General considerations:

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

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

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

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

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June 2014 – content:


- **A PHENOTYPE-BASED CLASSIFICATION OF NSAIDs HYPERSENSITIVITY: NEW PATIENTS, NEW CHALLENGES** (Quiralte J, Ávila-Castellano R, Cimbollek S. Allergy 2014; 69: 814–816).


- **HUMAN ALBUMIN CAUSES ANAPHYLAXIS DURING BEE VENOM IMMUNOTHERAPY** (Nakonechna A, Abuzakouk M. Ann Allergy Asthma Immunol 2014; 112: 559–560).

- **HYPEREOSINOPHILIC SYNDROME** (Hsieh FH. Ann Allergy Asthma Immunol 2014; 112: 484–488).
• PRIMARY IMMUNODEFICIENCY DISORDERS: GENERAL CLASSIFICATION, NEW MOLECULAR INSIGHTS, AND PRACTICAL APPROACH TO DIAGNOSIS AND TREATMENT (Ochs HD, Hagin D. Ann Allergy Asthma Immunol 2014; 112: 489-495).

• PROPERDIN DEFICIENCY-ASSOCIATED BRONCHIECTASIS (Wu Lee JX, Yusin JS, Randhawa I. Ann Allergy Asthma Immunol 2014; 112: 557-559).


ALLERGY:


  - **Angioedema:** (i) definition: localized and self-limiting edema of subcutaneous and submucosal tissue; (ii) cause: release of vasoactive mediators → temporary increase in vascular permeability; (iii) it can accompany urticaria (wheals) or present alone (no wheals); (iv) EAACI new classification of angioedema (does not include urticaria with angioedema) distinguishes 3 hereditary types and 4 nonhereditary types.

  - **Acquired angioedema (AAE):** (i) idiopathic histaminergic AAE (IHAAE): improves with antihistamines, no underlying cause is identified; (ii) idiopathic nonhistaminergic AAE (InH-AAE): antihistamine-refractory (4x dose); (iii) AAE related to angiotensin-converting enzyme inhibitors (ACEI-AAE): occurs in <1% of treated subjects; (iv) AAE with C1-INH deficiency (C1-INH-AAE): associated with underlying lymphoproliferative or autoimmune diseases.

  - **Hereditary angioedema (HAE):** (i) HAE with C1-INH deficiency (C1-INH-HAE): type I and type II; (ii) HAE with FXII mutation (FXII-HAE): autosomal dominant trait with low penetrance; (iii) HAE of unknown origin (U-HAE): similar to FXII-HAE but with no FXII mutations.

  - **Diagnosis of angioedema:** (i) clinical history (patient's age, sex and ethnicity; age of onset, site, duration and frequency of attacks; use of drugs); (ii) family history; (iii) analysis of complement proteins (C4, C1q, C1-INH level and function); (iv) genetic testing (SERPING1, F12); (v) testing for underlying diseases (e.g. autoimmune and lymphoproliferative diseases in C1-INH-AAE).

  - **Drugs to treat angioedema** (mostly studied in C1-INH-HAE): (i) plasma-derived or recombinant human C1-INH; (ii) ecallantide: inhibitor of kallikrein; (iii) icatibant: BK type 2 receptor antagonist; (iv) attenuated androgens (e.g. danazol); (v) tranexamic acid: agent of choice for prophylaxis in children, rarely contraindicated (e.g. in thrombophilia); (vi) freshly frozen plasma.


  - **IgE-mediated food allergy (FA):** (i) rising prevalence worldwide (6% of children and 4% of adults in the westernized world); (ii) etiology: genetic factors (currently not modifiable), environmental/exposure factors (targets for prevention); (iii) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (iv) >170 foods have been reported to cause allergic reactions; (v) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soy, seafood; (vi) diagnosis: specific IgE detection by SPT or in vitro testing (serum sIgE, component-resolved diagnosis), basophil activation test, food challenge (gold standard); (vii) 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); (viii) optimal treatment: restore tolerance by exposing patients to gradually increasing doses of allergen (immunotherapy).

- **Recommendations for primary prevention of FA:** (i) exclusive breastfeeding for the first 4-6 months of life; (ii) no special dietary restrictions for pregnant or lactating mothers; (iii) use of hypoallergenic formula if breastfeeding is insufficient in high-risk infants up to 4 months of age (then a standard milk can be used); (iv) introduction of complementary foods after 4 months of age, irrespective of atopic heredity; (v) no special dietary restrictions after 4 months for age, irrespective of atopic heredity.

- **Gaps in the evidence:** (i) effect of weaning timing; (ii) effect of introduction of different food antigens while breastfeeding vs while not breastfeeding; (iii) effect of maternal nutrition and environmental exposures during pregnancy and lactation on FA development in the child; (iv) preventive effect of different hydrolyzed formulas on FA including long-term effects; (v) effect of prebiotics and probiotics on the incidence and prognosis of FA.


  - Hypersensitivity diseases: (i) include asthma, rhinitis, anaphylaxis, drug, food, and insect hypersensitivity, eczema, urticaria and angioedema; (ii) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (iii) are not adequately coded in the International Coding of Diseases (ICD)-10 → misclassification → ↓ disease visibility, ↓ accuracy of official statistics.

  - Advantages of a good classification and coding of diseases: (i) improves communication between clinicians and patients; (ii) facilitates research; (iii) improves accuracy of disease statistics; (iv) improves communication with payers.

  - EAACI–WAO classification of hypersensitivity diseases: (i) appears to be easier and more accurate in the daily practice than ICD-10 classification; (ii) can be useful for the WHO to improve the revised ICD-11.


  - Asthma: (i) most common chronic respiratory disease; (ii) affects 300 million people worldwide; (iii) incidence is rising; (iv) multifactorial etiology: genetic susceptibility, environmental burden, epigenetics; (v) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (vi) features: airway inflammation, bronchial hyperreactivity, reversible airway obstruction, airway remodeling; (vii) typical symptoms: cough, wheezing, breathlessness, chest tightness; (viii) TH2-mediated inflammation occurs in ~80% of asthma cases (allergic asthma: ↑ production of IL-4, IL-5, IL-9 and IL-13; ↑ IgE synthesis; attraction of innate effector cell populations including eosinophils, mast cells and basophils).

  - Basophils: (i) represent <1% of blood leukocytes; (ii) participate in TH2 responses and IgE-mediated allergies; (iii) other potential functions: allergy initiation, antigen presentation, defence against ectoparasites.
• **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; (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) protocols recommend patient observation of 2 hrs for the first 3 doses and 30 min for subsequent doses (due to anaphylaxis risk in patients with severe asthma); (vii) efficacy has also been documented in mastocytosis, anaphylaxis (idiopathic; exercise-induced), eosinophilic chronic rhinosinusitis, atopic dermatitis.

• Authors show that **omalizumab** therapy reduced circulating basophil numbers in children with severe asthma.


  • **Food allergy (FA):** (i) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (ii) etiology: genetic factors (currently not modifiable), environmental factors (targets for prevention).

  • Authors performed a systematic review about the efficacy of different approaches to prevent FA development in children and adults → 74 studies were included (high heterogeneity; 1/3rd of studies were of high quality) → there is much still to learn.

  • Recommended approaches: (i) substituting cow’s milk by extensive or partially hydrolyzed casein or whey formulas for high-risk infants during the first 4 months of life; (ii) combining dietary and environmental modifications during infancy.

  • Approach with mixed results: breastfeeding for infants at high or normal risk.

  • Approaches with insufficient evidence: (i) changing diet of pregnant or breastfeeding women; (ii) giving supplements (e.g. fish oil, probiotics) to pregnant or breastfeeding women; (iii) using soy-based formula instead of cow’s milk; (iv) giving probiotics and probiotics to infants; (v) delaying the introduction of solid foods beyond 4 months of life; (vi) different strategies to prevent FA in older children or adults (e.g. BCG vaccination; supplements of fish oil and vitamins).
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ALLERGY (June issue):

- **A PHENOTYPE-BASED CLASSIFICATION OF NSAIDs HYPERSENSITIVITY: NEW PATIENTS, NEW CHALLENGES** (Quiralte J, Ávila-Castellano R, Cimbollek S. Allergy 2014; 69: 814–816):
  - Hypersensitivity to NSAIDs: (i) Non immune-mediated hypersensitivity: pharmacologic mechanism (inhibition of COX-1); cross-reactivity between COX-1 inhibitors; reactions include respiratory and/or cutaneous manifestations (e.g. aspirin-exacerbated respiratory disease); higher prevalence than allergy. (ii) Immune-mediated hypersensitivity (allergy): immunologic mechanisms (e.g. IgE- or T-cell-mediated); selective reactivity; less frequent than intolerance.
  - NSAIDs hypersensitivity clinical entities: (i) acute urticaria/angioedema induced by NSAIDs (cross-reactive); (ii) chronic urticaria/angioedema exacerbated by NSAIDs (cross-reactive); (iii) respiratory hypersensitivity induced by NSAIDs (cross-reactive); (iii) allergy to NSAIDs (immediate and delayed reactions).
  - Authors propose a new clinical entity within nonimmune-mediated NSAID hypersensitivity – isolated periorcular angioedema: (i) bilateral or unilateral angioedema minutes to hours after using COX-1 inhibitors; (ii) more frequent in children and young adults; (iii) concomitant respiratory allergies are common (mainly to house dust mites); (iv) patients have increased risk of allergic reactions after eating mite-contaminated food (mite ingestion reaction syndrome).

  - Anaphylaxis: (i) definition: acute life-threatening systemic hypersensitivity reaction; (ii) lifetime prevalence: 0.05-2%; (iii) mechanisms: release of mediators from mast cells and basophils (IgE-mediated, IgG-mediated, complement mediated, idiopathic); (iv) most common culprits: foods, drugs, hymenoptera venom, latex; (v) factors that influence severity: pathogenic mechanism, allergen properties and dose, route of exposure, degree of sensitization, affinity of sIgE, presence of cofactors; (vi) augmentation factors: exercise, alcohol, infections, NSAIDs, drugs, menses, stress; (vii) diagnosis: clinical history (NIAID/FAAN criteria: sensitivity=96.7%, specificity=82.4%), measurement of allergy mediators (e.g. serum tryptase, serum/urinary histamine or metabolites, serum PAF), allergy testing (e.g. sIgE detection by skin and in vitro tests); (viii) biphasic anaphylactic reactions (recurrent anaphylactic symptoms after resolution of the primary event) may occur in up to 20% of reactions; (ix) treatment in the acute setting: epinephrine (1st line therapy), antihistamines, corticosteroids, β2-agonists, oxygen, intravenous fluids; (ix) long-term management: allergen avoidance, epinephrine autoinjectors, immunotherapy (e.g. for venom-induced anaphylaxis).
  - Authors analyzed retrospectively 532 episodes of anaphylaxis presenting to the emergency department of a tertiary care hospital → (i) there were 507 uniphasic and 25 (4.5%) biphasic reactions; (ii) 12 biphasic reactions were clinically important (2 occurred during hospital stay; 1 required transfer to ICU for shock); (iii) there were no deaths; (iv) no risk factors for biphasic reactions could be detected.

Chronic urticaria (CU):

(i) Definition: recurrent wheals for >6 wks due to liberation of vasoactive mediators (e.g. histamine, serotonin, C3a, C5a, platelet-activating factor, neuropeptides, arachidonic acid metabolites [PGD2, LTC4, LTD4, LTE4]).

(ii) Lifetime prevalence: 1-20% of the population.

(iii) Impact: significant morbidity, ↓ QoL (similar to angina pectoris), high costs.

(iv) Classified in 2 types (both can co-occur in the same patient): spontaneous (CSU; no clear triggers; 50% of cases have ‘autoimmune’ features [IgG1/IgG3 to FcεRIα or IgE; ↑ frequency of HLA DRB1*04]; coagulation, fibrinolysis and complement systems may have a role in pathogenesis; wheals usually last between 4 and 24 hrs; concomitant angioedema may occur in ~50% of cases); inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise; wheals usually last <2 hrs after stimuli ceases, except for delayed pressure urticaria [similar to CSU wheals]).

(v) 1st-line treatment: nonsedating anti-H1 at usual dosing (50% of patients may not respond).

(vii) 2nd-line treatment: up to quadruple dose of anti-H1, such as desloratadine or levocetirizine (50% of patients may not respond → antihistamine-refractory CU).

(viii) Other therapies: mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, topical corticosteroids, systemic corticosteroids (3-10 days to control severe exacerbations; risk: side effects; key to success: limit the dose to a maximum of 20 mg every other day or 10-15 mg daily with subsequent dose tapering), biologic therapies (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A (only FDA-approved immunosuppressant drug for CU; side effects: ↑ blood pressure, renal damage; renal function reverts to normal within 4 to 6 wks after drug stopping), sulfasalazine, dapsone, colchicine (colchicine, dapsone or sulfasalazine are reasonable choices for neutrophilic CSU), chloroquine, hydroxychloroquine (may have particular efficacy for the hypocomplementemic urticarial vasculitis syndrome), calcineurin inhibitors, mycophenolate, pseudoallergen-free diet, anticholinergics, androgens, selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants.

(ix) Prognosis: 50% of cases may resolve spontaneously within 1 yr; 75% of cases within 5 yrs.

CU and coagulation: (i) coagulation and inflammation activate each other; (ii) coagulation factors, mainly tissue factor and thrombin, may participate in CU pathophysiology (whether activation of coagulation is a primary phenomenon or a secondary process enhancing or maintaining inflammation is controversial); (iii) mechanisms: activation of eosinophils (e.g. by IL-5, eotaxin, TNF-α, PAF, GM-CSF or autoimmune to FceRII) → eosinophils produce tissue factor and VEGF → blood coagulation extrinsic pathway is activated → thrombin is generated → thrombin acts on protease-activated receptors and activates C5 directly → endothelial cells and mast cells are activated, mast cells amplify the loop by producing tryptase (↑ thrombin generation) → ↑ vascular permeability; (iv) it is unclear if patients with CU and ↑ coagulation are at higher risk of thrombosis or CV disease; (v) D-dimer: a fibrin degradation product, can ↑ during urticaria crisis and normalize during remission, can be a biomarker of antihistamine-refractory CU; (vi) anticoagulant therapy: may benefit CU patients, especially those with increased levels of coagulation/vascular biomarkers (e.g. D-dimer, prothrombin fragment F1 +
2. FVIIa, fibrinogen, VEGF); successful reports with oral anticoagulants, heparin, protease inhibitors (nafamostat mesylate, camostat mesylate) and nadroparin + tranexamic acid.

- **Other conditions with ↑ levels of coagulation biomarkers:** urticarial vasculitis, bullous pemphigoid, atopic dermatitis, multiple drug allergy syndrome, nonallergic asthma.

**NATURAL EVOLUTION OF SKIN-TEST SENSITIVITY IN PATIENTS WITH IGE-MEDIATED HYPERSENSITIVITY TO CEPHALOSPORINS** (Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quaratino D. Allergy 2014; 69: 806–809):

- **β-lactams:** (i) antibiotic drugs that have the β-lactam ring; (ii) inhibit the synthesis of the bacterial membrane; (iii) include penicillins (PNCs), cephalosporins, carbapenems and monobactams; (iv) to April 2013, FDA had approved >34 β-lactams for human use; (v) European registry of drug-induced severe anaphylaxis (2002-2010) → 42.6% of cases were caused by penicillins and cephalosporins; (vi) most patients receiving PNCs or cephalosporins will produce specific IgG and IgM antibodies without experiencing any adverse reaction.

- **Cephalosporins:** (i) discovered by Giuseppe Brotzu in 1945 (cephalosporin C) from the fungus *Cephalosporium;* (ii) 1964 → cephalothin was marketed (1st semisynthetic cephalosporin); (iii) early cephalosporins (mid-1960s to mid-1980s): modification of the 5-membered thiazolidine ring attached to the β-lactam ring of PNC to a 6-membered dihydrothiazine ring → minor contamination by PNC; (iv) 1st-generation cephalosporins: modification of the R1 site of the basic cephalosporin structure; (v) from 2nd- to 5th-generation cephalosporins: modification at the R1 and R2 sites (objectives: ↑ activity against different bacteria, ↑ duration of action); (vi) cephalosporin side chains usually remain intact in the body (major factor for cross-reactivity between cephalosporins and PNCs).

- **IgE-mediated cephalosporin allergy:** (i) rate of anaphylaxis to cephalosporins=0.1-0.0001%; (ii) the value of skin testing with cephalosporins to predict allergy is not well established (parenteral compounds should be used; when there is no parenteral presentation available, the allergist can choose a related compound based on side chain similarity [e.g. oral cefuroxime axetil → parenteral cefuroxime]); (iii) there are more reported cases of anaphylaxis to cephalosporins in patients without a known PNC allergy compared to those with known PNC allergy; (iv) cephalosporin allergy in a PNC-allergic patient might be completely coincidental; (v) allergy to cephalosporins is caused mainly by reactions to the side chains of the molecules and less commonly to the β-lactam ring; (vi) cephalosporin allergy does not occur in ~10% of PNC allergic patients (old information from 1960s-1970s): cross-reactivity between PNCs and cephalosporins (mostly 1st-generation) are due mainly to similar R1 side chains (e.g. cephalaxin and ampicillin; cephadroxile and amoxicillin) or similar biosostere properties (e.g. PNC G and cephalothin); cross-allergy is negligible with 2nd- and later generation cephalosporins (distinct side chains from PNCs); (vii) cephalosporin allergy does not cross all cephalosporin generations: cross-reactivity depends on the similarity between the side chains; (viii) aztreonam and ceftazidime share an identical side chain (cross-reactivity).

- **Patients with IgE-mediated PNC allergy** may lose skin sensitivity over time if culprit drugs are avoided (up to 50% of patients may lose skin test-positivity 1 yr after the initial testing).

- **Authors followed up (for 5 yrs) 72 patients (13-80 yrs old) with confirmed IgE-mediated allergy to cephalosporins → group A (n=16): allergy to both PNCs and cephalosporins; group B (n=56): allergy only to cephalosporins → skin tests and serum-specific IgE assays were
repeated at 1 yr and, in case of persistent positivity, at 3 and 5 yrs after the 1st allergologic examination → (i) of all subjects, 49 (68.1%), 36 (50%) and 26 (36.1%) continued to have positive skin tests after 1, 3 and 5 yrs, respectively; (ii) 7 (43.7%) patients of group A became negative (2 after 1 yr; 2 after 3 yrs; 3 after 5 yrs); (iii) 38 (67.8%) patients of group B became negative (21 after 1 yr; 11 after 3 yrs; 6 after 5 yrs); (iv) group B patients became negative sooner and more frequently than group A subjects; (v) patients with a time interval <12 months between the last hypersensitivity reaction and the 1st allergologic evaluation became negative sooner and more frequently than patients with a time interval ≥12 months.

• Author’s commentary: >60% of subjects with IgE-mediated cephalosporin allergy may lose skin-test positivity over time → negative skin-test results in a patient with positive clinical history should be correctly interpreted → resting after 2-4 wks should be considered.


• The majority of patients seeking medical advice for allergic diseases are first seen in a primary care setting → authors give recommendations for allergy management in the primary care (allergic rhinitis, asthma, food allergy, urticaria/angioedema and contact allergy).
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

• ELECTRONIC CIGARETTES: NAVIGATING THE VAPOR (Nickels AS, Joshi AY, Dinakar C. Ann Allergy Asthma Immunol 2014; 112: 481-483):

  - Electronic cigarettes (e-Cigarettes): (i) novel nicotine delivery systems with similar look and handheld feel of traditional cigarettes; (ii) its use has markedly increased (sales in the US were projected to reach $1.7 billion in 2013); (iii) 3 essential components: a liquid cartridge (containing varying concentrations of nicotine and flavoring [e.g. tobacco, menthol, fruits]), an atomizer, and a battery; (iv) potential advantages: ↓ nicotine addiction, ↓ tobacco use; (v) limitations: safety and efficacy are not fully defined; (vi) potential risks: overestimation of safety and efficacy, addiction, indiscriminate use (including by young people; flavors are tempting), presence of carcinogens, inappropriate marketing, mining of tobacco cessation efforts; (vii) nicotine delivery from e-Cigarettes is variable and incompletely understood.

  - Recommendations: (i) high-evidence research on efficacy and safety of e-Cigarettes; (ii) better regulation by federal agencies and legislation; (iii) restricting its advertising and use in public.

• HUMAN ALBUMIN CAUSES ANAPHYLAXIS DURING BEE VENOM IMMUNOTHERAPY (Nakonechna A, Abuzakouk M. Ann Allergy Asthma Immunol 2014; 112: 559-560):

  - Venom immunotherapy (VIT): (i) well-established treatment for patients with a history of hymenoptera venom anaphylaxis; (ii) adverse reactions during VIT can occur.

  - Authors report the case of a 47-yr-old male beekeeper with bee venom allergy → after ~2.5 yrs of uneventful bee VIT, the patient had 2 episodes of anaphylaxis (6 wks apart) 10-15 min after receiving his VIT maintenance dose (100 mg/mL) → allergy testing: normal baseline tryptase; negative sIgE to ethylene oxide and latex; negative SPT to the diluent containing human serum albumin (HSA) and phenol; negative SPT to HSA, phenol and mannitol; immediate anaphylaxis after intradermal testing with the diluent (0.003 mg/mL of HSA, 0.04 mg/mL of phenol); negative intradermal testing with phenol and mannitol; immediate anaphylaxis after intradermal testing with HSA (5 mg/mL) → final diagnosis: anaphylaxis to HSA → VIT was discontinued.

  - Possible mechanisms of anaphylaxis in the patient: (i) sensitization to a contaminant in the HSA preparation; (ii) sensitization to a HSA epitope (after post-translational modification); (iii) formation of IgG immune complexes.

  - Author’s commentaries: (i) 1st report of anaphylaxis to HSA during bee VIT; (ii) albumin allergy should be considered in patients with unexplained allergic reactions during VIT.

• HYPEREOSINOPHILIC SYNDROME (Hsieh FH. Ann Allergy Asthma Immunol 2014; 112: 484-488):

  - Hypereosinophilic syndrome (HES): (i) heterogeneous disease characterized by persistent blood eosinophilia and eosinophil-induced organ damage; (ii) several phenotypes have been identified; (iii) in most cases the molecular pathogenesis is unknown (idiopathic).

  - Original definition (Chusid et al, 1975): (i) peripheral blood eosinophilia (>1,500 cells/µL) for >6 months; (ii) evidence of eosinophil-related organ damage; (iii) exclusion of other diseases causing eosinophilia.
• Proposed definition: (i) peripheral blood hypereosinophilia (>1,500 cells/µL) for ≥1 month checked on ≥2 occasions, and/or tissue hypereosinophilia (eosinophils comprising >20% of nucleated cells in the bone marrow; extensive organ infiltration determined by histology; histologic evidence of eosinophil degranulation in a target organ [e.g. major basic protein] in the absence of tissue eosinophils); (ii) evidence of eosinophil-mediated organ damage (generally multorgan system involvement as opposed to single system disease [e.g. GI eosinophilic diseases, eosinophilic myocarditis]); (iii) exclusion of other causes of hypereosinophilia.

• Classification: (i) primary HES: clonal expansion of an eosinophil lineage cell due to a primary eosinophil defect (e.g. myeloproliferative variant HES associated with PDGFRA fusion kinase (~15% of HES cases); other mutations in PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, ASCSL6, MYH11, ABDL and KIT [beyond PDGFRA, the other defects likely comprise <1% of HES cases]); (ii) secondary HES: polyclonal eosinophil expansion due to cytokines released by another disease (e.g. malignancy, lymphoproliferative disease, clonal nonmalignant T cells [e.g. lymphocytic variant HES]); (iii) familial HES: hypereosinophilia inherited in an autosomal dominant pattern (rare, typically asymptomatic, linkage to chromosome 5q31-33); (iv) overlap HES: hypereosinophilia with single-organ system involvement (e.g. eosinophilic GI disease, pulmonary eosinophilia syndromes, eosinophilic fasciitis, eosinophilic myocarditis); (v) HES with undetermined significance: hypereosinophilia with no target organ damage (progression to organ damage is not well defined); (vi) idiopathic HES (up to 50% of cases): undetermined molecular defect and mechanism despite thorough evaluation.

• Clinical presentation: (i) HES can affect nearly every organ system (CV system, nervous system, skin, lungs, GI tract, eye, blood/coagulation, etc.); (ii) symptoms can appear insidiously or acutely; (iii) lymphocytic variant HES has more tendency to cause skin symptoms (e.g. urticarial plaques, angioedema, erythroderma); (iv) myeloproliferative variant HES has more tendency to cause mucosal ulcerations, anemia, splenomegaly, hepatomegaly and fibrotic disease (especially in the heart).

• Treatment: (i) PDGFRA-associated myeloproliferative variant HES → tyrosine-kinase inhibitor imatinib mesylate; (ii) all other forms of HES → corticosteroids (generally 1st-line therapy), steroid-sparing agents (hydroxyurea, interferon α-2b, methotrexate, vincristine, cladribine, cytarabine, cyclophosphamide, etoposide, chlorambucil); (iii) refractory patients → HSCT, investigational agents (mepolizumab [anti-IL-5 mAb], alemtuzumab [anti-CD52 mAb]).

• Future challenges: (i) evidence-based refinements in nomenclature and diagnostic criteria; (ii) recognition of biomarkers to identify HES phenotypes and predict disease evolution; (iii) development of mechanism-based therapeutics for general clinical use.

• PRIMARY IMMUNODEFICIENCY DISORDERS: GENERAL CLASSIFICATION, NEW MOLECULAR INSIGHTS, AND PRACTICAL APPROACH TO DIAGNOSIS AND TREATMENT (Ochs HD, Hagin D. Ann Allergy Asthma Immunol 2014; 112: 489-495):

• 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.
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.

- 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 staphylo cocci or Gram-negative bacteria ('Fatal granulomatous' syndrome → chronic granulomatous disease).

Primary immunodeficiency diseases (PIDs): (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 subjects; (iii) impact: severe complications (infections, autoimmunity, immune dysregulation, allergies, autoinflammation), ↓ QoL, mortality risk, high costs; (iv) early diagnosis and treatment can be lifesaving; (v) Jeffrey Model Foundation PID warning signs are useful for general alert of PIDs; (vi) recognizing which part of the immune system is primarily affected, even in the absence of a definitive diagnosis, is important for selecting initial treatment; (vii) except for patients with SCID or severe life-threatening immune dysregulation, most cases of PID can be initially treated with immunoglobulin replacement therapy, prophylactic antibiotics and/or immunosuppressive drugs, while searching for a definitive diagnosis; (viii) genetic diagnosis is usually important for specific therapy, prognosis and genetic counseling; (ix) when indicated, definite therapy of severe PIDs (e.g. HSCT) 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 usually performed 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).

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 challenging; (vi) promising tool for early diagnosis and treatment of PID in patients presenting with a 1st episode of severe infection (PID screening).

The last IUIS update (2013) lists more than 250 known PIDs, classifying them in 9 categories (some genotypes can lead to phenotypes that fit in >1 category [e.g. CD40 ligand deficiency is classified as both antibody deficiency and CID]): (i) combined immunodeficiencies (CID); (ii) CID with associated or syndromic features; (iii) predominantly antibody deficiencies; (iv) diseases of immune dysregulation; (v) congenital defects of phagocyte number, function, or both; (vi) defects that involve innate immunity; (vii) autoinflammatory disorders; (viii) complement deficiencies; (ix) phenocopies of PIDs (conditions that resemble PIDs and are not due to germline mutations [e.g. autoantibodies against IL-17, somatic mutations in FAS]).

Novel PIDs: (i) CARD11 gene mutations: agammaglobulinemia, profound defective T-cell function despite normal T- and B-cell counts; (ii) PIK3CD gene gain-of-function mutations: recurrent sinopulmonary infections, bronchiectasis, susceptibility to EBV and CMV,
lymphadenopathy, splenomegaly, variable antibody levels, abnormal responses to polysaccharide vaccines, abnormal B-cell and T-cell phenotyping; (iii) IL-21 receptor deficiency: susceptibility to Cryptosporidium infection and chronic cholangitis, recurrent respiratory infections; (iv) TCF3 gene mutations (deficiency of the transcription factor E47): autosomal dominant agammaglobulinemia, differentiation block at the common lymphoid precursor stage; (v) PRKCD gene mutations (deficiency of protein kinase Cδ): CVID-like phenotype, recurrent infections, severe autoimmunity, abnormal B-cell phenotyping; (vi) NFKB2 gene mutations: CVID, immune dysregulation (alopecia totalis, autoantibodies, asthma), central adrenal insufficiency; (vii) VPS45 deficiency: congenital neutropenia, neutrophil dysfunction, life-threatening bacterial and fungal infections, myelofibrosis, nephromegaly secondary to extramedullary hematoepoiesis; (viii) STAT2 gene: severe viral infections (disseminated vaccine strain measles, prolonged febrile encephalitis after measles-mumps-rubella vaccine).

- **PIDs associated with an atopic phenotype:** (i) STAT3 mutations in patients with AD hyper-IgE syndrome (HIES); (ii) DOCK8 mutations in patients with AR HIES; (iii) STA5B, FOXP3 or CD25 mutations in patients with severe immune dysregulation (eczema, eosinophilia, autoimmunity, ↑ IgE); (iv) hypomorphic mutations in SCID-associated genes (RAG1/2, IL-7RA, DCLRE1C, ADA, LIG4, RMRP) in patients with Omenn syndrome (erythroderma, eosinophilia, hepatosplenomegaly, lymphadenopathy, ↑ IgE); (v) Kitz type 5 (SPINK5) mutations in patients with Netherton syndrome; (vi) KIT mutations in patients with mastocytosis; (vii) SERPING1 gene mutations in patients with hereditary angioedema secondary to C1-inhibitor deficiency; (viii) recurrent urticaria/angioedema in patients with autoimmune inflammatory syndromes; (ix) phospholipase C, gamma 2 (PLCG2) mutations in patients with familial cold urticaria.

- **Reasons for immune dysregulation and atopy in patients with CID:** (i) weak TCR stimulation → ↑ differentiation of TH2 cells; (ii) weak TCR stimulation → ↓ differentiation of regulatory T cells (which of our atopic patients actually has an underlying hypomorphic PID?).

- **Bousfiha AA et al. (J Clin Immunol. 2013; 33:1078-1087)** → phenotypic approach to help non-PID specialists to evaluate a patient with suspected PID.

- **PROPERDIN DEFICIENCY-ASSOCIATED BRONCHIECTASIS** (Wu Lee JX, Yusin JS, Randhawa I. Ann Allergy Asthma Immunol 2014; 112: 557-559):

  - **Complement system:** (i) complex system of ~30 proteins with a critical role in innate immunity; (ii) functions: killing of microbes, elimination of immunocomplexes; (iii) 3 activation pathways: classic, alternative, lectin.

  - **Properdin:** (i) a basic glycoprotein of 442 aminoacids; (ii) key component of the alternative complement pathway (properdin binds to, stabilizes and amplifies the C3 convertase C3bBb).

  - **Properdin deficiency:** (i) X-linked recessive primary immunodeficiency; (ii) main clinical feature: severe meningococcal infections presenting in the 2nd decade of life (there are reports of recurrent otitis media and pneumonia in children due to nonmeningococcal microbes [e.g. Haemophilus influenzae, Moraxella catarrhalis]); (iii) 3 types: type 1 (the most common; complete absence of properdin), type 2 (subnormal properdin levels [usually 1-10%]), type 3 (the rarest; normal properdin levels but defective function); (iv) carrier females of properdin type 1 deficiency usually have ↓ properdin levels (17-27 mg/L; ~50% of the reference range).
• Authors report the case of a 44-yr-old woman with recurrent sinopulmonary infections from childhood, severe pneumonias with sepsis (positive sputum culture results for Pseudomona, Aspergillus, Fusarium and Stenotrophomonas sp), bronchiectasis, oxygen-dependent chronic lung disease, GERD and hypothyroidism → family history: no suspicion of immunodeficiency in family members → laboratory analysis: normal results of CBC, basic metabolic studies, sweat chloride test, cystic fibrosis genetic panel, α1-antitrypsin testing, nuclear medicine aspiration scan, serum immunoglobulins with tetanus and pneumococcal titers, lymphoproliferation testing, dihydrorhodamine assay, total hemolytic complement assay, C3 protein, C4 protein, C3C level and mannose binding pathway; low activity of alternative pathway (10 mg/dL; reference range: >59 mg/dL); low level of properdin (18 mg/L; reference range: 23-67 mg/L) → final diagnosis: properdin deficiency → follow up: patient’s daughter, with a history of recurrent sinopulmonary infections, was also diagnosed with properdin deficiency at 11 yrs of age.

• Author’s commentaries: (i) 1st reported case of properdin deficiency presenting with chronic sinopulmonary infections, bronchiectasis and absence of meningococcal disease; (ii) evaluation of the complement alternative pathway should be considered in patients with severe chronic respiratory infections.

- Chronic rhinosinusitis (CRS): (i) definition: inflammation of nasal and paranasal mucosa lasting ≥12 wks; (ii) impact: significant morbidity, ↓ QoL, high costs.

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

- Aspirin-exacerbated respiratory disease (AERD): subgroup of CRSwNP characterized by the triad of CRSwNP, asthma and hypersensitivity to NSAIDs.

- Basophils: (i) physiologic role in defense against helminths and ectoparasites; (ii) pathologic role in allergic diseases; (iii) numbers are increased in asthma (bronchial mucosa and submucosa), allergic rhinitis (nasal submucosa) and inflammatory skin diseases (e.g. eczema).

Authors evaluated the presence of basophils in nasal polyps (NP) from 10 patients with AERD and 17 patients without AERD, and in uncinate tissue (UT) from 16 patients with CRSwNP, 15 patients with CRSsNP and 15 control cases → (i) UT from CRS patients had a trend toward higher basophil numbers than UT from controls; (ii) NP from patients without AERD had significantly higher basophil numbers than UT from patients and controls; (iii) NP from patients without AERD had significantly higher basophil numbers than NP from patients with AERD.

Author's commentary: basophils may play a pathogenic role in patients with CRS, especially in those with CRSwNP without AERD.


- Allergic transfusion reactions (ATRs): (i) frequent complication after transfusion of blood components; (ii) occur in ~2% of platelet transfusions; (iii) mechanisms are poorly understood (e.g. recipient’s antibodies to donor’s plasma proteins; recipient’s IgE antibodies to food or drug proteins in the donor blood); (iv) often occur intermittently in a same recipient (inconsistent with hypersensitivity to a ubiquitous plasma protein); (v) can result in anaphylaxis.

Authors performed a study to determine the natural history of and risk factors for ATRs after single donor apheresis platelet transfusions → (i) ATRs resembled IgE-mediated allergic reactions both clinically and biochemically; (ii) recipient atopy, particularly hay fever, was a risk factor for ATRs; (iii) donor atopy was not associated with ATRs; (iv) ATR rates decreased with increasing transfusion exposure (desensitization?).

Author’s commentary: antihistamines and antileukotrienes may help to prevent ATRs in recipients with risk factors (e.g. hay fever, previous ATRs).
  
  • Immune tolerance: nonresponsiveness of the adaptive immune system or active regulatory cell response to antigens.

  • 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 via the nasopharyngeal mucosa in genetically susceptible subjects → specific TH2 responses to aeroallergens → IgE-mediated allergic respiratory diseases).

  • Allergen immunotherapy: (i) only therapy that can alter the natural history of IgE-mediated allergy; (ii) conventional routes of administration: subcutaneous, sublingual; (iii) new potential routes of administration: intralymphatic, epicutaneous, intranasal, oral vestibular.

  • Sublingual immunotherapy (SLIT): (i) mechanisms: antigen presentation by tolerogenic mucosal dendritic cells (it is important to keep the allergen 2-3 min under the tongue; passive resorption is considered as the major mucosal crossing factor for peptides) → ↑ T regulatory responses, ↓ TH2 responses → ↑ production of IgG4, IgG1 and IgA, ↓ production of IgE; (ii) advantages: self-administration, convenience, safety; (iii) limitations: very low adherence (56% of patients discontinue SLIT during the 1st year; only 15% of patients complete 3 years of SLIT); (iv) reasons for SLIT discontinuation: cost, side-effects, no perception of efficacy.

  • Oral vestibule (OV) immunotherapy: (i) allergen administration in the pouch formed by lip and gingival mucosa; (ii) potential greater efficacy than SLIT (reasons: the OV region has more tolerogenic DCs and fewer mast cells compared to the sublingual region; allergens in the OV region are less likely to be swallowed too early; no major salivary ducts drain into the OV region → dilution of allergen is reduced).

  • Authors performed a multicenter, parallel-group, 1:1 randomized noninferiority phase II trial in 72 adults with allergic rhinoconjunctivitis induced by birch pollen → OV immunotherapy was noninferior than SLIT regarding immunologic responses (e.g. levels of specific IgE-blocking factor, specific IgE and specific IgG4) and adverse effects up to 36 wks of therapy.

  • Author’s commentaries: (i) the OV region might be a useful administration route for IT; (ii) further studies are necessary to evaluate safety and efficacy of OV immunotherapy before widespread clinical use.

• **LOWER VITAMIN D STATUS IS CLOSELY CORRELATED WITH ECZEMA OF THE HEAD AND NECK** (Noh S, Park CO, Bae JM, Lee J, Shin JU, Hong CS, Lee KH. J Allergy Clin Immunol 2014; 133: 1767-1770):

  • 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) pathogenic factors: ↓ skin barrier, immune dysregulation, sensitization to foods, microbial molecules or self antigens.
• **Vit D:** (i) regulates calcium, phosphorus and bone metabolism; (ii) regulates growth and differentiation of multiple cell types; (iii) protective effects in obesity, cancer, CV disease, immune function and maternal/fetal health; (iv) serum 25-hydroxyvitamin D (25-OH vit D) is the best marker to assess vit D status; (v) 50-90% of vit D is derived from skin exposed to sunlight; (vi) 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; (vii) 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.

• Authors measured serum 25-OH vit D levels in 82 patients with AD, 38 patients with asthma and 49 healthy controls → (i) AD patients had significantly lower vit D levels compared with asthma patients and controls; (ii) vit D levels were inversely associated with the total body area affected by eczema; (iii) eczema of the head and neck was the most significant factor affecting vit D levels, followed by eczema of the lower limb; (iv) vit D levels were not associated with AD severity, asthma severity and serum IgE levels.

• Author’s commentaries: (i) vit D deficiency in AD patients might be related to its impaired production in the skin (especially when areas normally exposed to sunlight, such as the head and neck, are affected); (ii) further studies are required to validate this theory.


  - **Deducator of cytokinesis 8 (DOCK8)** encodes a guanine nucleotide exchange factor that coordinates the actin cytoskeleton response to mitogenic and chemokine signals.
  
  - **DOCK8 deficiency:** (i) results in combined immunodeficiency; (ii) clinical features: severe viral infections (especially by HSV, VZV, HPV, molluscum contagiosum virus and JC viruses), fungal and bacterial infections, severe allergies, cancer susceptibility (e.g. squamous cell carcinoma, lymphoma); (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ DC migration, ↓ production of antiviral cytokines, impaired TLR/MyD88 pathway, lymphopenia, ↓ T-cell chemotaxis, ↓ T-cell activation, ↓ T-cell survival, ↓ T-cell and B-cell memory, ↓ CD8+ T-cell and NK-cell cytotoxicity, ↓ germinal center formation, ↓ germinal center B cells, ↓ antibody production, impaired lymphoproliferation to antigens; (iv) only curative treatment: HSCT.
  
  - **Interferon α (IFN-α):** (i) critical effector in antiviral immunity; (ii) mechanisms: ↓ viral replication, recruitment of antiviral immune cells, ↑ cross-presentation of viral antigens to CD8+ T cells, ↓ TH2-cell differentiation, ↑ NK-cell cytotoxicity, ↑ TLR9/MyD88-independent B-cell activation; (iii) plasmacytoid dendritic cells (pDCs) are the major IFN-α producing immune cells; (iv) previous reports showed IFN-α efficacy to treat HPV and HSV infections in DOCK8 patients.
• Authors report the case of two 68-year-old patients with **DOCK8 deficiency** and severe, progressive oral herpes labialis infection refractory to therapy with acyclovir, valacyclovir and topical pegylated IFN-α 2b → laboratory analysis: profound deficiency of pDCs (identified by the markers CD123 and BDCA4), ↓ IFN-α production by PBMCs and per cell after stimulation with CpG-A DNA → successful therapy: long-term therapy with subcutaneous pegylated IFN-α 2b.

• Author’s commentaries: (i) patients with **DOCK8 deficiency** can have ↓ pDC numbers and ↓ IFN-α production; (ii) **systemic IFN-α therapy** may be beneficial for DOCK8-deficient patients with viral infections unresponsive to conventional antiviral therapies.


  • **Asthma:** (i) definition: chronic inflammatory respiratory disease characterized by small airways inflammation, hyperresponsiveness, obstruction and remodeling; (ii) cornerstone of therapy: inhaled glucocorticoids (GC) and β2-adrenergic receptor agonists; (iii) some asthma patients do not respond to high-dose GC treatment (GC-resistant asthma); (iv) mechanisms of GC-resistance: ↑ expression of NFκB and AP-1, ↑ expression of the isoform GC receptor beta (GRβ), ↓ expression of histone deacetylase, polymorphisms in IL10, vit D deficiency.

  • **Vitamin D:** (i) calcitriol (1,25-dihydroxyvitamin D3) is the active form; (ii) hypovitaminosis D has been associated with ↑ occurrence and severity of asthma.

  • **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.

  • Authors performed a proof-of-concept RCT (low power) to evaluate the effect of calcitriol (0.25 µg twice/day for 4 wks) in patients with **GC-resistant severe asthma** → (i) calcitriol therapy modestly improved **clinical GC responsiveness**; (ii) there were no serious adverse events.

  • Author’s commentary: (i) calcitriol may improve clinical response to GC in GC-resistant asthma patients; (ii) further research is necessary to confirm this preliminary clinical data.