April 2014

General considerations:

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- 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.

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PEARLS IN ALLERGY AND IMMUNOLOGY April 2014

April 2014 – content:


• SKIN PRICK TEST AND BASOPHIL REACTIVITY TO CETUXIMAB IN PATIENTS WITH IgE TO ALPHA-GAL AND ALLERGY TO RED MEAT (Michel S, Scherer K, Heijnen IAFM, Bircher AJ. Allergy 2014; 69: 403–405).

• A 37-YEAR-OLD MAN REFERRED FOR ASSISTANCE WITH PERSISTENT ASTHMA, ATOPIC DERMATITIS, AND CHRONIC CONJUNCTIVITIS (Bielory L. Ann Allergy Asthma Immunol 2014; 112: 290-295).

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• BENEFICIAL ROLE FOR SUPPLEMENTAL VITAMIN D3 TREATMENT IN CHRONIC URTICARIA: A RANDOMIZED STUDY (Rorie A, Goldner WS, Lyden E, Poole JA. Ann Allergy Asthma Immunol 2014; 112: 376-382).

• DETECTION OF IgE BINDING COMPONENT TO INFlixIMAB IN A PATIENT WITH INFlixIMAB-INDUCED ANAPHYLAXIS (Hwang SH, Yoo H-S, Yoon MK, Park H-S. Ann Allergy Asthma Immunol 2014; 112: 393-394).

• INTEGRATIVE APPROACH TO ALLERGY AND ASTHMA USING COMPLEMENTARY AND ALTERNATIVE MEDICINE (Silvers WS, Bailey HK. Ann Allergy Asthma Immunol 2014; 112: 280-285).


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- **VALIDATION OF CONTROL OF ALLERGIC RHINITIS AND ASTHMA TEST FOR CHILDREN (CARATKIDS) – A PROSPECTIVE MULTICENTER STUDY** (Linhares DVBR, da Fonseca JAL, Borrego LM, Matos A, Pereira AM, Sá-Sousa A, Gaspar A, Mendes C, Moreira C, Gomes E, Rebelo FF, Cidrais Rodrigues JC, Onofre JM,
ALLERGY:

  - **Cough**: (i) clinical definition: ‘forced expulsive manoeuvre, usually against a closed glottis, with a typical sound’; (ii) essential protective reflex for airways; (iii) warning sign of disease (airways, heart, upper GI tract); (iv) classification: acute (<3 wks), subacute (3-8 wks), chronic (>8 wks).
  - **Work-related chronic cough (WRCC)**: (i) CC occurring in a particular work environment; (ii) frequent occupational symptom (up to 18% of the population); (iii) impact: physical, mental, social and financial burden to the worker; (iv) risk factors: long-time work, male gender, high exposure to respiratory irritants and sensitizers; (v) management depends on the etiology, and includes allergen/irritant avoidance, antiinflammatory drugs and immunotherapy.
  - **Classification of WRCC**: (i) occupational CC (OCC): CC directly caused by agents in the work environment (sensitizers [allergic OCC], irritants [irritant-induced OCC] or microorganisms [hypersensitivity pneumonitis]); (ii) work-exacerbated CC (WECC): CC worsened at work, but resulting from a condition unrelated to the work environment.
  - **Causes of WRCC** (i, ii and v are the most common): (i) work-related asthma (WRA), which includes occupational asthma (sensitizing- or irritant-induced) and work-exacerbated asthma; (ii) work-related rhinosinusitis; (iii) work-related laryngeal syndromes (irritable larynx syndrome, vocal cord dysfunction); (iv) nonasthmatic eosinophilic bronchitis; (v) COPD; (vi) hypersensitivity pneumonitis; (vii) GERD; (viii) laryngopharyngeal reflux; (ix) the ‘World Trade Center Cough Syndrome’; (x) the ‘cough and airways irritancy syndrome’; (xi) chronic obstructive pulmonary disease (COPD); (xii) other connective tissue diseases; (xiii) interstitial lung diseases; (xiv) lung cancer.
  - **Diagnosis of WRCC**: (i) a multidisciplinary approach (allergist, pneumologist, ENT specialist) is often necessary to find the cause; (ii) procedures to find the cause: clinical history, laboratory analysis (CBC, sputum eosinophils, total IgE, specific IgE, specific IgG, BAL analysis, FENO), imaging studies (X-rays, CT scans, rhinolaryngoscopy, endoscopy), lung function tests (spirometry, DLCO, nonspecific and specific bronchial challenges), nasal provocation tests, cough provocation tests, lung biopsy, esophageal pH monitoring; (iii) diagnostic approach should first consider the commonest diseases (WRA, work-related rhinosinusitis, COPD).

  - **Histamine**: (i) biogenic amine with effects on many cell types through 4 receptors (H1R–H4R); (ii) roles: inflammation, immunity, wound healing, organ function (digestive, nervous and circulatory systems); (iii) is present at significant concentrations in the GI tract, mainly during inflammatory processes (protective vs pathogenic effects are poorly defined); (iv) can have both pro-inflammatory and anti-inflammatory effects, depending on which histamine receptor is activated; (v) may negatively or positively influence parasitic and bacterial infections; (vi) can be metabolized by oxidative deamination (diamine oxidase, DAO) or by ring methylation (histamine-N-methyltransferase, HNMT); (vii) cells that can store histamine: mast cells, basophils; (viii) cells that can synthesize histamine: mast cells, basophils, gastric enterochromaffin-like cells, histaminergic neurons, platelets, DCs, T cells; (ix) some bacterial...
species in the microbiota can secrete histamine; (x) histamine-rich food: alcohol, aged cheese, cured meat, spinach, tomatoes, yeast products; (xi) histamine liberators: citrus fruit.

- **Histamine actions:** (i) through H1R: ↑ vascular permeability, ↑ mucus secretion, itching, bronchoconstriction, activation of nociceptive nerves, ↑ attention, regulation of food/water intake and sleep, ↑ IL-12 secretion, ↑ TH1 responses; (ii) through H2R: ↑ secretion of gastric acid, ↓ proinflammatory cytokines (IL-12, IL-23, TNF-α), ↓ TH1 and TH2 responses, ↑ IL-10 production, ↑ Treg polarization; (iii) through H3R: activates enteric neurons, regulates sleep–wake cycle, cognition, energy levels and inflammation; (iv) through H4R: ↑ pruritus, ↑ cytokine secretion by iNKT cells, ↑ TH2 polarization.

- **Gut diseases where histamine plays a role:** (i) food allergy; (ii) scombroidosis (antihistamines are beneficial; corticosteroids do not help; cooking contaminated fish is useless because toxins are heat-resistant; histamine-producing bacteria in fish: Morganella morganii, Enterobacter aerogenes, Raoultella planticola, Raoultella ornithinolytica, Photobacterium damselae); (iii) histamine intolerance (impaired histamine degradation by DAO or HNMT; histamine-rich food and histamine liberators should be avoided); (iv) irritable bowel syndrome (ketotifen [mast cell stabilizer, H1R antagonist] may be beneficial); (v) intestinal bowel disease (IBD).

- **Histamine and its receptors in allergies:** (i) anti-H1R are used to treat allergies; (ii) combined H1R and H4R antagonists may improve allergy treatment; (iii) H2R antagonists may ↑ risk of IgE-mediated food allergies; (iv) H2R agonists may improve treatment of allergy and inflammatory disorders, including IBD and IBS; (iv) oral DAO or compounds that ↑ DAO activity (e.g. vit C, vit B-6) can relieve histamine-mediated diseases.


  - **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 allergens in genetically susceptible subjects → specific TH2 responses → IgE-mediated allergies).

  - ~30% of the population in industrialized countries suffers from IgE-mediated allergies.

  - **Allergen immunotherapy (AIT):** (i) only therapy that has proved to provide long-term benefit and modulation of allergic disease; (ii) has been widely used to treat asthma, allergic rhinitis and venom allergy; (iii) promising therapy for atopic dermatitis and food allergy; (iv) it is necessary to improve AIT efficacy, safety and convenience.

  - **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 the 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, allergens on virus-like particles), (iv) adding immune response modifiers (monophosphoryl lipid A [TLR-4 agonist], CpG-containing DNA [TLR-9 agonist], TLR8
agonists, probiotics, bacterial lysates, virus-like particles); (v) using other administration routes (epicutaneous, intralymphatic, intradermal, intranasal, oral); (vi) personalizing AIT schemes; (vii) inhibiting IgE-mediated cell activation by engaging the inhibitory receptor FcγRIIB (Fcγ-Fcε fusion molecules; allergen-Fcγ fusion molecules).

- **Allergen-specific IgG can inhibit IgE-mediated mast cell degranulation** by 3 mechanisms: (i) allergen-neutralization (blocking antibodies); (ii) engagement of the inhibitory FcγRIIB → coaggregation of FcγRIIB and FcεRI by IgG and IgE antibodies simultaneously bound to allergen → recruitment of phosphatase SHIP1 → inhibition of FcεRI-mediated signaling; (iii) engagement of the inhibitory FcγRIIB → ↑ internalization of specific IgE/FcεRI → down-regulation of FcεRI-bound IgE (novel mechanism in mice, reported in the current article).

- **Author’s commentary:** IgE replacement on mast cells occurs slowly → a rapid IgG-dependent elimination of IgE from the cell surface may allow long-term desensitization of mast cells.


  - **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), sneezing, itching, mouth breathing, snoring, nasal voice, cough, ‘allergic shiners’ (darkened lower eyelids due to chronic congestion), minor epistaxis; (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); (viii) treatment: (depends on severity): allergen avoidance, antihistamines (oral, intranasal), corticosteroids (intranasal, oral), antileukotrienes, decongestants (oral, topical), allergen immunotherapy.

  - **Chronic rhinosinusitis:** (i) definition: inflammation of nasal and paranasal mucosa lasting ≥12 wks; (ii) clinical manifestations: nasal blockage/discharge, facial pain/pressure, hyposmia; (iii) diagnosis: clinical history, nasal endoscopy, allergy testing, X-rays, CT; (iv) treatment: nasal douching, corticosteroids (oral, intranasal), antibiotics, surgery, antihistamines, antileukotrienes, decongestants, allergen immunotherapy, biological agents.

  - **Occupational rhinitis (rhinosinusitis):** (i) inflammation of the nasal (nasosinusal) mucosa due to causes attributable to a particular work environment; (ii) has to be distinguished from ‘work-exacerbated rhinitis’ (pre-existing rhinitis that is exacerbated by workplace exposures).

  - **Occupational upper airway disease: (i) includes occupational rhinitis and rhinosinusitis; (ii) mechanisms: irritation, sensitization; (iii) 2-3 times more prevalent than occupational asthma; (iv) probably underdiagnosed (reasons: reluctance of patients to complain for fear of losing their job; diagnostic tests are frequently not validated and time-consuming); (v) might progress to occupational asthma (opportunity for prevention); (vi) diagnosis: clinical history, allergy testing (skin, in vitro), specific nasal provocation (poorly standardized), work removal and resumption’ test; (vii) management: allergen/irritant avoidance (e.g. adequate ventilation, protective clothing and masks, relocation of the worker), antiinflammatory drugs, immunotherapy; (viii) prevention: appropriate occupational hygiene.
**Work agents related to airway inflammation:**

(i) High molecular weight (HMW) agents (>5 kDa):
- Plant- or animal-derived biological substances generating IgE responses (e.g. flour, latex, mites, dander);
(ii) Low molecular weight (LMW) agents (<5 kDa):
- Chemicals causing irritation (e.g. chlorine, ozone, acids, ammonia, water-soluble gases), haptens causing immune responses (e.g. di-isocyanates [polyurethane foams, coatings], persulphate salts [hair bleachings], acid anhydrides [epoxy resins], aldehydes, metals [platinum salts, chromium, nickel], woods).

**Mechanisms of airway irritation (not well defined):**

(i) Activation of sensory afferent nerve fibers (e.g. the TRP ankyrin 1 channel is activated by acrolein, tear gas, vehicle exhaust, ozone, H\(_2\)O\(_2\) and hypochlorite) → local release of neuropeptides (substance P, neurokinins) → inflammation → ↑ number of nerve fibers → persistent inflammation (even after the culprit agent is eliminated);
(ii) Activation of epithelial cells and innate immune cells (iNKT cells, γδ T cells).

**‘Reactive upper airway dysfunction syndrome’ (RUDS):** persistent upper airway symptoms after acute injury to the upper airways.

**Knowledge gaps:**

(i) Mechanisms of action of irritants;
(ii) Relationships between occupational dermatitis and airway disease;
(iii) Possible predictors of progression to occupational asthma.


- Allergic diseases have dramatically increased (probably due to environmental and lifestyle factors; unlikely due to a genetic cause).
- Modern lifestyle (↓ breastfeeding, ↓ exercise, ↑ exposure to pollutants and cigarette smoke, diet rich in salt, sugar and high-saturated fats) → ↑ allergy prevalence.
- Environmental exposures during pregnancy (diet, allergens, pollutants, stress), birth (mode of delivery) and early life (allergens, pollutants, breastfeeding, diet, infections, stress) likely influence allergy development.
- Ideas to prevent allergy development: (i) Improve skin barrier, (ii) Adequate breastfeeding, (iii) Promote early exposure to allergens via the oral and GI routes, (iv) Avoid active and passive tobacco smoke, (v) Avoid exposure to pollutants (e.g. traffic, indoor painting), (vi) Use probiotics and prebiotics during pregnancy and infancy, (vii) Use of bacterial lysates, (viii) Vit D supplementation, (ix) Supplementation with n-3 PUFAs, (x) Use of cow’s milk hydrolysates when indicated, (xi) Primary allergen-specific immunoprophylaxis (before IgE sensitization occurs), (xii) Secondary allergen-specific immunoprophylaxis (before symptoms occur).
- Currently there is no way to fully prevent allergy development → there is an urgent need to identify environmental protective and risk factors for allergy development.

**House dust mites:**

(i) Important cause of persistent respiratory allergies; (ii) Dermatophagoides pteronyssinus (Der p) is a main allergy-causing species; (iii) Der p allergens can activate the innate immune system (pro tease activity, molecular mimicry with TLR agonists).

**Authors show that:**

(i) Immunoreactive Der p 1 was present in human colostrum and breast milk at similar amounts as dietary egg antigen; (ii) Der p 1-positive human breast milk induced in
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* vitro degranulation of basophils from Der p-allergic patients; (iii) in a mouse model of asthma, oral exposure to Der p through breast milk strongly promoted IgE-sensitization.

- **Author’s commentary:** allergen administration to the neonate by the oral route may contribute to IgE-sensitization (controversial opinion because early food administration seems to prevent food allergy; it may depend on the antigen properties).

- **SKIN PRICK TEST AND BASOPHIL REACTIVITY TO CETUXIMAB IN PATIENTS WITH IGE TO ALPHA-GAL AND ALLERGY TO RED MEAT** (Michel S, Scherer K, Heijnen IAFM, Bircher AJ. Allergy 2014; 69: 403–405):
  - Galactoseα1,3-galactose [α-Gal]: major blood group oligosaccharide of nonprimate mammals.
  - Allergy to α-Gal: (i) pathogenesis: tick bites (α-Gal is present within the GI tract of the ticks Amblyomma americanum and Ixodes ricinus), parasitic infestations or use of cetuximab → production of specific IgE to α-Gal; (ii) clinical manifestations: delayed allergic reactions (3-6 hrs) after ingestion of red meat containing α-Gal (beef, pork, lamb), immediate allergic reactions to cetuximab (a chimeric mouse-human IgG1 mAb that targets EGFR; approved for use in colorectal cancer and squamous cell carcinoma of the head and neck; contains α-Gal on the Fab portion); (iii) diagnosis: detection of specific IgE to α-Gal by *vitro* testing (skin testing appears inaccurate); (iv) allergy to α-Gal can rarely remit spontaneously after tick bite avoidance for 1 to 2 yrs; (v) IgE to α-Gal is not associated with rhinitis or asthma; (vi) bovine- and porcine-derived gelatin can be considered a potential occult source of α-Gal (gelatin can be present in colloids, tablets, capsules, vaccines, confectioneries [e.g. marshmallows], food thickeners, glazes, yogurt, mayonnaise, ice cream, sausage coatings, salami, fruit juice, wine, “hydrolyzed protein” in shampoo, collagen implants, “catgut” sutures).
  - Authors suggest that skin prick test and basophil activation test using cetuximab might have good sensitivity to diagnose α-Gal allergy.
A 37-YEAR-OLD MAN REFERRED FOR ASSISTANCE WITH PERSISTENT ASTHMA, ATOPIC DERMATITIS, AND CHRONIC CONJUNCTIVITIS

(1) Ocular itching can occur in: (i) dry eye, (ii) ocular allergies, (iii) ocular irritation (reactions to perfumes, sprays and cosmetics are usually irritative, rarely allergic).

(2) Ocular allergies: (i) clinical entities: allergic conjunctivitis, atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), contact allergy; (ii) it is essential to differentiate between usually benign (allergic conjunctivitis) and vision-threatening allergies (AKC, VKC); (iii) diagnosis: clinical history, ocular examination and imaging, allergy testing, conjunctival smear.

(3) Allergic conjunctivitis: (i) most common type of ocular allergy; (ii) IgE-mediated; (iii) proliferative changes are absent; (iv) frequently accompanied by allergic rhinitis.

(5) VKC: (i) more frequent in warm weather; (ii) usually starts before puberty and resolves by age 20; (iii) patients usually have other allergies; (iv) clinical features: itching, redness, swelling, discharge, photophobia, giant papillae, Trantas dots (eosinophil collections), corneal damage.

(6) Contact allergy: (i) lymphocyte-mediated reactions to haptens (e.g. poison ivy, neomycin, nickel, latex, atropine); (ii) can affect eyelid and conjunctiva; (iii) patch testing can identify the culprit allergen; (iv) treatment: allergen avoidance, topical or systemic corticosteroids.

(7) Giant papillary conjunctivitis: (i) irritant-induced reaction to limbal sutures, contact lenses, ocular prostheses or limbal dermoids (not a true allergy); (ii) clinical features: papillae in the superior palpebral conjunctiva, cornea is not affected; (iii) treatment: removal of irritative stimuli.

(8) AKC: (i) chronic severe ocular allergy with sight-threatening fibrosis; (ii) usually bilateral (severity might be asymmetrical); (iii) more frequent in adults with atopic dermatitis (~5% of patients have some ocular involvement); (iv) can persist through life; (v) pathogenesis: conjunctival barrier defect, allergic inflammation; (vi) clinical features: itching, pain, redness, chemosis, dryness, photophobia, limbal proliferation, giant papillae, Trantas dots, conjunctival scarring, blepharitis, madarosis, eyelid eczema, altered lid margins, ptosis, corneal ulcers, keratoconus, cataracts, retinal detachment, visual loss, staphylococcal infections; (vii) therapeutic options: allergen avoidance, antihistamines, mast cell stabilizers, lubricants, topical corticosteroids (cornerstone of acute-phase treatment; monitor side effects if using >10 days), cyclosporine, allergen immunotherapy, omalizumab, surgery, corneal transplantation.

A CRITICAL APPRAISAL OF OMALIZUMAB AS A THERAPEUTIC OPTION FOR CHRONIC REFRACTORY URTICARIA/ANGIOEDEMA

Lang DM. Ann Allergy Asthma Immunol 2014; 112: 276-279;

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), both 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-
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(vii) other therapies: mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A, sulfasalazine, chloroquine, dapsone, calcineurin inhibitors, mycophenolate, pseudoallergen-free diet, anticholinergics, 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) FDA-approved for [uncontrolled asthma + serum IgE levels between 30 and 700 IU/mL + sensitization to perennial allergens] and antihistamine-refractory CU (approval on May 21, 2014); (iii) dose (for asthma) is calculated in a chart, based on body weight and pretreatment IgE levels (between 30 and 700 IU/mL); (iv) alternative formula when the chart is not suitable: ≥0.016 mg/kg per IgE unit every 4-wk period; (v) suggested maximum dose: 750 mg every 4 wks; (vi) rate of anaphylaxis in patients with severe refractory asthma receiving omalizumab=1/1000; (vii) protocols recommend patient observation of 2 hrs for the first 3 doses and 30 min for each subsequent dose; (viii) efficacy has also been documented in CU, mastocytosis, anaphylaxis (idiopathic; exercise-induced), eosinophilic chronic rhinosinusitis, atopic dermatitis.

- **Omalizumab for chronic urticaria/angioedema (CUA):** (i) several observational studies and RCT show that omalizumab can be beneficial and safe for patients with antihistamine-refractory CUA (mainly spontaneous CUA; weaker evidence for inducible CUA); (ii) calculated NNTs to become hive-free and itch-free at doses of 150 and 300 mg for 12 wks = 5.9 and 2.6, respectively; (iii) benefit can be observed within days of therapy onset; (iv) some patients have complete remission of symptoms; (v) dosing has followed the asthma scheme, a fixed regimen or an individualized algorithm; (vi) limitations for routine use: cost, availability; (vii) areas of uncertainty: biomarkers to predict response (not all patients improve), mechanism of action, optimal dosing, optimal duration of treatment.


- **Anaphylaxis:** (i) definition: acute 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 (IgE-mediated, IgG-mediated, complement mediated, idiopathic); (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%.

- **Effects of stress on allergy:** (i) stress → secretion of corticotropin-releasing hormone (CRH) → activation of CRH receptor-1 (CRHR-1) on mast cells → mast cell degranulation, ↑ expression of FcεRI; (ii) stress → ↑ release of neuropeptides (substance P [SP], neurotensin [NT]) → ↑ expression of functional CRHR-1, mast cell degranulation through NTR and NK1R.
Authors report the case of a 33-yr-old woman with recurrent (16 episodes) severe “idiopathic” anaphylaxis (diffuse pruritus, erythema, angioedema, hoarseness, wheezing, shortness of breath, colicky abdominal pain, nausea, vomiting, low blood pressure, diffuse myalgias and polyarthralgias) appearing on periovulatory days. A more detailed clinical history revealed that the episodes were apparently precipitated by emotional stress (worrying about a new pregnancy [she had already 9], anxiety, family preoccupation). Diagnostic tests: anaphylaxis after progesterone skin testing, anaphylaxis after placebo skin testing. Successful treatment: stress reduction (benzodiazepines for a short period, psychotherapy) and family support.

Stress-induced anaphylaxis may result from interactions among CRH, SP and NT on mast cells.

BENEFICIAL ROLE FOR SUPPLEMENTAL VITAMIN D3 TREATMENT IN CHRONIC URTICARIA: A RANDOMIZED STUDY (Rorie A, Goldner WS, Lyden E, Poole JA. Ann Allergy Asthma Immunol 2014; 112: 376-382):

- Vit D: (i) regulates calcium, phosphorus and bone metabolism; (ii) regulates the growth and differentiation of multiple cell types; (iii) protective effects in obesity, cancer, CV disease, immune function and maternal/fetal health; (iv) hypovitaminosis D has been associated (frequently but not uniformly) with occurrence or severity of allergy (allergic sensitization, wheezing, asthma, allergic rhinitis, food allergy, atopic dermatitis) and chronic urticaria (CU); (v) a possible role for vit D in the prevention and treatment of immune-mediated diseases (e.g. cancer, CV disease, arthritis, transplant rejection, autoimmunity, allergy) has been suggested.

- 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.

- Authors performed a RCT to assess the effects of vit D3 supplementation (for 12 wks) on 42 patients (≥19 yrs of age) with CU. (i) supplementation with 4,000 IU/day, but not 600 IU/day, resulted in a 40% decrease of total USS score at wk 12; (ii) serum 25-OH vit D levels ↑ with high vit D3 supplementation; (iii) there was no correlation between 25-OH vit D levels and USS score; (iv) no adverse events occurred.

- Author’s commentary: add-on therapy with high-dose vit D3 (4,000 IU/day) can be beneficial and safe for patients with CU.

DETECTION OF IgE BINDING COMPONENT TO INFLIXIMAB IN A PATIENT WITH INFLIXIMAB-INDUCED ANAPHYLAXIS (Hwang SH, Yoo H-S, Yoon MK, Park H-S. Ann Allergy Asthma Immunol 2014; 112: 393-394):

- Several mechanisms are suggested in monoclonal antibody (mAb) infusion-related anaphylaxis (IgE- and non-IgE-mediated hypersensitivity reactions, cytokine release syndrome).

- Infliximab: (i) chimeric anti-TNF-α mAb (constant region of human IgG1 + variable regions of mouse anti-TNF-α); (ii) molecular weight=149.1 kDa; (iii) indications: several inflammatory diseases; (iv) common adverse reactions: URTIs, headache, nausea (infusion reactions occur in ~5% of patients); (v) immediate hypersensitivity reactions: rare, generally mild, most severe reactions occur by the 10th infusion and are associated with a long reinfection interval.
• Authors report the case of a 28-year-old man with ankylosing spondylitis (for 11 yrs) who presented anaphylaxis (urticaria, chest discomfort, dyspnea, wheezing and tachypnea, which resolved with antihistamines and steroids) after the 29th injection of infliximab (400 mg every 8 wks for 44 months) → previous history: bronchial asthma, allergic rhinitis, shrimp allergy → laboratory studies: serum total IgE=688 kU/L; negative SPT and intradermal test with infliximab (0.001, 0.01, 0.1, 1, and 10 mg/mL); negative sIgE to infliximab (ELISA); negative BAT to infliximab; positive IgE immunoblot analysis (remarkable band of 149 kDa not observed in the 2 controls) → successful management: switch to adalimumab (another TNF-α inhibitor).

• Author’s commentary: 1st report of an IgE-binding component of infliximab in a patient with infliximab-induced anaphylaxis.

• INTEGRATIVE APPROACH TO ALLERGY AND ASTHMA USING COMPLEMENTARY AND ALTERNATIVE MEDICINE (Silvers WS, Bailey HK. Ann Allergy Asthma Immunol 2014; 112: 280-285):

• Authors review the benefit of complementary and alternative medicine (CAM) on allergies.

• Problems with conventional therapy for allergies: lack of symptom control, adverse effects, low accessibility, high cost → many allergic patients use CAM.

• Benefits of CAM: (i) some therapies have good evidence to ↓ allergy symptoms; (ii) placebo effect; (iii) improvement of physician-patient relationship (some patients strongly believe in CAM and are happy to discuss CAM therapies).

• Broad categories of CAM: (i) natural products (vit D, vit C, vit E, mineral supplements, ω3-fatty acids, antioxidants, probiotics, herbal supplements); (ii) mind and body medicine (meditation, yoga, breathing techniques, self-management training, journaling, patient support groups, cognitive-behavioral therapy); (iii) manipulative and body-based practices (spinal manipulation, acupuncture, massage therapy); (iv) lifestyle (↓ stress, ↑ exercise, better diet).

• Traditional Chinese Medicine integrates herbal therapy, acupuncture, acupressure, massage, mind-body therapy and dietary therapy.

• Potentially effective herbal remedies: (i) for asthma: caffeine (theophylline is a metabolite), choline, magnesium, Pinus pinaster pine bark (Pycnogenol), Chinese herbal formula (contains Ganoderma lucidum, Sophora flavescens and Glycyrrhiza uralensis; Food Allergy Herbal Formula-2 has been effective in blocking even peanut-induced anaphylaxis in animal models); (ii) for allergic rhinitis: butterbur (Petasites hybridus), capsaicin.

• Important recommendations: (i) it is important to know about CAM modalities (efficacy, safety, dosing, drug-CAM interactions); (ii) evidence-based CAM can be integrated into conventional therapy (as efficacy is confirmed, certain CAM modalities will transition into mainstream medicine); (iii) treatment of allergic patients should be individualized.

• IS THE CONSISTENCY MORE IMPORTANT THAN THE INGREDIENTS FOR STEROID TREATMENT IN EOSINOPHILIC ESOPHAGITIS? (Parrish DW, Sharma S, Kumar S. Ann Allergy Asthma Immunol 2014; 112: 286-289):

• Eosinophilic esophagitis (EoE): (i) pathogenesis: immune reaction to food or respiratory allergens in the esophagus → infiltration of eosinophils into esophageal mucosa (usually
patchy) → chronic eosinophilic inflammation → esophageal dysfunction; (ii) common causal foods in children: milk, egg, soy, wheat, beef, chicken; (iii) common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg; (iv) frequent association with respiratory and skin allergies; (v) often misdiagnosed as GERD.

• Diagnosis of EoE: (i) clinical history: abdominal pain, vomiting, dysphagia, food impaction, heartburn, cough, choking, food aversion, failure to thrive; (ii) esophageal endoscopy: white exudative plaques, mucosal rings (‘trachealization’), strictures, linear furrows, edema; (iii) esophageal biopsy (positive result: ≥15 eosinophils per high-power field; limitation: 5 biopsies represent only <0.02% of the esophageal surface → false negative results can occur, especially in mild cases); (iv) allergy testing (SPT, in vitro sIgE detection, patch test) with food and respiratory allergens; (v) food elimination-reintroduction trials; (vi) detection of eosinophil-mediated inflammation (e.g. cationic eosinophil granule proteins) by SPECT imaging.

• Treatment of EoE: (i) diet options: 6-food elimination diet (milk, egg, wheat, soy, fish/seafood, peanut/tree nuts), diet guided by allergy tests, aminoacid formula, (ii) corticosteroids (most recommended regimen: to swallow viscous budesonide respules mixed into a slurry-type solution with a sucrose-containing artificial sweetener); (iii) biologic therapies targeting the eosinophil (e.g. anti-IL-5 mAb, anti-IL-5R mAb).

• Authors report the case of a 2-yr-old boy (author’s son) with EoE and intolerance to the sucrose-containing artificial sweetener (present in both the viscous budesonide preparation and the milk formula; the family helped a lot to get the correct diagnosis) → successful treatment: utilization of powdered sugar [viscous budesonide + 2 tsp of powdered sugar] and an unflavored aminoacid-based formula.

• Author’s commentaries: (i) the consistency (thick enough to coat the esophagus), rather than the mixing ingredient, is likely the most important aspect of the steroid mixture for EoE treatment; (ii) it is essential to find a mixing food that the child tolerates (e.g. powdered sugar, honey, pancake syrup, pureed meal); (iii) parents’ ideas must be considered by the physicians.

• STRESS AND ALLERGIC DISEASES – STILL UNDER RECOGNIZED AND UNDERTREATED (Marshall GD. Ann Allergy Asthma Immunol 2014; 112: 275):

• Stress: (i) individual level: fear, anxiety, depression; (ii) family level: family violence, family instability; (iii) community level: neighborhood violence, terrorism.

• Relation between stress and allergies: (i) stress → worsening of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, food allergy, anaphylaxis) and chronic urticaria; (ii) allergic diseases → ↑ stress, ↓ QoL; (iii) stress → activation of coronary artery-associated mast cells → cardiac events.

• Proposed pathogenic mechanisms of stress: (i) ↑ CRH production → mast cell activation, ↓ IL-10 secretion by Tregs; (ii) ↑ neuropeptide secretion; (iii) dysfunctional HPA; (iv) ↓ cortisol production; (v) cortisol insensitivity.

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

- B-cell activating factor (BAFF) → activation of BAFF receptor (BAFFR) on B cells → ↑ B-cell development and survival, adequate T-cell independent B-cell responses.

- Homozygous deletion in the BAFFR-encoding TNFRSF13C gene → detention of B-cell development at the stage of transitional B cells → CVID.

- Authors report that a homo- or heterozygous P21R mutation in BAFFR (single-nucleotide polymorphism Pro21>Arg [c.62C>G; rs77874543]) may contribute to CVID development → mechanisms: ↓ ligand-independent BAFFR multimerization, ↓ binding to BAFF, ↓ NF-κB activation in B cells, ↓ proliferation and IgM production by primary B cells.

- **Observations:** (i) P21R mutations in BAFFR did not affect BAFFR expression levels, B-cell counts and B-cell subsets; (ii) P21R had an allele frequency of 10.2% in CVID patients and of 6.7% in controls (OR=1.57); (iii) the P21R allele is also found in healthy individuals (in contrast to the CVID-causing homozygous deletion of the BAFFR gene); (iv) heterozygous TACI mutations have also been described as risk factors for CVID.

- **Author’s commentary:** ‘risk alleles’ in BAFFR, in combination with ‘risk alleles’ in other genes (e.g. TACI), probably result in CVID.


- **TH2-promoting cytokines:** IL-4, IL-13, TSLP (in the skin and airways), IL-25, IL-33.

- The relationship between TH2-promoting cytokines (IL-4, IL-13 and TSLP) and their receptors are complex: (i) receptors are expressed on many types of immune cells at different quantities; (ii) receptor subunits can exist in surface-bound or soluble forms; (iii) receptor subunits can exist in isolation or in partnership with other subunits; (iv) receptor subunits are shared among different cytokine receptor complexes (the common gamma chain stabilizes different receptor complexes); (v) genetic polymorphisms and posttranscriptional modifications in receptors can
alter interactions with their ligands and modify downstream signaling events; (vi) environmental exposures (e.g. allergens) can modify receptor expression.

• **Biologic therapies in asthma:** (i) include monoclonal antibodies, cytokine-trapping fusion molecules and engineered cytokines with diverse binding affinity to specific receptor chains (superkines); (ii) important for patients who do not respond to conventional therapy; (iii) may benefit specific asthma endotypes/phenotypes (e.g. lebrikizumab in patients with ↑ periostin/IL-13); (iv) ~30 drugs are currently in clinical trials and dozens in development; (v) outcomes of most trials with biologic therapies have been disappointing; (vi) main limitations: lack of efficacy (complexity of disease endotypes, immune system redundancy), high cost, low accessibility, side effects; (vii) the inhibition of TH2-promoting cytokines can affect normal immune functions (e.g. TSLP is important for thymic function and Treg-cell generation).

• **Examples of biologic therapies for asthma:** (i) anti-IL-4Ra mAb: dupilumab (blocks IL-4 and IL-13 pathways), AMG-317; (ii) IL-4Ra antagonist: pitrakinra (blocks IL-4 and IL-13 pathways); (iii) IL-4 trapping agent: altrakincept; (iv) anti-IL-13 mAb: lebrikizumab, tralokinumab, anrakinzumab; (v) anti-TSLP: AMG 157.


  - **Innate lymphoid cells:** (i) type 1 (ILC1s): produce TH1 cytokines; (ii) type 2 (ILC2s): produce TH2 cytokines (IL-5, IL-13) after stimulation with IL-25, IL-33, TSLP or LTD4; (iii) type 3 (ILC3s): produce TH17 cytokines (IL-17, IL-22).

  - **ILC2s:** (i) defined as lineage-negative lymphocytes that express the chemoattractant receptor homologous molecule expressed on TH2 lymphocytes (CRTH2); (ii) highly express the master TH2 cytokine transcription factor GATA-binding protein 3; (iii) source of TH2 cytokines; (iv) promote allergen-induced airway hyperresponsiveness and type 2 lung inflammatory responses; (v) may have a role in asthma and allergic disease; (vi) human ILC2s have been detected in the skin, peripheral blood, GI tract, lung, bronchoalveolar lavage and nasal polyps.

  - Authors studied 7 cat-allergic adults (20-27 yrs old) with allergic rhinitis → (i) CRTH2+ ILC2s increased in the peripheral blood 4 hrs after a nasal cat allergen challenge (potential mechanism: ↑ recruitment of ILC2s from the bone marrow by inflammatory mediators [e.g. PGD2]); (ii) ILC2s highly expressed CD84 (a member of the SLAM/CD2 family with a role in T-cell-B-cell contact), although other cells can also express CD84 (e.g. T lymphocytes); (iii) cat allergen challenge did not increase CD84 expression on ILC2s or CD4+ cells.

  - **Author’s commentary:** inhibition of ILC2s is a potential strategy to ↓ allergic inflammation.

• **IMPACT OF DOWN SYNDROME ON THE PERFORMANCE OF NEONATAL SCREENING ASSAYS FOR SEVERE PRIMARY IMMUNODEFICIENCY DISEASES** (Verstegen RHJ, Borte S, Bok LA, van Zwieten PHT, von Döbeln U, Hammarström L, de Vries E. J Allergy Clin Immunol 2014; 133: 1208-1205):

  - **Severe combined immunodeficiency (SCID):** (i) definition: genetic defects causing marked ↓ in T-cell development and function → lack of cellular and humoral immunity → severe infections (including opportunistic), fatal course if not treated (HSCT, gene therapy, enzyme replacement treatment).
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.

therapy); (ii) newborns can be screened for SCID by measuring TREC 
(T-cell receptor excision circles) in dried blood spot samples (DBSS) obtained from regular Guthrie cards.

- **Agammaglobulinemia:** (i) **definition:** genetic mutations that block B-cell maturation → ↓ circulating B cells (<2% of peripheral blood lymphocytes) → ↓ production of immunoglobulins → severe infections; (ii) newborns can be screened for agammaglobulinemia by measuring KREC 
(kappa-deleting recombination excision circles) in DBSS.

- **TREC levels:** (i) reflect TCR gene recombination; (ii) associated to T-cell neogenesis; (iii) excellent sensitivity to screen newborns for SCID.

- **KREC levels:** (i) reflect BCR gene recombination (kappa light chain); (ii) associated to B-cell neogenesis; (iii) newborn screening test for B-cell lymphocytopenia.

- **Diseases or conditions** (other than SCID or agammaglobulinemia) that can present low TREC/KREC levels: prematurity, inflammatory conditions, 22q11 deletion syndromes.

- **Down syndrome:** (i) 1 in 600 to 900 newborns; (ii) patients can have features of immunodeficiency: smaller and abnormal thymus, ↓ T-cell and B-cell counts, ↓ responses to several protein and polysaccharide antigens.

- Authors show that patients with Down syndrome can have low TREC and KREC.

- **INNATE LYMPHOID CELLS AND ASTHMA** 


  - Authors review the recent data regarding innate lymphoid cells (ILCs) and their role in asthma.

  - **ILCs:** (i) innate lymphocytes that are activated in non-antigen-specific ways to rapidly produce cytokines → immune responses (dependent or independent of adaptive immunity); (ii) are thought to arise from a common precursor cell expressing the transcription factor inhibitor of DNA binding 2; (iii) likely important for immunity in the skin and mucosas (e.g. ILC3s are normally abundant in the small intestine and protect against intestinal infection).

  - **ILCs:** (i) type 1 (ILC1s): produce TH1 cytokines (IFN-γ); (ii) type 2 (ILC2s): produce TH2 cytokines (IL-5, IL-13); (iii) type 3 (ILC3s): produce TH17 and TH22 cytokines (IL-17, IL-22).

  - **Role of ILCs in asthma:** (i) ILC2s ↑ allergic inflammation through secretion of TH2 cytokines (pathologic role); (ii) ILC2s can restore airway epithelial cell integrity after injury (homeostatic role); (iii) ILC1s can ↑ eosinophil apoptosis and ↓ eosinophilic airway inflammation; (iv) ILC3s can ↑ IL-17-mediated airway inflammation and asthma.

  - **Vit A deficiency →** (i) ↓ ILC3s → susceptibility to intestinal bacterial infection; (ii) ↑ ILC2s → protection against intestinal helminth infection.

  - **Important questions:** (i) Is targeting ILCs worthwhile in the treatment of disease? (ii) Are there more subsets of ILCs?

- **KINDLIN-3–INDEPENDENT ADHESION OF NEUTROPHILS FROM PATIENTS WITH LEUKOCYTE ADHESION DEFICIENCY TYPE III** 

Neutrophil migration to inflamed tissue: (i) rolling on the vessel wall (selectin-mediated); (ii) firm adhesion to endothelium (chemokine receptor- and integrin-mediated); (iii) diapedesis.

Integrins: (i) adhesion molecules involved in firm adhesion of neutrophils; (ii) activation of integrins to a high-affinity binding conformation requires interaction with kindlin-3; (iii) the most prominent integrin on neutrophils is complement receptor (CR) 3 (Mac-1, CD11b/CD18, αMβ2) followed by lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18, αβ2).

Leukocyte adhesion deficiency (LAD): (i) LAD-I: mutations in CD18 (ITGB2 gene); (ii) LAD-II: mutations in GDP-fucose transporter 1 (SLC35C1 gene); (iii) LAD-III: mutations in kindlin 3 (FERMT3 gene).

LAD-III: (i) rare autosomal recessive immunodeficiency; (ii) clinical features: severe nonpurulent bacterial and fungal infections (usually not as severe as in LAD-I), Glanzmann thrombasthenia-like bleeding tendency; (iii) pathogenesis: defective activation of integrins on leukocytes and platelets due to kindlin 3 defect.

Authors show a kindlin-3–independent activation of CR3 (low affinity) in neutrophils from patients with LAD-III.

Author’s commentaries: (i) neutrophil adhesion induced by certain stimuli (e.g. fMLP, PMA) can occur in a CR3-dependent manner in the complete absence of kindlin-3; (ii) kindlin-3–dependent CR3 activation → high-affinity CR3 (kindlin-3 is essential to obtain maximal affinity of CR3); (iii) kindlin-3–independent CR3 activation → low-affinity CR3 (may allow initial adhesion under certain conditions); (iv) LAD-III neutrophils retain some adhesive capacity → infections in LAD-III are usually less severe that in LAD-I.


- Recombinase activating gene (RAG) 1 and 2: proteins with an essential role in the generation of T- and B-cell receptors. RAG1: DNA binding and cleavage; RAG2: cofactor for RAG1 function.
- RAG homozygous mutations can have diverse clinical presentations: (i) T/B/NK* severe combined immunodeficiency (SCID); (ii) Omenn syndrome (typical and atypical); (iii) CD4+ T-cell lymphopenia; (iv) hyper-IgM syndrome; (v) CID with γδ T-cell expansion; (vi) granulomatous disease; (vii) CID with autoimmune cytopenias and/or organ-specific autoimmune disease.
- RAG heterozygous mutations can result in immunodeficiency or immune dysregulation (e.g. autoantibody production or T-cell lymphopenia); epigenetic or additional genetic factors might be involved.
- Authors report a 9-yr-old boy with features of immunodeficiency and immune dysregulation (stunted growth, chronic diarrhea, recurrent pulmonary infections, bronchiectasis, immune complex glomerulonephritis with severe glomerulosclerosis, autoimmune hemolytic anemia, tinea capitis, recurrent urticaria) catalogued since 2 months of age as IPEX-like syndrome → laboratory analysis: lymphopenia, ↓ CD4+CD45RA+ T cells, ↓ TRECs, ↓ KRECs, restricted TCR repertoire, ↓ CD19+ B cells, ↓ IgG, ↓ IgA, severely impaired T-cell function → genetic analysis: homozygous p.Ser480Gly mutation in RAG1 (10% of V(D)J recombination efficiency.
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.


- **Vaccines**: ↓ morbidity and mortality of many infectious diseases (eg. eradication of smallpox).
- **Primary immunodeficiencies (PIDs)**: (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 subjects; (iii) impact: severe complications (infections, autoimmunity, neoplasms), ↓ QoL, high costs; (iv) early diagnosis and treatment can be lifesaving.
- **Important considerations about vaccines**: (i) unvaccinated children have ↑ risk of serious infection and even death; (ii) some parents believe that vaccines have severe side effects, including autism, despite overwhelming scientific evidence to the contrary; (iii) it is essential to ↑ vaccination rates in the population to reinforce and maintain herd immunity.
- **Important considerations about vaccines in patients with PID**: (i) live vaccines (oral poliovirus, measles, mumps, rubella, yellow fever, varicella, herpes zoster, smallpox, rotavirus, live attenuated influenza, BCG, live S typhi) are contraindicated in patients with severely reduced T-cell function; (ii) live vaccines should be avoided in PID patients with immunosuppression or incomplete immune reconstitution after HSCT (always evaluate immune reconstitution before using live vaccines in patients treated with HSCT, enzyme therapy or gene therapy); (iii) oral poliovirus, yellow fever, live attenuated influenza and typhoid vaccines are contraindicated in patients with severe B-cell deficiencies (e.g. XLA, CVID); (iv) BCG and live typhoid vaccine are contraindicated in patients with certain phagocyte or innate immune defects (e.g. CGD, MSMD); (v) newborn PID screening is an essential tool to prevent the administration of live vaccines to patients with severe T-cell and B-cell defects; (vi) inactivated or subunit vaccines are usually safe in patients with PID; (vii) patients with T-cell or B-cell defects may not produce protective antibodies after vaccinations; (viii) patients receiving intravenous immunoglobulin may not produce protective antibodies after vaccinations; (ix) some vaccines are strongly recommended in patients with certain types of PID (e.g. pneumococcal and meningococcal vaccination in patients with complement deficiencies); (x) patients with T-cell defects might benefit from vaccination with T cell–independent antigens (pneumococcal, meningococcal and H influenzae type b vaccines) and seasonal killed influenza vaccine; (xi) patients with severe T-cell and B-cell defects can be infected by live poliovirus shed from orally vaccinated contacts; (xii) family

compared with wild-type RAG1) → planned treatment: HSCT from his 15-yr-old HLA-matched brother (clinically healthy except for generalized vitiligo) → laboratory analysis in the brother: ↓ naive T-cells, ↓ TRECs, ↓ KRECs, ↓ T-cell proliferation to tetanus antigen → genetic analysis in the brother: homozygous p.Ser480Gly mutation in RAG1 (compensating mutations in RAG1, RAG2 or DCLRE1C were excluded; reversions were excluded).

- **Author’s commentaries**: (i) 1st report of a homozygous pathogenic RAG mutation in a clinically healthy teenager except for vitiligo; (ii) the same RAG mutation can result in different phenotypes (possibly contributing factors: epigenetics, gene-gene interactions, random V(D)J recombination followed by antigen receptor selection, chance infections); (iii) genetic testing should be considered for unaffected siblings of patients with PIDs with variable penetrance (e.g. RAG, MHCII or ADA defects), especially if they are potential donors for HSCT.
contacts of PID patients should be appropriately vaccinated to prevent infection and transmission to the patient; (xiii) it is important for family members of patients with T-cell and B-cell defects to receive all standard immunizations (excluding live poliovirus); (xiv) individual assessment of the immune status by an expert immunologist is recommended before using live vaccines in patients with partial T-cell deficiencies or in other difficult situations where risk-benefit evaluation is mandatory; (xv) family education is obligatory to avoid complications of live viral vaccines; (xvi) a pregnant women should routinely receive only the Tdap and inactivated influenza vaccines, however, pregnant women at high risk for a child with PID and without a clear immunization history should receive pneumococcal, meningococcal and H influenzae type b vaccines so that transferred IgG antibodies can protect the potentially immunodeficient newborn while definitive diagnosis and treatment are undertaken; (xvii) if a varicella rash develops in a close contact after receiving varicella or zoster vaccines, the risk of transmission to the PID patient is minimal unless blisters develop at the site of vaccine administration; in this case, isolation of the patient is recommended and VZV immunoglobulin could be given prophylactically; treatment of the close contact or the patient, if infected, would consist of intravenous acyclovir or oral valacyclovir; (xviii) killed trivalent influenza vaccine is preferred for close contacts of a PID patient, although live attenuated influenza vaccine has a low rate of transmission; (xix) in any newborn with a suspicion of severe PID due to family history, defer all live vaccines until PID has been ruled out (especially in places where newborn PID screening is not available).


• THE EDITOR’S CHOICE (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2014; 133: 977-978):

• Nutrition: environmental factor that influences the development of the infant’s immune system.

• Increased diversity of complementary food introduced in the 1st yr of life was associated to ↓ asthma and food allergy.

• Anti–IL-13 therapy for 12 wks was not efficacious in patients with severe refractory asthma.

• Subcutaneous guselkumab (anti-IL-23 mAb) was beneficial for patients with moderate-to-severe psoriasis.

• Early-life determinants of asthma development from birth to age 20 yrs: (i) risk factors: parental asthma and allergic rhinitis, smoking during pregnancy; (ii) protective factors: vaccination in early childhood, day care initiation between 18 and 36 months of age; (iii) neutral factors: diet, breastfeeding, pets at home.

• Sputum gene expression of 6 biomarkers discriminated asthma inflammatory phenotypes and predicted response to inhaled corticosteroids → (i) expression of CLC, CPA3 and DNASE1L3 was ↑ in patients with eosinophilic asthma and ↓ after treatment with ICS; (ii) expression of IL1B, ALPL and CXCR2 was ↑ in patients with neutrophilic asthma.

• An abnormal immune response (↑ IL-5, ↑ IL-13, ↓ IL-17) to pathogenic airway bacteria (Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae) in infancy increased the risk of childhood asthma.

  Dedicator of cytokinesis 8 (DOCK8) deficiency: (i) autosomal recessive hyper-IgE syndrome with features of combined immunodeficiency; (ii) clinical features: skin viral infections, fungal infections, pneumonias, severe allergies, cancer susceptibility; (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ dendritic cell migration, ↓ production of antiviral cytokines, lymphopenia, ↓ T-cell priming, ↓ T-cell chemotaxis, ↓ T-cell survival, ↓ CD8+ T-cell activation, ↓ NK-cell cytotoxicity, ↓ germinal center formation, ↓ germinal center B cells, ↓ antibody production; (iv) progressive multifocal leukoencephalopathy caused by JC virus is the only known viral CNS infection affecting DOCK8 patients.

• Authors report the case of a 6-yr-old boy with neurologic symptoms (headache, dizziness, paresthesia, urinary incontinence, weakness) → previous history: severe atopy (early-onset eczema, food allergies, anaphylaxis, eosinophilic esophagitis, asthma) requiring many courses of oral corticosteroids; recurrent URTIs; chronic mild otitis; eosinophilia (peak at 9000 eosinophils/µL); ↑ IgE (peak at 472 IU/mL); routine immunizations including VZV vaccination at age 1 yr; 3 episodes of rash (2 by HSV, one diagnosed as zoster) coinciding with oral corticosteroid use → diagnosis: vaccine strain VZV–induced CNS vasculopathy (abnormal findings in brain CT and MRI [widespread infarction produced by stenosis of multiple large cerebral arteries]; CSF abnormalities [including positive anti-VZV IgG antibodies]; presence of VZV DNA in the CSF [Oka varicella vaccine strain]) → successful treatment: intravenous **acyclovir**, systemic corticosteroids → genetic analysis: compound heterozygous **DOCK8 mutation** (maternal allele carrying a large deletion of exons 1 to 13; paternal allele with the c.1266delC [p.Y423TfsX18] mutation) → Western blot: lack of DOCK8 protein expression.

• Author’s commentaries: (i) vaccine strain VZV reactivation can result in CNS vasculopathy in immunodeficient patients (in this case, DOCK8 deficiency and frequent systemic corticosteroid use were likely conditioning factors for viral reactivation); (ii) **DOCK8 deficiency** should be considered in patients with severe allergies (even with no history of severe infections).
PEDiATRIC ALLERGY AND IMMUNOLOGY:


  - **Asthma:** (i) multifactorial airway inflammatory disease (genetic, epigenetic and environmental factors); (ii) usually presents before 5 yrs of age; (iii) the first 3 yrs of life might be a critical period for asthma initiation and airway remodeling (mainly influenced by environmental factors); (iv) frequently underdiagnosed or misdiagnosed in early life (wrong labels: chronic bronchitis, wheezy bronchitis, reactive airways, recurrent pneumonia, recurrent upper RTIs, GERD); (v) not every wheezing infant will develop asthma (40% of children wheeze within 1st yr of life but only 30% of preschoolers with recurrent wheezing will have asthma at 6 yrs); (vi) there is no accurate single screening test to predict which young children with recurrent wheezing will develop asthma; (vii) 17q21 locus: most replicated asthma susceptibility region of the genome.

  - **Factors that may predict asthma development in infants <3 yrs of age:** (i) 3 episodes of wheezing per year, (ii) wheezing without colds, (iii) parental atopy, (iv) personal history of eczema or allergic rhinitis, (v) ↑ total IgE, (vi) IgE-sensitization to respiratory or food allergens, (vii) peripheral eosinophilia ≥4%; (viii) exposure to high levels of indoor allergens.

  - **Respiratory viral infections** (RSV, HRV, parainfluenza, coronavirus, influenza, adenovirus, bocavirus, human metapneumovirus): (i) pathogenic factor in ~90% of acute wheezing episodes in the first 3 yrs of life; (ii) pathogenic factor for asthma development and exacerbations.

  - **Early-life respiratory infections** (virus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis) + allergen sensitization → synergism to promote asthma development.

  - **Wheezing during early childhood:** (i) common condition (~50% of children have ≥1 wheezing episode before 6 yrs of age, most of them do not continue wheezing at school age); (ii) 80-90% of episodes are associated with viral infections (mainly RSV and HRV); (iii) factors that affect wheezing severity: age, genetics, basal lung function, atopy, exposure to pollutants; (iv) clinical syndromes: acute viral bronchiolitis, recurrent viral-induced wheezing, viral-induced asthma.

  - **Viral bronchiolitis:** (i) definition: initial episode of virus-induced lower RTI in a child <2 yrs of age; (ii) 2 major culprit viruses: RSV and HRV; (iii) other culprit viruses: human metapneumovirus, parainfluenza virus; (iv) leading cause of hospitalization during winter among young children; (v) major role in the development of wheezing and asthma (especially for severe RSV-induced bronchiolitis); (vi) it remains uncertain whether severe bronchiolitis is a cause of asthma [“the first hit”] or a marker for asthma susceptibility; (vii) it is not defined how to prevent asthma and recurrent wheezing after severe bronchiolitis.

  - **Virus-induced recurrent wheezing:** (i) 2 categories, which may overlap: children who wheeze exclusively during viral infections (episodic viral wheeze), and children who wheeze after multiple triggers (e.g. virus, allergens, exercise); (ii) outpatient HRV-induced wheezing might ↑ asthma risk; (iii) early treatment with high-dose ICS or montelukast might be beneficial during upper RTIs to prevent severe wheezing episodes.

  - **Relations between microbes and asthma:** (i) viral respiratory infections, especially by RSV, may initiate asthma in an atopic patient; (ii) viral respiratory infections, especially by HRV, are the
most frequent infectious cause of asthma exacerbation; (iii) atypical bacterial infections (M pneumoniae, C pneumoniae) can ↓ asthma control (macrolide therapy may help); (iv) respiratory allergies are a risk factor for respiratory infections; (v) asthma may ↓ the ability to ‘shut-off’ HRV-induced inflammation; (vi) type and diversity of microbiota (intestinal and respiratory) influence tolerogenic vs allergic responses (Lactobacillus sp, Bifidobacterium sp and high microbial diversity may ↓ allergy risk; Staphylococcus, Proteobacteria and Acinetobacter sp may ↑ allergy risk); (vii) probiotics, prebiotics (fiber, SCFA) and microbial lysates may help to prevent or treat allergies by increasing Treg and Th1 responses; (viii) natural delivery favors skin/mucosal colonization by tolerogenic microbiota and ↓ allergy risk.

• HRV: (i) nonenveloped, single-stranded RNA virus (Picornaviridae family); (ii) 3 distinct species (A, B, C); (iii) >150 serotypes with many more distinct strains that can infect humans; (iv) HRV-A is composed of >70 serotypes, HRV-B has >25 serotypes, HRV-C has a rapidly expanding number of distinct serotypes; (v) HRV infection is ubiquitous (most common cause of common cold); (vi) HRV-C species are likely to be more virulent and wheezing-inducing.

• RSV: (i) enveloped, negative-stranded, RNA virus (Paramyxoviridae family); (ii) nearly all children have serologic evidence of RSV infection in the first 2 yrs of life but only 40% develop bronchiolitis; (iii) early use of palivizumab (anti-RSV mAb) in premature infants reduced wheezing days during the 1st yr of life.

• Airway 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).

• Allergic sensitization → ↑ FcεRI expression on plasmacytoid DCs → ↓ antiviral immunity (e.g. ↓ production of type I and type III interferons in response to influenza and HRV infection).

• 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 responses (e.g. early allergen IT); (iii) ↓ respiratory infections (e.g. use of viral-specific vaccines or bacterial-derived immunostimulants); (iv) ↓ interactions between atopic and antimicrobial 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.


• Severe asthma: (i) includes untreated, difficult-to-treat and therapy-resistant asthma; (ii) occurs in ~5% of asthmatic school children; (iii) impact: high morbidity, significant mortality, high costs; (iv) features: significant airflow limitation, air trapping and airway remodeling; (v) >80% of patients with difficult-to-treat asthma show poor adherence to therapy.

• Problematic severe asthma: (i) includes difficult-to-treat and therapy-resistant asthma; (ii) 2 phenotypes (not mutually exclusive): exacerbation phenotype (≥1 severe exacerbations during the preceding year; no day or night symptoms in between), chronic symptoms phenotype (day and/or night symptoms ≥twice a week during the preceding 3 months).

• Risk factors for severe asthma: (i) genetic variants affecting epithelial barrier, innate immunity or adaptive immunity (variants that ↑ asthma risk in one environment may ↓ risk in another
environment), (ii) comorbidities (e.g. nasosinusal disease, obesity, GERD), (iii) respiratory infections (e.g. Mycoplasma pneumoniae), (iv) pollutants (e.g. smoking, particulate matter), (v) sensitization to fungi (e.g. severe asthma with fungal sensitization), (vi) TH17/neutrophilic inflammation in the airways; (vii) multiple allergies; (viii) marked airway remodeling.

- Proposed biomarkers to diagnose severe asthma: sputum eosinophils; FENO; basophil activation testing; imaging findings (HRCT, MRI); ‘omics’ analysis in blood, BAL, exhaled breath condensate and urine.

- A patient with uncontrolled asthma may have: (i) unawareness of disease severity; (ii) a physician who is undertreating; (iii) comorbidities (e.g. GERD, obesity, chronic rhinosinusitis, vocal cord dysfunction); (iv) low adherence to treatment; (v) treatment-resistant disease; (vi) an alternative diagnosis.

- ~5% of children with asthma do not benefit with conventional therapy (inhaled corticosteroids, LABA, antileukotrienes) → it is important to develop new therapies.

- Potential therapies for severe asthma: (i) small-particle ICSs and LABAs targeting small airways; (ii) once daily LABAs (e.g. vilanterol); (iii) inhaled long-acting anticholinergics (e.g. tiotropium); (iv) low-dose theophylline (↓ steroid resistance); (v) vit D (immunomodulatory effects); (vi) macrolides (antimicrobial and immunomodulatory action); (vii) antifungal therapy (in patients with fungal sensitization); (viii) inhibitors of kinases; (ix) CRTH2 antagonists (block PGD2 action on TH2 cells, eosinophils and mast cells); (x) biologic therapy; (xi) bronchial thermoplasty (not approved for children <12 yrs of age).

- Biologic therapies for asthma: (i) important for patients who do not respond to conventional therapy; (ii) may benefit specific asthma endotypes/phenotypes (e.g. lebrikizumab in patients with ↑ periostin/IL-13); (iii) ~30 drugs are currently in clinical trials and dozens in development; (iv) outcomes of most trials have been disappointing; (v) main problems: lack of efficacy, high cost, low accessibility, side effects.

- Examples of biologic therapies for asthma: (i) anti-IgE mAb: omalizumab (the only FDA-approved biologic to treat asthma), (ii) anti-IL-4Rα mAb: dupilumab (blocks IL-4 and IL-13 pathways), AMG-317; (iii) IL-4Rα antagonist: pitikrinra (blocks IL-4 and IL-13 pathways); (iv) IL-4 trapping agent: altrakincept; (v) anti-IL-5 mAb: mepolizumab, reslizumab; (vi) anti-IL-5R mAb: benralizumab (reduce eosinophil and basophil count); (vii) anti-IL-13 mAb: lebrikizumab, tralokinumab, anrukinzumab; (viii) anti-TNF-α therapies: etanercept, infliximab, adalimumab, golimumab (risk of severe side effects); (ix) TLR7 agonists: imiqimod, resiquimod; (x) TLR9 agonist: QbG10.

- Asthma is a complex clinical syndrome with multiple genotypes, endotypes and phenotypes → it is very unlikely that there is one “magic bullet” to cure all patients with asthma.

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

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.

- **Asthma:** (i) most common chronic respiratory disease in childhood; (ii) multifactorial disease (genetic susceptibility + environmental burden + epigenetics); (iii) features: airway inflammation, bronchial hyperreactivity, reversible airway obstruction, airway remodeling; (iv) typical symptoms: cough, wheezing, breathlessness, chest tightness; (v) **airway remodeling** is regularly observed in asthmatic adults (severity-dependent); (vi) remodeling may start **early in life**.

- **Features of airway remodelling:** (i) ↑ mucus-secreting cells, (ii) basement membrane (BM) thickening, (iii) subepithelial fibrosis, (iv) ↑ extracellular matrix, (v) smooth muscle hypertrophy and hyperplasia, (vi) ↑ vascularity, (vii) epithelial-mesenchymal transition.

- Authors show that **remodeling** (BM thickening; subepithelial deposition of laminin and collagen IV) can start at an early age even **before clinical presentation of asthma**.

- **Author’s commentaries:** (i) slight epithelial defects can induce inflammatory and proliferative processes in deeper parts of the bronchial mucosa; (ii) BM thickening may be the 1st change in the bronchial mucosa of children predisposed to asthma (target for early treatment).


  - **Control of Allergic Rhinitis and Asthma Test for Children (CARATKids):** the 1st questionnaire that assesses simultaneously allergic rhinitis and asthma control in children.

  - Authors suggest that the questionnaire **CARATKids** is ready to be used in clinical practice.