma Immunol 2014; 112: 262-263):

• TNF-α inhibitors: (i) can induce lymphocyte apoptosis; (ii) can cause leukopenia, neutropenia, thrombocytopenia and pancytopenia; (iii) British Society for Rheumatology recommends CBC count monitoring in patients taking TNF-α inhibitors.

• Authors report the case of a 64-yr-old woman with seronegative rheumatoid arthritis and rheumatoid-associated lung disease who developed asymptomatic lymphopenia (lymphocyte count=307/µL; ↓ CD3, CD4, CD8 and CD19 cell counts; IgG=666 mg/dL; ↓ lymphocyte proliferation assays to antigens and mitogens) after 5 doses of etanercept (50 mg/wk). Lymphocyte count was normal (2,015/mL) one wk before etanercept initiation. Lymphopenia resolved 3 months after etanercept discontinuation.

RADIOCONTRAST-INDUCED IODIDE SIALADENOPATHY AND NEUTROPHILIC DERMATOSIS (Fok JS, Ramachandran T, Berce M, Smith WB. Ann Allergy Asthma Immunol 2014; 112: 262-263):

• Hypersensitivity reactions to iodinated radiocontrast medium (iRCM): (i) hypersensitivity to the iRCM carrier molecule rather than iodine itself; (ii) immediate reactions (IHRs) can be IgE-mediated or non-IgE-mediated (mechanisms: altered blood osmolarity and ion concentration, direct activation of mast cells and basophils, activation of complement system, activation of
bradykinin-induced contact system); (ii) delayed reactions (DHRs): mostly mild reactions (e.g. maculopapular exanthema, delayed urticaria), serious reactions can occur (e.g. Stevens-Johnson syndrome, Sweet syndrome [febrile neutrophilic papules, plaques and nodules]).

- **Mild IHRs**: (i) ionic iRCM: 10% of procedures; (ii) nonionic iRCM: 1% of procedures.
- **Severe IHRs**: (i) ionic iRCM: 0.2% of procedures; (ii) nonionic iRCM: 0.02% of procedures.
- **Drug challenge with iRCM**: intravenous administration at 45-min intervals using 5 cc, 15 cc, 30 cc and 50 cc (cumulative dose = 100 cc).
- **Iodine can cause**: (i) iodide mumps: acute sialadenitis, pathogenic mechanism is not fully defined (physicochemical reaction to excessive iodide ion?), renal insufficiency is a risk factor (iodine is excreted by the kidneys), likely recurrent after exposure; (ii) iododerma: rare painful neutrophilic pustular cutaneous reaction, dermal microabscesses are a cardinal feature, pathogenic mechanism: inflammatory response to high iodide concentrations?
- Authors report the case of a 78-yr-old man (medical history: hypertension, chronic renal insufficiency, diabetes mellitus, hypothyroidism, aortic aneurysm) who developed acute sialadenitis (severe pain and swelling in the submental and parotid area) and a Sweet syndrome-like eruption (multiple, painful, dark purplish nodules and blisters, fever, ↑ CRP, skin biopsy consistent with Sweet syndrome) after administration of iRCM (100 mL of Ultravist 370, containing 769 mg/mL of iopromide [370 mg/mL of iodine]).
- **Author’s commentary**: iodide mumps was likely caused by a direct reaction to iodine while Sweet-like syndrome was probably mediated by hypersensitivity to iRCM.

- **T-CELL BIOLOGY IN IMMUNOTHERAPY** (Steinke JW, Lawrence MG. Ann Allergy Asthma Immunol 2014; 112: 195-199):
  - **Allergen immunotherapy (AIT)**: only therapy that has proved to provide long-term benefit and modulation of allergic disease.
  - **Mechanisms of AIT (more established for subcutaneous IT)**: (i) ↑ specific T regulatory cells; (ii) ↑ IL-10–secreting B regulatory cells (BR1 cells [CD25\text{high}, CD71\text{high}, CD73\text{low}]); (iii) deletion, energy and suppression of effector T cells (TH2, TH1, TH17); (iv) ↑ specific IgG4 and IgA; (v) ↓ specific IgE (poor correlation with clinical improvement); (vi) very early desensitization of mast cells and basophils (within hours; mediated by upregulation of histamine 2 receptors?); (vii) ↓ migration and activation of allergy effector cells (eosinophils, basophils, mast cells).
  - **Mechanism of action of T regulatory cells**: (i) production of IL-10 and TGF-β; (ii) expression of suppressive costimulatory molecules (CTLA-4, PD-1); (iii) consumption of IL-2; (iv) production of adenosine by CD39 and CD73; (v) consumption of aminoacids.
  - **Bee venom SCIT → IL-10-producing peripheral T regulatory cells** appear quickly (within 7 days) but full tolerance may require 3-5 yrs of treatment.
  - **Frequency of Fel d 1-specific T cells in allergic patients**: 1/7,000 – 1/30,000 (similar frequencies have been found in other allergen-specific T cells).
Advances in pediatric asthma: (i) maternally microchimerism might protect against the development of asthma; (ii) different TLR signaling mechanisms might be involved in the pathogenesis of atopic and nonatopic asthma; (iii) many pregnant women incorrectly stop or reduce their asthma medications; (iv) obesity during pregnancy was associated with ↑ risk of asthma and wheezing in offspring; (v) clinical predictive scores for asthma are useful because currently no single biomarker can predict asthma development; (vi) lipid-activated nuclear receptors can control macrophage/dendritic cell function and allergy development (therapeutic target); (vii) increased airway smooth muscle at preschool age is associated with asthma at school age; (viii) IL-33 is a relatively steroid-resistant mediator that promotes airway remodeling in patients with severe therapy-resistant asthma (therapeutic target); (ix) mild early viral wheeze is associated with asthma remission while atopic multiple-trigger wheeze associates with asthma persistence; (x) FENO might be a better marker for asthma phenotypes in preschool children compared to measures of airway hyperresponsiveness and lung function; (xi) acetaminophen use may ↑ eosinophilic inflammation and asthma risk; (xii) variants at the 17q21 locus were associated with childhood asthma and specific wheezing phenotypes; (xiii) HRV infections can ↑ asthma risk and glucocorticoid resistance; (xiv) RSV bronchiolitis is a risk factor for asthma; (xv) early use of palivizumab (anti-RSV mAb) reduced wheezing days during the 1st yr of life; (xvi) long-term oral corticosteroid use is a risk factor for severe or atypical varicella virus infection (early use of VZV immune globulin or antiviral therapy after exposure is encouraged); (xvii) air pollution ↑ asthma risk (e.g. chronic diesel exhaust particle can ↑ Foxp3 methylation and ↑ risk of childhood wheezing and asthma); (xviii) bisphenol A (widely used in food container linings) can ↑ asthma risk in children; (xix) farm exposure and ‘tolerogenic microbiota’ ↓ asthma risk; (xx) mouse allergen can be a major risk factor of asthma in urban homes; (xxi) maternal smoking, stress and obesity were independently associated with childhood wheeze; (xxii) stress in later childhood may ↑ risk of adult-onset asthma; (xxiii) early introduction of wheat, rye, oats, barley, fish and egg seems to ↓ risk of asthma, allergic rhinitis and atopic sensitization; (xxiv) longer duration of exclusive breast-feeding was protective against the development of nonatopic but not atopic asthma; (xxv) weight loss and environmental control measures might ↑ asthma control; (xxvi) increased LPS-induced TNF-α production at early life was associated with childhood asthma; (xxvii) the Pediatric Asthma Control and Communication Instrument accurately measured asthma control in English- and Spanish-speaking children; (xxviii) strategies to improve asthma management: ↑ medication adherence, ↑ use of guidelines; (xxix) impulse oscillometry can detect small-airways dysfunction at an early age (important to start early therapy); (xxx) a specific bronchodilator cutoff criterion (e.g. ≥12% increase in FEV1) may not be accurate for asthma diagnosis in children; (xxxi) high-resolution CT and MRI with 3He can detect ventilatory abnormalities more accurately, especially in the peripheral airways and alveolar spaces; (xxxii) quantitative imaging of the lungs is an evolving tool to understand airway pathophysiology at early life; (xxxiii) several biomarkers hold promise for selecting and monitoring asthma therapy (e.g. FENO, serum IgE, periostin, urinary leukotrienes); (xxxiv) FENO (indicator of local inflammation) and blood eosinophilia (indicator of systemic inflammation) offered independent information in
relation to wheeze prevalence, asthma diagnosis and asthma events; (xxxv) LTD4 levels and methacholine bronchial provocation can predict response to antileukotriene therapy; (xxxvi) protectin D1 is an anti-inflammatory lipid mediator (↓ production in patients with severe asthma); (xxxvii) chitinase-like protein YKL-40 is related to asthma and airway remodeling (↑ levels in children with severe asthma); (xxxviii) variations in ERK pathway genes might influence asthma development; (xxxix) patients with mild asthma have an altered microbial composition in the respiratory tract (similar to that observed in patients with more severe asthma); (xl) microRNAs regulate key pathogenic mechanisms in allergic inflammation (e.g. activation and polarization of T cells, eosinophil development, epithelial activation); (xli) microRNAs are potential biomarkers and therapeutic targets; (xlii) oral corticosteroids do not appear useful during acute lower respiratory tract illnesses in preschool children with recurrent wheeze; (xliii) prenatal and/or early-life use of probiotics ↓ risk of atopic sensitization but might not ↓ risk of asthma/wheeze; (xliv) in a real-world study, patients (≥12 yrs of age) were more adherent to ICS + LABA than ICS + antileukotriene; (xlv) ICS + LABA therapy appears more effective than ICS + antileukotriene therapy; (xlvi) both SCIT and SLIT are beneficial for asthma patients (evidence is stronger for SCIT); (xlvii) for every 4 patients with well-controlled asthma who stop regular use of low-dose ICS, 1 will have an exacerbation in the next 6 months that is attributable to stopping ICS → step-down therapy should be done carefully (avoid step-down at the cold season); (xlviii) new drugs for asthma: AMG 853 (a potent, selective, orally bioavailable, dual antagonist of D-prostanoid and CRTH2), lebrikizumab (anti–IL-13 mAb), dupilumab (anti–IL-4Ra mAb), benralizumab (anti–IL-5R mAb), bronchial thermoplasty.

• **Futuristic approach in asthma:** use of clinical, laboratory, imaging, respiratory-function, histologic and genetic data to identify specific asthma phenotypes and endotypes → give individualized therapy (e.g. leukotriene-induced asthma → give antileukotrienes).

• **AN ALGORITHM FOR TREATING CHRONIC URTICARIA WITH OMALIZUMAB: DOSE INTERVAL SHOULD BE INDIVIDUALIZED** (Uysal P, Eller E, Mortz CG, Bindslev-Jensen C. J Allergy Clin Immunol 2014; 133: 914-915):

  - Chronic urticaria (CU): (i) definition: recurrent wheals for >6 wks (concomitant angioedema may occur); (ii) lifetime prevalence: 1-20% of the population; (iii) impact: significant morbidity, ↓ QoL (similar to angina pectoris), 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 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-refractory CU); (vii) other reported therapies: mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNFα, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A, sulfasalazine, dapsone, calcineurin inhibitors, mycophenolate, 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.

  - Omalizumab: (i) recombinant humanized anti-IgE mAb → binds to free IgE → ↓ IgE binding to its receptors, ↓ expression of IgE receptors → ↓ IgE-mediated inflammation; (ii) approved for [uncontrolled asthma + serum IgE levels between 30 and 700 IU/mL + sensitization to perennial allergens]; (iii) dose is calculated in a chart, based on body weight and pretreatment IgE levels.
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.

- Authors report an algorithm for treating antihistamine-refractory CU with omalizumab in a dose-individualized basis → (i) 27 patients (6 children and 21 adults) were included; (ii) 23 patients had spontaneous CU, 11 patients had inducible CU (e.g. delayed pressure urticaria, cold urticaria, urticaria factitia, heat contact urticaria); (ii) 15 patients achieved excellent disease control with a maintenance dose of omalizumab 150 mg every 5 to 8 wks (3 of them could stop omalizumab without any relapse); (iii) 8 patients achieved excellent disease control with a maintenance dose of omalizumab 300 mg every 4 to 8 wks; (iv) 4 patients did not respond to omalizumab 300 mg every week; (v) no serious adverse events were reported during the study.

- Author’s commentary: omalizumab (individualized regimen) can be an effective and safe therapy for patients with antihistamine-refractory CU (both spontaneous and physical).

  - Recombinase activating gene (RAG) 1 and 2: proteins that play an essential role in the generation of T- and B-cell receptors. RAG1: DNA binding and cleavage; RAG2: essential cofactor for RAG1 function.
  - RAG mutations have diverse clinical presentations: (i) T/B/NK+ severe combined immunodeficiency (SCID); (ii) Omenn syndrome; (iii) CD4+ T-cell lymphopenia; (iv) hyper-IgM syndrome; (v) immunodeficiency with γδ T-cell expansion and granulomas.
  - Authors report 2 siblings with early-onset recurrent infections (viral, bacterial) and autoimmune features (anemia, neutropenia, eczema, nephrotic syndrome) → laboratory analysis: mild lymphopenia, ↓ naive CD4+ T-cell counts, ↑ IgG/IgM autoantibodies (including anti–IFN-α) → genetic analysis: compound heterozygous RAG1 mutations (c.1420C>T [p.Arg474Cys]; c.2949delA [p.Lys983AsnfsX9]) → treatment: 10/10 HLA-matched HSCT (one children responded very well, the other had several episodes of GVHD and concern for graft failure) → family testing: healthy mother (carrier of the c.2949delA mutation) had several autoantibodies.
  - Author’s commentaries: (i) RAG1/2 mutations may result in combined immunodeficiency with autoimmune cytopenias and/or organ-specific autoimmune disease (incomplete penetrance is possible); (ii) autoantibody generation may depend on an underdeveloped thymus with ↓ AIRE expression; (iii) RAG1/2 mutations may contribute to unexplained immune dysregulation in the general population (e.g. the c.2949delA mutation in RAG1, even in heterozygous state, can result in autoantibody production); (iv) patients with moderate-to-severe infections, lymphopenia and autoimmune features should be screened for RAG1/2 mutations.

• **Phaeohyphomycosis**: group of superficial, cutaneous, subcutaneous or systemic infections caused by >100 species of dematiaceous fungi; characteristics: dematiaceous yeast-like cells, hyphae, pseudohyphae (sclerotic bodies, characteristics of chromoblastomycosis, are absent).

• **Phialophora verrucosa**: (i) may cause subcutaneous Phaeohyphomycosis (early onset, resistant to many systemic antifungals); (ii) isolated from soil, wood and rotting vegetation worldwide.

• **CARD9**: (i) adaptor protein in antifungal defense (fungal recognition by Dectin-1, Dectin-2 and Mincle on macrophages and DCs → formation of the CARD9–BCL10–MALT1 complex → NF-κB activation → production of inflammatory cytokines → TH17-cell differentiation); (ii) CARD9 deficiency → ↓ TH17-cell differentiation → chronic mucocutaneous candidiasis.

• Authors report 4 Chinese patients with phaeohyphomycosis caused by P verrucosa (persistent red plaques and nodules on the face; no history of other opportunistic infections) → histologic analysis: intense inflammatory infiltrations with dematiaceous hyphae, P verrucosa was isolated → laboratory analysis: ↓ TH17-cell counts, ↓ serum levels of TH17 cytokines (IL-17, IL-22), ↓ expression of mature CARD9 protein, ↓ production of inflammatory cytokines (IL-6, TNF-α, IL-1α, IL-23p19) from macrophages and immature DCs after stimulation with P verrucosa spores → genetic analysis: mutations in CARD9 gene (2 compound heterozygous mutations in patient 1 [c.191-192insTGCT and c.472C>T, p.L64fsX59 and p.Q158X]; 1 homozygous frameshift mutation in patients 2, 3 and 4 [c.819-820insG, p.D274fsX60]) → intriguing feature: patients did not have Candida infections.

• **CARD9 mutations** can result in TH17-cell defects and infections by opportunistic filamentous fungi such as Phialophora verrucosa.

• **CD49d-EXPRESSING NEUTROPHILS DIFFERENTIATE ATOPIC FROM NONATOPIC INDIVIDUALS** (Sigua JA, Buelow B, Cheung DS, Buell E, Hunter D, Klancnik M, Grayson MH. J Allergy Clin Immunol 2014; 133: 901-904):

  • Authors show that: (i) atopic subjects had a significantly higher frequency of CD49d-expressing neutrophils in the peripheral blood and nasal lavage compared to nonatopic controls; (ii) CD49d+ neutrophils are recruited to the nasal mucosa in response to an allergen challenge.

  • Author’s commentary: CD49d+ neutrophils may have a pathogenic role in allergic diseases.

• **IMMUNOTHERAPY: WHAT LIES BEYOND** (Casale TB, Stokes JR. J Allergy Clin Immunol 2014; 133: 612-619):

  • **Immune tolerance**: nonresponsiveness of the adaptive immune system or active Treg cell response to antigens; mechanisms: Treg generation, anergy/deletion of reactive lymphocytes.

  • **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 (e.g. exposure to aeroallergens in genetically susceptible subjects → specific TH2 responses to aeroallergens → IgE-mediated allergic respiratory diseases).

  • **Allergen immunotherapy (AIT)**: (i) only therapy that can alter the natural history of IgE-mediated allergies (sublingual IT for 4-5 yrs generated sustained benefits for 7-12 yrs); (ii) objective: restore tolerance to specific allergens; (iii) has been widely used to treat asthma, allergic rhinitis.
and venom allergy; (iv) promising therapy for atopic dermatitis and food allergy; (v) effective AIT should change a patient’s allergen-specific response from an allergic profile (TH2) to a nonallergic profile (Treg, TH1); (vi) current modalities used in clinical practice: subcutaneous IT (approved in US), sublingual IT (not approved in US) [it is unclear which modality has better outcomes]; (vii) limitations: side effects (especially with SCIT), long treatment duration (≥3 yrs); insufficient efficacy (except for venom IT [≥90% efficacy]), (viii) in patients with respiratory allergies, <5% of candidates for AIT actually receive it; (ix) it is necessary to improve AIT efficacy, convenience and safety.

- **How to ↑ efficacy and safety of AIT?** (i) adding omalizumab (anti-IgE mAb); (ii) adding adjuvants (e.g. aluminum salts to slower allergen release from injection site); (iii) using modified allergens (e.g. allergoids [altered allergens using formaldehyde or glutaraldehyde to ↓ allergenicity while preserving immunogenicity], recombinant hypoallergenic allergens, tolerogenic peptides, recombinant DNA vaccines), (iv) adding immune response modifiers (monophosphoryl lipid A [TLR4 agonist], CPG-containing DNA [TLR-9 agonist], TLR8 agonists, probiotics, bacterial lysates); (v) using other administration routes (epicutaneous, intralymphatic, intradermal, intranasal, oral); (vi) personalizing OIT schemes.

- **LOW-AFFINITY ALLERGEN-SPECIFIC IgE IN CORD BLOOD AND AFFINITY MATURATION AFTER BIRTH** (Kamemura N, Kawamoto N, Nakamura R, Teshima R, Fukao T, Kid H. J Allergy Clin Immunol 2014; 133: 904-905):

  - **IgE:** (i) important role in defense against some parasitic infections; (ii) its production is dysregulated in allergic diseases; (iii) cord blood and newborn blood often contain allergen-specific IgE (allergens cross the placenta → intrauterine allergen sensitization); (iv) high-affinity IgE is generated through sequential class switching (µ→γ→ε), in which an intermediary IgG phase is necessary for affinity maturation by somatic hypermutation; (v) low-affinity IgE is generated through direct class switching (µ→ε) and is much less mutated.

  - Authors show the presence of low-affinity ovomucoid-specific IgE in cord blood and detected affinity maturation after birth (high-affinity ovomucoid-specific IgE in peripheral blood of 6- and 14-month-old infants).

  - Further studies are required to assess: (i) the prognostic value of low-affinity IgE in cord blood; (ii) the mechanisms of affinity maturation after birth.


  - **Allergen immunotherapy (AIT):** (i) only therapy that can alter the natural history of IgE-mediated allergies; (ii) objective: restore tolerance to specific allergens.

  - **Mechanisms of AIT** (more established for subcutaneous IT): (i) ↑ specific T regulatory cells; (ii) ↑ IL-10-secreting B regulatory cells (BR1 cells [CD25high, CD71high, CD73low]); (iii) deletion, anergy and suppression of effector T cells (TH2, TH1, TH17); (iv) ↑ specific IgG4 and IgA; (v) ↓ specific IgE (poor correlation with clinical improvement); (vi) very early desensitization of mast cells and basophils (within hours; mediated by upregulation of histamine 2 receptors?); (vii) ↓ migration and activation of allergy effector cells (eosinophils, basophils, mast cells).
Mechanism of action of CD4+ Treg cells: (i) production of IL-10 and TGF-β; (ii) expression of suppressive costimulatory molecules (CTLA-4, PD-1); (iii) consumption of IL-2; (iv) production of adenosine by CD39 and CD73; (v) consumption of aminoacids.

Other cells with regulatory activity: CD8+ Treg cells, double-negative (CD4^CD8^) Treg cells, B regulatory cells, NK regulatory cells.

Dominant T-cell subsets against environmental allergens: (i) in healthy subjects → allergen-specific IL-10–secreting Treg cells; (ii) in allergic subjects → IL-4–secreting TH2 cells.

Futuristic therapy: use of readily-accessible cost-effective biomarkers (e.g. in blood, saliva, nasal secretion or skin) to define an AIT-responsive endotype of allergic diseases. Example: levels of C1q and stabilin 1 were increased in AIT-responders compared to AIT-nonresponders.

Challenges to use prophylactic AIT: (i) early-life intervention is required (safety concerns); (ii) lack of early biomarkers to predict allergy.

TGF-β signaling → induction of RUNX1 and RUNX3 → induction of the FOXP3 promoter → generation of FOXP3-expressing Treg cells.

Mutations in FOXP3 gene → immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome.

IL-10 signaling → IL-10R activation → Tyk-2 activation → activation of the phosphatase SHP-1 → dephosphorylation (within minutes) of CD28 and ICOS → inhibition of effector T cells.

IL-10 family: (i) IL-19: produced by B cells and monocytes in response to GM-CSF; promotes IL-4 and IL-13 production. (ii) IL-20: produced by keratinocytes and monocytes; involved in skin inflammation (e.g. psoriasis). (iii) IL-22: produced by activated T cells and mast cells; induce acute-phase reactants by hepatocytes. (iv) IL-24: produced by monocytes, macrophages and TH2 cells; controls cell survival and proliferation; important role in wound healing, psoriasis and cancer. (v) IL-26: expressed in certain herpesvirus-transformed T cells.

**PENICILLIN ALLERGY AS A PUBLIC HEALTH MEASURE** (Solensky R. J Allergy Clin Immunol 2014; 133: 797-798):

- False-negative diagnosis of drug allergy can lead to severe reactions after exposure.
- False-positive diagnosis of drug allergy can lead to unnecessary avoidance and use of alternative drugs.
- Penicillin (PNC) allergy: (i) self-reported in ~10% of the population; (ii) confirmed in ~1% of the population; (iii) false-positive diagnosis of PNC allergy → unnecessary use of alternative antibiotics (e.g. quinolones, vancomycin, clindamycin, cephalosporins) that ↑ cost, bacterial resistance (e.g. methicillin-resistant S aureus, vancomycin-resistant enterococcus) and C infection; (iv) reasons for false-positive diagnosis of PNC allergy: assumption that every rash during PNC therapy is caused by PNC allergy, wrong interpretation of skin or in vitro allergy tests; (v) appropriate PNC skin testing can ↓ the rate of false-positive diagnosis of PNC allergy.

**PENICILLIUM MARNEFFEI INFECTION AND IMPAIRED IFN-γ IMMUNITY IN HUMANS WITH AUTOSOMAL-DOMINANT GAIN-OF-PHOSPHORYLATION STAT1 MUTATIONS** (Lee PPW, Mao
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.


- **STAT1**: important molecule for interferon’s signalling. (i) Complete AR STAT1 deficiency → severe impairment of IFN-γ-mediated and IFN-α/β-mediated immunity → life-threatening intracellular bacterial and viral diseases. (ii) Partial AR STAT1 deficiency → mild impairment of IFN-γ-mediated and IFN-α/β-mediated immunity → milder intracellular bacterial and viral diseases; (iii) Dominant negative STAT1 mutations → impairment of IFN-γ-mediated immunity → susceptibility to mycobacterial diseases; (iv) AD gain-of-function (GOF) STAT1 mutations → ↓ production of TH17 cells → fungal infections, autoimmunity, esophageal carcinoma.

- **GOF STAT1 mutations** → ↑ response to interferons and IL-27 → impaired function of STAT3 → TH17-cell deficiency → susceptibility to certain fungal (e.g. CMC) and bacterial infections, autoimmunity (e.g. hypothyroidism, autoimmune hepatitis, SLE, type I diabetes mellitus), malignancy (e.g. esophageal carcinoma). New reported phenotypes: IPEX-like syndrome; disseminated coccidioidomycosis, histoplasmosis and fusariosis; ↓ B-cell function.

- **Penicillium marneffei**: (i) pathogenic fungus endemic in Southeast Asia; (ii) cause opportunistic infections in AIDS patients (AIDS-defining illness) and other immunodeficiencies (e.g. SCID, CVID, hyper-IgM syndrome, hyper-IgE syndrome, anti-IFN-γ autoantibodies, diabetes mellitus, immunosuppressive therapy); (iii) affected individuals often have disseminated disease with rapid progression to multiorgan failure and death; (iv) pathogenicity: inhalation of conidia → lung disease → dissemination as intracellular yeast via the reticuloendothelial system.

- Authors report 3 Chinese patients with CMC and disseminated infection by Penicillium marneffei → laboratory analysis: excessive phosphorylation of STAT1 after stimulation with IFN-α or IFN-γ, ↓ CD3+/IFN-γ+ T cells, ↓ CD3+/IL-17A+ T cells, ↓ IFN-γ production after stimulation with C albicans or P marneffei → genetic analysis: AD GOF mutations in the DNA binding or coiled-coil domain of STAT1 gene.

- **GOF STAT1 mutations** can result in disseminated infections by Penicillium marneffei.

- **TH17 DIFFERENTIATION CAPACITY DEVELOPS WITHIN THE FIRST 3 MONTHS OF LIFE** (Dijkstra KK, Hoeks SBEA, Prakken BJ, de Roock S. J Allergy Clin Immunol 2014; 133: 891-894):

  - **TH17 cells**: (i) important for defense against extracellular bacteria and fungi; (ii) frequent pathogenic role in autoimmunity.

  - The neonatal immune system responds differently to the adult system (e.g. cytokine production, receptor expression, cell differentiation capacity).

  - Authors show that neonatal T cells: (i) develop the capacity to differentiate into TH17 cells before the age of 3 months; (ii) tend to become Treg cells during at least the 1st yr of life → after birth, immunity against pathogens rises while the immune system remains to have a regulatory profile (to tolerate allergens and food antigens).

- **THE EDITORS’ CHOICE** (Leung DYM, Szeffler SJ. J Allergy Clin Immunol 2014; 133: 662-663):

  - **Nasal transcriptomics** can identify childhood asthma phenotypes (TH2-high → higher risk for atopy, asthma and rhinitis).
• 90% of the bronchial airway transcriptome is expressed in the nasal airway (highly correlation between both airway sites).

• ↑ levels of nasal IL-13 are associated with asthma exacerbations.

• Tiotropium: (i) improves symptoms and lung function in patients with uncontrolled asthma; (ii) reduces cough (mechanism: inhibition of TRPV1 [transient receptor potential V1] effect in sensory nerves).

• RAG1 mutations can result in late-onset combined immunodeficiency with autoimmunity.

• 1 in 5746 subjects of European descent might be homozygous or compound heterozygous for pathogenic RAG1/2 mutations (most of them not presenting with SCID or Omenn syndrome).

• RAG1 mutation carriers can be predisposed to autoimmunity (the contribution of RAG1/2 mutations to autoimmune diseases might be much higher than previously estimated).

• NK cells can play a role in the promotion of respiratory allergies (potential therapeutic target).

• Genetics can influence the response to inhaled corticosteroids.

• Mutations in adenosine deaminase (ADA) gene → severe combined immunodeficiency (SCID); autoimmunity can occur (defective B-cell tolerance plays a pathogenic role). Therapeutic options: bone marrow transplantation, gene therapy, enzyme replacement therapy.

• Gene therapy in patients with ADA-SCID restored B-cell proliferation and antibody secretion → ↓ risk of autoimmunity.
PEDIATRIC ALLERGY AND IMMUNOLOGY:


  • Author’s report the case of a 4-yr-old girl with acute laryngotracheal bronchitis who developed hemolysis (fever, weakness, abdominal discomfort, hypotension, anemia [Hb=4.8 g/dL], ↑ indirect bilirubin, hemoglobinuria, ruptured erythrocytes in the blood smear, positive direct antiglobulin test [DAT], splenomegaly) after receiving intravenous ceftriaxone. → diagnosis: drug-induced immune hemolytic anemia (DIIHA) → successful treatment: ceftriaxone cessation, oxygen, intravenous fluids, systemic corticosteroids (authors declare that they made a mistake using steroids in this case), sodium bicarbonate.

  • DIIHA: (i) rare condition; (ii) can be life-threatening; (iii) pathogenic mechanisms are controversial; (iv) hemolysis usually appears within 2 wks after drug initiation.

  • Proposed mechanisms of DIIHA: (i) binding of drug-induced antibodies to proteins (or drug-protein complexes) on the membrane of red blood cells (RBCs) → elimination of RBCs by macrophages and/or the complement system; (ii) drug-induced protein adsorption (IgG, complement) on the membrane of RBCs.

  • Drug-dependent antibodies (DDABs): (i) detected in vitro only in the presence of drug; (ii) DDABs typically show a positive DAT and negative elution; (iii) cefotetan, ceftriaxone and piperacillin are frequent causes of DDAB production; (iv) treatment: drug cessation, corticosteroids should not be used.

  • Drug-independent antibodies (DIABs): (i) can be detected in vitro in the absence of drug; (ii) mechanism: drug causes production of RBC autoantibodies (identical effect to warm autoimmune hemolytic anemia); (iii) DIABs show a positive DAT and positive elution (detection of specific autoantibodies); (iv) fludarabine, methyldopa and β-lactamase inhibitors are frequent causes of DIAB production; (v) treatment: drug cessation, systemic corticosteroids.


  • Allergic rhinitis (AR): (i) definition: IgE-mediated inflammation of the nasal mucosa; (ii) prevalence: up to 40% of the population; (iii) impact: ↓ physical, mental and psychological well-being; ↓ QoL; high costs; ↑ risk of asthma and other comorbidities/complications; (iv) 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; (v) 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 and ↓ concentration, fatigue, stress, ↓ school/work performance, systemic inflammation; (vi) diagnosis: clinical history, anterior rhinoscopy, allergy testing (25% of AR cases are ‘local’ [entopy], which means that specific IgE is not detected by skin or serum tests); (vii) differential diagnosis (may coexist with AR): 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, leakage of CSF, malignancy, GERD, foreign body; (viii) 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); (ix) strategy to prevent AR: promote early tolerance to respiratory allergens.

- **Immune tolerance:** (i) definition: nonresponsiveness of the adaptive immune system or active Treg response to antigens; (ii) mechanisms: anergy/deletion of effector lymphocytes, generation of Treg cells; (iii) importance: to prevent self-destruction and inflammatory responses to beneficial or harmless exogenous molecules (e.g. food, commensal bacteria, allergens).

- Loss of immune tolerance → allergic or autoimmune disorders (e.g. exposure to aeroallergens in genetically susceptible subjects → specific TH2 responses to allergens → allergic rhinitis).

- **Early interventions** to induce immunologic tolerance → ↓ TH2 immune responses, induction of allergen-specific Treg cells → ↓ IgE-mediated allergies.

- **Factors that promote immune tolerance:** (i) ↑ tolerogenic gut microbiota (Lactobacillus sp, Bifidobacterium sp); (ii) ↑ tolerogenic dendritic cells; (iii) ↑ tolerogenic molecules (retinoic acid, TGF-β, TSLP [in the gut environment], indoleamine-2,3-dioxygenase, IL-10, IL-35, IgG4, IgA, adenosine); (iv) ↑ regulatory cell responses (CD4+CD25+ Tregs, Th3 cells, Tr1 cells, CD8+ Tregs, regulatory B cells); (v) balanced TH1 responses.

- **Ideas to induce early tolerance to respiratory allergens:** (i) improve skin barrier; (ii) adequate breastfeeding, (iii) early exposure to allergens, (iv) avoid active and passive tobacco smoke; (v) use of probiotics and prebiotics during pregnancy and infancy, (vi) use of cow’s milk hydrolysates when indicated, (vii) use of bacterial lysates, (viii) vit D supplementation, (ix) supplementation with n-3 long chain polyunsaturated fatty acids from fatty fish and fish oil; (x) primary allergen-specific immunoprophylaxis (before IgE sensitization occurs); (xi) secondary allergen-specific immunoprophylaxis (after IgE sensitization occurs).

- **Early specific immunotherapy:** “SIT started within 12 months after onset of allergic symptoms”.

- **Secondary, allergen-specific immunoprophylaxis:** “administration of an allergen extract to prevent onset of allergic symptoms in healthy but already IgE-sensitized children”; objectives: restore tolerance before symptoms develop, prevent “molecular spreading”.

- **Component-resolved prophylaxis:** “the administration of allergenic molecules (component-resolved) to prevent onset of allergic symptoms in healthy but already IgE-sensitized children”.

- **Molecular spreading:** “the sequential development of antibody (IgE) responses to distinct non-cross-reacting molecules from the same antigenic (allergenic) source, starting with an ‘initiator’ molecule”.

- **Initiator molecule:** “the allergenic molecule, within an allergenic source, responsible for the induction of the 1st IgE antibody response to that allergenic source”.

- **‘Epitope spreading’:** “the evolution of T-cell responses during an autoimmune reaction and spreading from one single T-cell epitope to many T-cell epitopes within an individual molecule”.

  - Immediate drug hypersensitivity reactions: (i) usually occur within 1 hr of drug intake; (ii) usually IgE-mediated; (iii) urticaria and anaphylaxis are the most reported entities.
  - Non-immediate drug hypersensitivity reactions: (i) usually occur 24–48 hrs after drug intake (interval can be as short as 1 hr); (ii) usually T-cell mediated; (iii) most frequent reactions: maculopapular exanthema, non-immediate urticaria.
  - Hypersensitivity reactions to beta-lactams (BLs): (i) frequently reported in children; (ii) amoxicillin and cephalosporins are the most frequent culprits.
  - False-negative diagnosis of BL allergy can lead to severe reactions after exposure.
  - False-positive diagnosis of BL allergy can lead to the unnecessary use of alternative antibiotics that ↑ cost and bacterial resistance.

  Authors studied 783 children (1–14 yrs old) with suspected hypersensitivity to BLs → (i) only 62 patients (7.92%) were confirmed as being allergic; (ii) 9 patients had immediate reactions: 2 diagnosed by in vitro testing, 2 by skin testing and 5 by drug provocation test (DPT); (iii) 53 patients had non-immediate reactions: 2 diagnosed by skin testing, 51 by DPT; (iv) most frequent culprit drugs: amoxicillin-clavulanate, amoxicillin; (v) most frequent reactions: maculopapular exanthema (usually confused with viral infections), urticaria, angioedema.


  - Secretory IgA: (i) essential role in mucosal immunity; (ii) main function: immune exclusion (aggregating, immobilizing and neutralizing pathogenic microbes and harmful molecules in mucosal surfaces); (iii) IgA production has been associated with oral tolerance; (iv) a defective IgA response can be a risk factor for allergy development (e.g. patients with selective, partial or transient IgA deficiency have ↑ prevalence of allergies, including food allergy).

  Authors compared egg-white-(EW)-specific IgA and IgA2 levels between EW-allergic and EW-tolerating children → conclusions: (i) IgA2 antibodies may have a role in the induction of food tolerance; (ii) ↓ allergen-specific IgA2 levels may be associated with food allergy development.


  - The ontogeny of allergic disease in humans is not well characterized.
  - Prevalence of allergic diseases has globally increased over the last 30–40 yrs (not explainable by genetic factors alone; environmental and epigenetic factors seem very important).

  Pregnancy → TH2 and Treg environment (IL-4, IL-10, IL-13, TGF-β) → downregulation of the maternal TH1 response against fetopaternal antigens → ↑ pregnancy success.
• Environmental exposures during pregnancy (e.g. diet, allergens, pollutants, microbiome) and birth (e.g. mode of delivery, early use of antibiotics) may influence gene expression (epigenetics) and allergy development.

• Currently there is no way to fully prevent allergy development.


• Food allergy (FA) affects up to 4–5% of children in some countries.

• Delayed introduction of foods to high-risk infants can increase the likelihood of FA.

• The mean wheal diameter in SPT and food-specific IgE levels directly correlate with the likelihood of clinical reactivity to foods.

• Component-resolved diagnosis (e.g. measurement of Ara h 2 from peanut) can help to predict clinically relevant FA.

• 80% of young children with milk and egg allergy can tolerate these foods in baked forms (extensively heated proteins); in these patients, ingestion of baked products can accelerate the development of tolerance to all forms of milk and egg.

• Management of FA is changing toward active induction of tolerance (immunotherapy).

• Much remains to be discovered about the optimal way to prevent, diagnose and manage FA.


• Effector-memory CD4+ T cells (TEM cells): subset of T cells with immediate effector function that can rapidly produce inflammatory mediators (TEM-TH2 cells play a key role in food allergy).

• T regulatory cells: subset of T cells that play a key role in food tolerance.

• Authors treated 18 hen’s egg-allergic children (4–14 yrs old) with egg oral immunotherapy (OIT) → (i) Treg cell numbers increased after desensitization achievement; (ii) the Treg/TEM ratio increased 2.3 times after OIT (similar to the ratio observed in healthy controls); (iii) OIT did not modify the numbers of monocytes, basophils, neutrophils or eosinophils.


• Primary eosinophilic gastrointestinal disorders (EGID): eosinophilic esophagitis (EoE), eosinophilic gastroenteritis, eosinophilic colitis, eosinophilic proctitis.

• Other diseases that can cause mucosal eosinophilia: inflammatory bowel disease, irritable bowel syndrome, celiac disease.

• Mast cell–eosinophil interaction: (i) mast cell-derived IL-13 can recruit eosinophils; (ii) mucosal mast cells can be increased in adults and children with EoE.
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.

- Authors studied biopsies from 12 children with EGID (excluding EoE; average age=10.4 yrs) and 14 healthy controls (average age=12.3 yrs) → (i) there was a significant positive correlation between eosinophil and mast cell counts in control samples; (ii) there was no correlation between eosinophil and mast cell counts in EGID patients (disrupted mast cell–eosinophil interaction?); (iii) study limitation: the utilized staining only detects granulated mast cells (increased degranulated mast cells in EGID patients might have not been detected).


- Allergic diseases affect ~30% of the population under 30 yrs of age.

- Modern lifestyle is associated with increased allergy prevalence. Features of modern lifestyle: ↓ breastfeeding; ↓ exercise; ↑ exposure to pollutants and cigarette smoke; diet rich in salt, sugar and high-saturated fats.

- Prevention of IgE-mediated allergies: (i) primary → to prevent IgE-sensitization against defined allergens; (ii) secondary → to prevent clinical symptoms in an already IgE-sensitized patient; (iii) tertiary → to prevent sequelae and complications of established allergic diseases (e.g. remodeling); (iv) preventive measures should be safe, effective, convenient and fair.

- Ideas to prevent allergy development: (i) improve skin barrier; (ii) adequate breastfeeding, (iii) early vs late exposure to allergens, (iv) avoid active and passive tobacco smoke; (v) avoid exposure to pollutants (e.g. traffic, indoor painting); (vi) use of probiotics and prebiotics during pregnancy and infancy, (vii) use of cow’s milk hydrolysates when indicated, (viii) use of bacterial lysates, (ix) vit D supplementation, (x) supplementation with n-3 long chain polyunsaturated fatty acids; (xi) primary allergen-specific immunoprophylaxis (before IgE sensitization occurs); (xii) secondary allergen-specific immunoprophylaxis (after IgE sensitization occurs).

- Despite advances in medicine, currently there is no way to fully prevent allergy development.


- Asthma: (i) complex syndrome with multiple endotypes/phenotypes; (ii) several pathogenic aspects are poorly understood; (iii) ‘omics’ analysis (genomics, transcriptomics, proteomics, lipidomics, metabolomics) in body samples (sputum, blood, urine, etc) can help to identify disease biomarkers; (iv) current pharmacologic therapy is not disease modifying; (v) 4–5% of asthmatic children have therapy-resistant asthma (significant costs, morbidity and mortality).

- Potential interventions for pediatric asthma: anti-IgE mAb (omalizumab), anti-IL-5 mAb (mepolizumab, reslizumab), anti-IL-5R mAb (benralizumab), anti-IL-4Rα mAb (dupilumab), IL-4Rα antagonist (pitirakinra), anti-IL-13 mAb (lebrikizumab, tralokinumab), anti-TNF-α mAb (golimumab), anti-mRNA therapy (e.g. targeting the mRNA of CCR3), immunomodulatory compounds (macrolides, cyclosporine, methotrexate, TLR agonists), allergen-specific immunotherapy (after symptoms start), allergen-specific immunoprophylaxis (before symptoms start), bacterial lysates (e.g. OM-85), probiotics, prebiotics, vitamin D, vaccines (to prevent respiratory viral infections), web-based telemanagement.

• Early life → immature TH1 responses → ↑ risk of tolerance failure and allergy development.

• Microbial signals from certain environmental pathogens and ‘tolerogenic’ gut microbiota → normal post-natal maturation of immune functions → protection against allergic sensitization.

• T regulatory responses in the airway mucosa → immune tolerance → ↓ respiratory allergies.

• Early viral respiratory infections (HRV, RSV) + allergen sensitization → synergism to promote asthma development.

• Severe viral infection → ↑ secretion of type 1 interferons, which diffuse locally and systemically → ↑ FcεR1 expression on airway mucosal DCs, DC precursors and monocyte precursors → ↑ IgE-facilitated allergen presentation to Th2 memory cells → ↑ Th2 inflammation at the infection site and at distant tissues (spread of atopic inflammation).

• Strategies to prevent asthma development: (i) ↓ primary IgE-sensitization to aeroallergens (e.g. early allergen exposure via the oral mucosa); (ii) ↓ consolidation of allergen-specific Th2 immunity (e.g. early allergen IT); (iii) ↓ respiratory viral infections (e.g. use of viral-specific vaccines or bacterial-derived immunostimulants); (iv) ↓ interactions between atopic and antiviral pathways in children with intermittent wheeze (e.g. use of omalizumab in atopic wheezers prior to asthma diagnosis); (v) ↓ progression from intermittent to persistent/chronic atopic asthma.


• 1922 → Schultz et al. reported a case of ‘Agranulocytic angina’ (1st case of severe neutropenia, which might be the 1st recognized PID).

• 1950 → Glanzmann et al. reported 2 infants with fatal candidiasis and lymphopenia; lack of immunoglobulins was detected 8 yrs later (1958) → severe combined immunodeficiency.

• 1954 → Bruton reported an 8-yr-old boy with recurrent pneumococcal infections and no detectable gamma-globulin → agammaglobulinemia?

• 1957 → Good et al. reported 4 boys with abscesses and lymphadenitis due to staphylococci or Gram-negative bacteria (‘Fatal granulomatous’ syndrome → chronic granulomatous disease).

• Primary immunodeficiencies (PIDs): (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 to 1:100,000 subjects; (iii) impact: severe complications (infections, autoimmunity, neoplasms), ↓ QoL, high costs; (iv) early diagnosis and treatment can be lifesaving; (v) genetic diagnosis is usually important for therapy, prognosis and genetic counseling; (vi) when indicated, definite therapy of severe PIDs (e.g. HCT) should not be delayed while waiting for genetic diagnosis.

• Diagnosis of PIDs can be difficult because: (i) >200 different PID-causing genes have been described; (ii) clinical and laboratory presentation of PIDs can be very variable (e.g. RAG mutations can present with SCID, Omenn syndrome or hyper-IgM syndrome; WASP mutations can present with Wiskott-Aldrich syndrome, X-linked thrombocytopenia or X-linked neutropenia); (iii) current PID diagnostic approach is often dominated by phenotypic and functional characterization (time-consuming); (iv) genetic diagnosis is classically performed since 1977 by Sanger sequencing (laborious, time-consuming, not available for several genes).
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.

- **Next-generation sequencing (NGS):** (i) rapid, accurate, low-cost, high-throughput DNA sequencing technology that has identified mutations in novel PID-causing genes (e.g. STAT1 mutations in patients with chronic mucocutaneous candidiasis; PLDN mutations in Hermansky–Pudlak syndrome type 9); (ii) simultaneously amplify and sequence millions of DNA fragments within few days; (iii) can be used to sequence the whole-genome or the whole-exome (sum of all exons and their adjacent nucleotides; approximately 85% of PID-causing deleterious mutations occur in these regions); (iv) useful diagnostic tool for complex PIDs, particularly for patients with atypical disease presentation; (v) differentiation between pathogenic mutations and irrelevant genetic variations can be very challenging; (vi) promising tool for early diagnosis and treatment of PID in patients presenting with a 1st episode of severe infection (PID screening).

  - Atopic dermatitis (AD): (i) common chronic skin disease (2-10% of adults, 15-30% of children); (ii) prevalence has ↑ globally; (iii) proposed risk factors: genetic susceptibility (e.g. skin barrier defects), Cesarean delivery, ↓ breastfeeding, “Western” diet, early use of broad-spectrum antibiotics, ↓ farm exposure, ↓ helminth infections, ↓ tolerogenic gut microbiota, ↑ exposure to pollutants, irritants and allergens, ↓ exposure to UV light, obesity, ↓ exercise, vit D deficiency; (iv) impact: ↓ QoL, high costs, ↑ predisposition to skin infections and other allergies.
  - Vit D: (i) important nutrient in bone health; (ii) involved in obesity, cancer, cardiovascular diseases, immune function and maternal/fetal health.
  - Effects of vit D on immune system: (i) ↑ skin barrier function; (ii) ↑ production of antimicrobial peptides (β-defensins, cathelicidin); (iii) ↑ phagocytic activity of macrophages; (iv) ↓ maturation of dendritic cells; (v) ↓ TH1, TH17 and TH9 responses; (vi) ↑ differentiation of Treg cells; (vii) ↓ function of B-lymphocytes; (viii) ↓ production of IgE; (ix) ↑ IL-10 production by mast cells.
  - Hypovitaminosis D has been associated (frequently but not uniformly) with ↑ occurrence or severity of allergy (allergic sensitization, wheezing, asthma, allergic rhinitis, food allergy, AD).
  - Authors performed a case–control study to investigate the relationship between vit D deficiency and AD in Hong Kong Chinese children → (i) vit D deficiency and insufficiency was prevalent in the studied population, (ii) vit D deficiency was associated with AD and high total IgE; (iii) serum vit D levels correlated inversely with both long- and short-term AD severity; (iv) prospective trials are necessary to address the benefits of vit D supplementation on AD outcomes.

  - Biodiversity: variability among living organisms, including diversity within species, between species and of ecosystems; it concerns both environmental and commensal microbiota.
  - The human body carries an ecosystem of microbes weighing around 1.5 kg (the microbiome).
  - Microbial signals from certain environmental pathogens and ‘tolerogenic’ microbiota (skin, gut, airways) → induction and maintenance of tolerance → protection against allergies.
Modern urban life $\rightarrow$ ↓ diversity and abnormal composition of environmental microorganisms (macrobiome) $\rightarrow$ dysbiosis (↓ biodiversity and altered composition of the human microbiota) $\rightarrow$ immune dysregulation $\rightarrow$ ↑ inflammatory diseases (allergies, autoimmune diseases, obesity, depression, autism, Alzheimer disease, many forms of cancer).

Risk factors for immune dysregulation: (i) genetic susceptibility; (ii) ↓ microbiota diversity; (iii) ↓ ‘tolerogenic’ microbiota (e.g. Lactobacillus, Bifidobacterium), (iv) ↓ exposure to maternal ‘tolerogenic’ microbiota (e.g. gammaproteobacteria living on the skin, the axilla and the vagina); (v) cesarean delivery; (vi) ↓ breastfeeding; (vii) “Western” diet; (viii) early use of broad-spectrum antibiotics; (ix) ↓ farm exposure; (x) ↓ certain helminth infections; (xi) ↑ exposure to pollutants, irritants and allergens; (xii) ↓ exercise; (xiii) vit D deficiency.

Tolerance is an active process influenced by the environment (e.g. babies put everything in their mouth).

Everything a child eats, drinks, touches or breaths modulates the microbiome $\rightarrow$ every child should have: (i) a balanced diet, (ii) frequent physical activity, (iii) a ‘healthy’ environment.

Fecal microbiota transplant has been successfully used to restore the microbiota balance in severe therapy-resistant Clostridium difficile infections.

56,000 species of animals and plants are currently classified as threatened due to human activity, which accelerates the natural rate of species extinction by 100–1000 times.