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.

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May 2014 – content:


- **CURRENT UPDATE ON CELLULAR AND MOLECULAR MECHANISMS OF HEREDITARY ANGIOEDEMA** (Walford HH, Zuraw BL. Ann Allergy Asthma Immunol 2014; 112: 413-418).


- **INFLUENCE OF β2-ADRENOCEPTOR 16 GENOTYPE ON PROPRANOLOL-INDUCED BRONCHOCONSTRICTION IN PATIENTS WITH PERSISTENT ASTHMA** (Anderson WJ, Short PM, Manoharan A, Lipworth JLR, Lipworth BJ. Ann Allergy Asthma Immunol 2014; 112: 475-476).


- **THERAPY OF CHRONIC URTICARIA: A SIMPLE, MODERN APPROACH** (Kaplan AP. Ann Allergy Asthma Immunol 2014; 112: 419-425).


- **GENETIC VARIATION IN schaflen GENES IN A PATIENT WITH A RECAPITULATION OF THE MURINE Elektra PHENOTYPE** (Recher M, Karjalainen-Lindsberg ML, Lindlöf M, PhDc, Söderlund-Venermo M, Lanzi
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ALLERGY:

  
  - **Adverse drug reaction (ADR):** “any noxious, unintended, and undesired effect of a drug (including excipients) that occurs at doses used for prevention, diagnosis, or treatment” (WHO).
  
  - **Drug hypersensitivity reactions (DHRs):** (i) **definition:** ADRs that clinically resemble allergic reactions; (ii) **frequency:** 15% of all ADRs; (iii) **prevalence:** >7% of the general population; (iv) **impact:** significant morbidity, mortality risk, ↓ QoL, high costs, postmarketing withdrawal of drugs; (v) **almost any drug** can cause DHRs (typically unpredictable); (vi) **diagnosis** (often challenging): detailed clinical history (EAACI/ENDA questionnaire is a useful tool; symptoms are often suggestive, but not necessarily definitive for diagnosis), *in vivo* and *in vitro* allergy tests (few tools are available and validated), **drug challenges** (gold standard); (vii) **therapy:** avoidance of culprit drug, use of alternative drugs, drug desensitization, preparation for unexpected HDRs.
  
  - **Classification of DHRs based on symptom onset:** (i) **immediate:** usually within 1-6 hrs after drug exposure (e.g. IgE-mediated anaphylaxis); (ii) **nonimmediate/delayed:** typically from 1 hr to several days after drug exposure (e.g. delayed urticaria, maculopapular rash, fixed drug eruption, vasculitis, blistering diseases, DRESS syndrome, acute generalized exanthematous pustulosis [AGEP], symmetrical drug-related intertriginous and flexural exanthemas [SDRIFE], hepatitis, nephritis, pneumonitis, cytopenias), several factors influence the timing of symptoms (route of exposure, role of drug metabolites, presence of cofactors [exercise, infections, etc]).
  
  - **Classification of DHRs based on pathogenic mechanism:** (i) **immune-mediated (allergy):** specific antibodies or T cells against a drug or its metabolites; (ii) **non-immune mediated (non-allergic):** no proven immunological mechanism (the ‘term' anaphylactoid is no longer recommended).
  
  - **Suggested pathogenic mechanisms of non-allergic DHRs:** (i) **nonspecific mast cell or basophil degranulation** (e.g. opiates, RCM, vancomycin), (ii) **bradykinin accumulation** (e.g. angiotensin-converting enzyme inhibitors), (iii) **complement activation** (e.g. protamine), (iv) **alteration in arachidonate metabolism** (e.g. NSAIDs), (v) **pharmacological action inducing bronchospasm** (e.g. β-blockers, sulfur dioxide released by pharmaceutical formulations containing sulfites).
  
  - **Classification of drug allergy based on pathogenic mechanism:** type I: IgE-mediated (e.g. anaphylaxis); type II: IgG-mediated (e.g. drug-induced cytopenias); type III: immune complex-mediated (e.g. serum sickness, vasculitis); type IVa: TH1/monocyte-mediated (e.g. eczema); type IVb: TH2/ eosinophil-mediated (e.g. DRESS syndrome); type IVc: cytotoxic T-cell-mediated (e.g. SJS/TEN); type IVd: T cell/neutrophil-mediated (e.g. AGEP).
  
  - **Mechanisms of immune activation against drugs:** (i) **hapten concept:** hapten (or metabolized prohapten [e.g. sulfonamides]) joins to a self protein (carrier) and creates neoantigens → APCs uptake the conjugate, process it and present drug/peptides in HLA molecules to T cells → adaptive immune activation; (ii) **p-i concept** (pharmacological interactions with immune receptors): drug (or metabolites) interact directly with HLA/peptide molecules and TCRs → adaptive immune activation; (iii) **modification of protein/carbohydrate drugs** (e.g. insulin, enzymes, biologics) → creation of neoantigens → adaptive immune activation.
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- **Allergy testing for DHRs** (its clinical value depends on suspected drug, pathogenic mechanism and clinical presentation): (i) suspicion of type I drug allergy → test for specific IgE antibodies (SPT [high safety, availability, simplicity and specificity; low cost and sensitivity], intradermal testing [more sensitivity, less safety], serum specific IgE, in vitro BAT, in vitro histamine release, in vitro LT production, serum tryptase, serum/urinary histamine or metabolites); (ii) suspicion of type II or III drug allergy → test for specific IgG/IgM antibodies (serum specific IgM or IgG, Coombs' test, in vitro hemolysis test, determination of complement factors and circulating immune complexes); (iii) suspicion of type IV drug allergy → test for specific T cells (late-reading intradermal test, patch test, lymphocyte proliferation/activation testing, genetic risk markers); (iv) biologic testing has many limitations (low sensitivity, unavailability, cost); (v) drug provocation test is the gold standard to diagnose/exclude DHRs; (vi) testing subjects with no prior history of a DHR is not recommended, in particular in preoperative settings.

- **Drug provocation test (DPT):** (i) also referred to as drug challenge, graded challenge or test dosing; (ii) gold standard test to confirm or rule out drug hypersensitivity (in some clinical situations, it might be more useful to look for safe drug alternatives instead of performing a DPT); (iii) especially important when skin or in vitro allergy testing results are unstandardized, unavailable or inconclusive (particularly required for NSAIDs, local anesthetics, non-β-lactam antibiotics, and β-lactams when skin tests are negative); (iv) does not modify immune response; (v) cannot differentiate between allergic and nonallergic DHRs; (vi) risky procedure (must be done in an appropriate environment under close monitoring and with patient’s informed consent); (vii) the oral route is preferred whenever possible; (viii) should be performed at least ≥1 month after the DHR; (ix) guideline-based protocols should be followed, if they exist; (x) premedication should be avoided (it can mask a progressing anaphylaxis or give a false-negative result); (xi) DPT is contraindicated when there is a high risk of severe anaphylaxis, vasculitis or severe delayed DHRs (severe concurrent illness and pregnancy are relative contraindications); (xii) some authors consider prolonged DPTs (performed at home) in patients (especially children) with a history of nonimmediate and nonsevere DHR, even without previous skin tests; (xiii) a negative DPT does not assure 100% tolerance to the drug in the future (NPV of DPT with β-lactams=94–98%; NPV of DPT with NSAIDs >96%); (xiv) after a 1st negative DPT, retesting (2-4 wks later) can be considered in patients with a history of severe immediate DHR.

- **False-negative diagnosis** of drug allergy can lead to severe reactions after exposure.

- **False-positive diagnosis** of drug allergy can lead to unnecessary anxiety, fear, drug avoidance and use of alternative drugs (‘allergy’ to one drug may lead to the misconception that ‘the patient is allergic to all drugs’).

- **Examples of drug allergy:** (i) antiepileptic drugs and allopurinol cause mainly T-cell-mediated reactions; (ii) NMBAs cause mainly IgE-mediated reactions; (iii) β-lactams may lead to both types of reaction; (iv) diclofenac and other carboxylic acid NSAIDs can cause immune-mediated liver injury (hypothesis: hepatic metabolism and selective modification of hepatic proteins).

- **Viral infections can alter or mimic DHRs:** (i) HHV6 and HHV7 can reactivate and cause flares in patients with DRESS syndrome; (ii) antibiotic use during acute EBV infection ↑ risk of drug-induced exanthema (e.g. the “ampicillin rash”); (iii) acute EBV or CMV infection can present with a prolonged postviral maculopapular or urticarial rash; (iv) HHV6 and HHV7 cause roseola, a nonspecific maculopapular rash; (v) HHV-6 replication can be induced in vitro by amoxicillin.

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Drug desensitization (DS): (i) induction of transient tolerance to a compound responsible for a DHR; (ii) used when the drug is obligatorily needed and no reasonable alternative therapy exists (e.g. penicillin in pregnant women with syphilis; sulfonamides in HIV-infected patients; quinolones in some patients with cystic fibrosis; antituberculosis drugs; tetanus vaccine; desferoxamine in patients with hemochromatosis; taxanes and platinum salt-based drugs for cancer; mAbs for several neoplasms; aspirin in cardiac or rheumatic patients); (iii) mainly performed in IgE-mediated reactions but also seems to work for non-IgE reactions (mainly uncomplicated exanthemas or fixed drug eruption); (iv) DS is a risky procedure; (v) DS must be done in an appropriate environment under close monitoring and with patient’s informed consent (DS for severe reactions should be performed in the ICU); (vi) guideline-based DS protocols should be followed, if they exist; (vii) initial dose depends on the patient’s history (usually 1/10,000, up to 1/1,000,000 when there was a history of anaphylaxis); (viii) tolerance can only be maintained by continuous drug administration; (ix) DS is contraindicated in severe delayed reactions and vasculitis; (x) premedication with corticosteroids and H1-antihistamines may not reliably prevent IgE-dependent anaphylaxis.

It is thought that DPT of >4-5 steps may induce DS ('DS by testing') → there is a gray area determining crossover from a DPT to DS → it is proposed that DPT protocols should have ≤4 steps and DS protocols ≥6 steps.

Futuristic approach in allergic diseases (including HDRs): use of clinical, laboratory, imaging, histologic and genetic markers to identify specific genotypes/endotypes/phenotypes → give individualized therapy (optimize efficacy and safety).

Goals of pharmacogenetics: (i) to identify specific alleles that can predict efficacy and safety of a drug (e.g. HLA-B*57:01 ↑ risk of severe abacavir hypersensitivity; HLA-B*58:01 ↑ risk of allopurinol-induced SJS/TEN/DRESS; HLA-B*15:02 ↑ risk of carbamazepine-induced SJS/TEN; HLA-A*3101 ↑ risk of carbamazepine-induced delayed DHRs including SJS/TEN/DRESS; HLA-B*57:01 ↑ risk of flucoxacilline-induced liver injury; polymorphisms of FcεRIβ, STAT6, IL-4, IL-13, IL4-RA and TNFa may ↑ risk of penicillin allergy); (ii) to define personalized therapies based on the patient’s genetic profile.

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

Multiple drug hypersensitivity syndrome (MDH): (i) definition: DHRs to ≥2 chemically different drugs, (ii) frequency: 1-10% of patients with documented DHRs (~30% of patients consulting in a drug allergy unit report more than one ‘drug allergy’); (iii) MDH must be differentiated from cross-reactivity (due to structural similarities, common metabolic pathways or pharmacologic mechanisms), flare-up reactions (exacerbation of an existing drug allergy by the early switch of therapy to a novel drug) and multiple drug intolerance syndrome (intolerance to ≥3 neither structurally nor pharmacologically related drugs; no confirmation of hypersensitivity after allergy evaluation; possibly driven by patient anxiety); (iv) T-cell activation by different compounds has been clearly demonstrated in MDH.

Recommendations from the ICON on drug allergy document: (i) when an allergic drug reaction is suspected, DHR is the preferred term (allergic and nonallergic DHRs may be difficult to differentiate based only on clinical manifestations); (ii) lifelong avoidance of the drug and cross-reactive drugs is recommended when anaphylaxis has occurred; (iii) allergy testing should be
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Done ≥4-6 wks after complete resolution of the suspected DHR; (iv) some drug tests may turn falsely negative >6-12 months after the DHR → retesting 2-4 wks later should be considered; (v) PPV and NPV of skin tests vary among drug classes (‘good’ for immediate DHRs to β-lactams, muscle relaxants, platin salts and heparins; ‘moderate to low’ for most other drugs); (vi) skin testing is helpful for diagnosis of immediate DHRs to iodinated RCM; (vii) a DPT is the gold standard to identify the drug eliciting a DHR; (viii) for DPT, the oral route is preferred whenever possible; (ix) contraindications must be observed before performing DPT; (x) immediate treatment for complete recovery should be available during a DPT; (xi) patients who had severe immediate reactions to β-lactams and who displayed negative allergy results at the 1st evaluation (including DPT) can be considered for retesting 2-4 wks after initial evaluation (‘resensitization by testing’; necessary in 0.3% of patients); (xii) for currently available biological tests to diagnose drug allergy, a negative result does not exclude the imputability of the drug, whilst a positive result shows sensitivity to the drug but does not confirm causality; (xiii) HLA-B*5701 screening reduces the risk of DHR to abacavir and is mandatory before starting treatment; (xiv) a clear, regularly updated list of drugs to avoid and possible alternatives should be given to patients with a DHR; (xv) the search for safe alternatives may require DPTs in a hospital setting when the alternatives belong to the same drug class; (xvi) specific questioning for a history of drug allergy by every physician prior to issuing a prescription is essential from both a medical and legal viewpoint; (xvii) preventive measures (e.g. slow injection, premedication with glucocorticosteroids and antihistamines) can be useful mainly for non-allergic DHRs (e.g. to vancomycin, some NMBAs, iodinated RCM and chemotherapy drugs) but might not prevent IgE-dependent anaphylaxis; (xviii) in the absence of generally accepted protocols for drug DS, reference to successfully applied existing protocols is recommended; (xix) DS to aspirin may be considered in selected asthmatic patients with AERD or nasal polyps; (xx) DHRs must be reported to the appropriate agencies; (xxi) further research regarding DHRs is necessary (epidemiology, pathogenic mechanisms, potentiating factors, specific allergenic determinants, utility of allergy testing, validation of biologic testing, novel in vitro diagnostic methods, standardizing DPT and DS protocols, virus-drug interactions, pharmacogenomics); (xxii) graduate and postgraduate education/training on DHRs should improve; (xxiii) government and pharmaceutical industry should provide financial support for DHR research; (xxiv) national and international DHR databases registries should be implemented.


• 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 shinners’ (darkened lower eyelids due to chronic congestion), minor epistaxis; (v) comorbidities complications: conjunctivitis, sinusitis, rhinosinusitis, Eustachian tube dysfunction, middle ear effusion, otitis, ↓ hearing, lymphoid hypertrophy adenoids, tonsils, pharyngitis, asthma, dental malocclusion, atopic eczema, pollen-food syndrome, sleep disordered breathing (snoring, microarousals, obstructive sleep apnea/hypopnea, chronic nonrestorative sleep), daytime sleepiness, difficulty concentrating, fatigue, stress, impaired school or work performance, systemic inflammation; (vi) diagnosis: clinical history, anterior rhinoscopy, allergy testing (25% of AR cases are ‘local’

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[entopy], which means that specific IgE is not detected by skin or serum tests); (vii) treatment: (depends on severity): allergen avoidance, antihistamines (oral, intranasal), corticosteroids (intranasal, oral), antileukotrienes, decongestants (oral, topical), allergen immunotherapy.

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

- **Systemic inflammation → ↑ atherosclerosis, coronary heart disease, stroke.**

- **Chronic inflammatory airway disorders** (e.g. COPD, asthma, rhinitis) have been reported to be associated with vascular diseases of the heart and CNS.

- **Intermittent claudication:** (i) leg pain during walking that disappears within 10 min after standing still; (ii) sign of peripheral arterial disease.

- **Authors classified 1017 subjects** (20–64 yrs of age) into 4 groups: asthma only (n=81), asthma–rhinitis overlap (n=292), rhinitis only (n=299) and controls (n=345) → (i) prevalence of intermittent claudication: 2.5%, 3.4%, 6.4% and 2.3%, respectively; (ii) after adjusting for relevant confounding factors, rhinitis without asthma was associated with intermittent claudication (RRR:4.63), independently of the presence of atopy.


  - Authors present a 7-page update of the WHO/IUIS Allergen Nomenclature Database → (i) it reflects recent progress in identification, cloning and sequencing of allergens, isoallergens and variants; (ii) allergens for which names have been updated include respiratory allergens (birch and ragweed pollen, midge larvae, horse dander) and food allergens (peanut, cow’s milk, tomato, cereal grain).

  - **Official nomenclature of allergenic proteins:** (i) 1st published in 1986; (ii) revised and updated by the IUIS Allergen Nomenclature Sub-Committee ([www.allergen.org](http://www.allergen.org)); (iii) allergen names are composed of an abbreviation of the scientific name of its source (genus: 3–4 letters; species: 1–2 letters) and an Arabic numeral (e.g. Der p 1 for the 1st described allergen from Dermatophagoides pteronyssinus); (iv) closely related molecular species of an allergen are named by 4 digits following the main allergen number (the first 2 digits designate isoallergens [allergens from a single species with similar molecular masses, similar biochemical functions and sequence identities >67%]; 3rd and 4th digits distinguish isoallergen variants [proteins with >90% sequence identity]).

  - **Examples of the updated nomenclature:** (i) the entry Bos d 8 has been demerged into 4 separate allergens: Bos d 9.0101 (αS1-casein), Bos d 10.0101 (αS2-casein), Bos d 11.0101 (β-casein), and Bos d 12.0101 (κ-casein) [observation: the name Bos d 8, which is widely used, has been kept to designate the whole casein fraction]; (ii) names of tomato allergens have been changed (from Lyc e 1–Lyc e 4 to Sola l 1–Sola l 4) to reflect the establishment of Solanum lycopersicum instead of Lycopersicon esculentum as the official scientific name of the tomato.
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ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

• CODE RED: A CASE OF ANAPHYLAXIS TO A SODA (James Ch, Horbal J, Tcheurekdjian H, Hostoffer R. Ann Allergy Asthma Immunol 2014; 112: 474-475):

- 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) 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. in venom-induced anaphylaxis).

• Gum arabic (gum acacia): (i) edible carbohydrate with a small amount of glycoprotein; (ii) obtained from the acacia Senegal tree; (iii) commonly used as a food emulsifier and stabilizer; (iv) properties: complete water solubility, lack of taste and odor, low viscosity; (v) generally considered nontoxic; (vi) may cause allergic reactions in the occupational setting (e.g. asthma, contact urticaria and eczema in workers of a candy factory; respiratory allergies in a worker of a pharmaceutical industry); (vii) an extensive search on cases of anaphylaxis to gum arabic alone yielded no results (although there is a reported case of anaphylaxis induced by coffee and gum arabic-coated coffee beans).

• Authors report the case of a 21-yr-old subject with anaphylaxis (urticaria, angioedema, dyspnea, wheezing, inability to complete full sentences, immediate recovery with epinephrine) one hour after drinking 4 oz of Mountain Dew Code Red (a soda that contains gum arabic) → allergy testing: positive SPT to gum acacia (4 mm induration); negative SPT to gum karaya and gum tragacanth; sIgE to gum arabic=0.36 (ImmunoCAP).

• Author's commentary: 1st reported case of anaphylaxis to gum arabic alone.

• CURRENT UPDATE ON CELLULAR AND MOLECULAR MECHANISMS OF HEREDITARY ANGIOEDEMA (Walford HH, Zuraw BL. Ann Allergy Asthma Immunol 2014; 112: 413-418):

- Bradykinin (BK) → ↑ endothelial permeability (mechanism: ↓ vascular endothelial cadherin [major protein of the endothelial adherens junction]), vasodilation (mechanism: ↑ nitric oxide) → ↑ vascular leakage → angioedema.

- Metabolism of BK: activation of FXII → FXII converts prekallikrein intro kallikrein → kininogenases (kallikrein, FXII, plasmin) convert HMWK into BK; kallikrein activates more FXII in a positive feedback loop → BK acts through receptors type 1 and type 2 (most important) → BK is catabolized mainly by kininases (angiotensin-converting enzyme [ACE], aminopeptidase P [APP], carboxypeptidase N [CPN], neutral endopeptidase, dipeptidyl peptidase IV).
• C1 esterase inhibitor (C1-INH) regulates several proteases (C1r, C1s, MASP-1, MASP-2, kallikrein, activated FXII, activated FXI, plasmin) → inhibition of the plasma complement, contact and fibrinolytic systems (including BK production).

• C1-INH deficiency or dysfunction (AD mutations in the SERPING1 gene [located on chromosome 11q12.1]; >200 different mutations have been described [mainly missense, frameshift, nonsense or splicing defects]; de novo mutations occur in ~25% of cases) → ↑ activity of FXII and kallikrein → ↑ production of BK → hereditary angioedema (HAE): recurrent painful angioedema without urticaria, unpredictable, potentially fatal (↓ patient's QoL).

• HAE (OMIM 106100): (i) type I (85% of cases): ↓ C1-INH levels; (ii) type II (15% of cases): normal C1-INH levels, ↓ C1-INH function (mutations in SERPING1 gene mostly in exon 8 near the Arg444 reactive site); (iii) type III (very rare): normal C1-INH levels and function.

• Functional C1INH levels in HAE are generally 5-30% of normal despite one functioning gene → additional mechanisms must account for C1INH levels <50% of normal (e.g. mutated C1INH proteins may interfere with the biosynthesis or secretion of normal C1INH protein in the same cell through a process called transinhibition).

• Type III HAE: (i) normal C1-INH levels and function; (ii) positive family history; (iii) more frequent in women; (iv) associated to ↑ estrogen levels (estrogen ↑ activation of the kallikrein-kinin pathway and expression of BK type 2 receptors); (v) mutations in the F12 gene (encoding FXII; chromosome 5q35.3) occur in ~25% of cases and may contribute to pathogenesis; (vi) patients tend to have fewer abdominal attacks and more cutaneous and facial swellings.

• HAE type III could be a multifactorial disease: (i) F12 mutations may be a condition for the expression of symptoms; (ii) other genetic factors (e.g. low level of kininase activity) may ↑ or ↓ disease expression; (iii) environmental factors (e.g. estrogen) may ↑ disease expression; (iv) further studies are needed to evaluate influencing factors.

• Epidemiology of HAE: (i) prevalence: 1/50,000 subjects; (ii) mean age of onset: 8-12 yrs (50% of cases start by 10 yrs of age; nearly all cases by 20 yrs of age); (iii) diagnosis delay: 8 yrs in average; (iv) >50% of patients may experience a life-threatening attack; (v) many patients receive ineffective therapies and unnecessary medical procedures before diagnosis.

• HAE attacks: (i) clinical manifestations: nonpruritic painful angioedema without urticaria, abdominal pain, vomiting, constipation, diarrhea, genitourinary symptoms, throat tightness, circulatory collapse, loss of consciousness; (ii) most common sites: skin, GI tract, respiratory tract (>50% of patients may experience ≥1 laryngeal attack); (iii) prodromal symptoms: erythematous serpiginous rash (erythema marginatum), fatigue, weakness, local discomfort, tingling sensation; (iv) frequency average (if untreated): 1 attack every 10 days (can be variable); (v) duration average: 2-5 days; (vi) peak of symptoms: 12-36 hrs; (vii) triggers (not always present): trauma, medical/dental procedures (e.g. surgery), infections, exercise, stress, drugs (e.g. ACE inhibitors, estrogens), menses; (viii) pregnancy might aggravate or reduce attacks; (ix) disease severity is variable (influencing factors: polymorphisms in other genes [e.g. B2 receptor gene, kininases], hormones, trauma, stress, infection).

• Diagnosis of HAE: (i) clinical history; (ii) family history; (iii) analysis of circulating complement components (C4, C1q, C1-INH level and function); (iv) genetic testing (SERPING1, F12).
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**Management of HAE:** (i) treatment of acute attacks; (ii) short-term prophylaxis (e.g. before a surgery; not always successful in preventing attacks); (iii) long-term prophylaxis (mainly in patients with recurrent severe attacks); (iv) avoidance of triggers.

**Drugs to treat HAE attacks:** (i) plasma-derived or recombinant human C1-INH; (ii) ecallantide (inhibitor of kallikrein); (iii) icatibant (BK type 2 receptor antagonist). For the 3 agents, many patients improve in <30 min, 75% of patients improve in <4 hrs, complete alleviation is often achieved in 8-12 hrs (none of the therapies completely control symptoms in every patient). Good safety profile for the 3 agents (3% risk of anaphylaxis with ecallantide).

**Drugs to prevent HAE attacks:** (i) attenuated androgens (e.g. danazol): low price, can ↑ APP levels, significant dose-dependent side effects, usually contraindicated in children, pregnancy, breastfeeding and history of prostate cancer, high-dose androgens given for a week before a scheduled procedure can be used for short-term prophylaxis; (ii) plasma-derived C1-INH replacement therapy: good safety profile, very expensive (highest annual cost of any drug in the US); reduce 50% of attacks; (iii) tranexamic acid: agent of choice in children, rarely contraindicated (e.g. in thrombophilia); (iv) 2 U of freshly frozen plasma may help as short-term prophylaxis when C1INH concentrates are not available.

**Acquired angioedema with C1-INH deficiency (ACID):** (i) recurrent episodes of BK-mediated angioedema due to C1-INH consumption; (ii) pathophysiology: lymphoproliferative diseases, autoimmune diseases, malignancies → autoantibody production (including antibodies to C1-INH) → activation of the classical complement pathway → consumption of C1q, C1-INH and C4 → ↑ activity of FXII and kallikrein → ↑ BK production → ACID; (iii) usually presents after 40 yrs of age; (iv) clinical manifestations: similar to HAE.


**Eosinophilic esophagitis (EoE):** (i) prevalence in general population: ~1/2,000 subjects (may be underestimated); (ii) prevalence in US children: ~1/200; (iii) incidence is rising (~15% of adults undergoing endoscopy for dysphagia); (iv) male to female ratio=3:1; (v) impact: significant morbidity, ↓ QoL, high cost; (vi) pathogenesis: genetic susceptibility, environmental insults to the esophageal epithelium (e.g. allergens, infections, irritants) → epithelial barrier dysfunction (e.g. ↓ expression of the cell adhesion protein DSG-1), ↑ secretion of TSLP and IL-33 → ↑ allergen entry through the epithelium → immune reaction to food or respiratory allergens → infiltration of eosinophils into esophageal mucosa → chronic inflammatory infiltrate (eosinophils, mast cells, a special basophil population, TH2 cells, iNKT cells) → esophageal fibrosis, remodelling (e.g. transdifferentiation of epithelial cells to a myofibroblast phenotype) and dysfunction; (vii) TSLP and eotaxin-3 gene polymorphisms can ↑ risk of EoE; (viii) TSLP-mediated basophil response is likely to play an important role in EoE pathogenesis; (ix) IgE does not seem to play an essential role in EoE pathogenesis; (x) common causal foods in children: milk, egg, soy, wheat, beef, chicken; (xi) common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg; (xii) frequent association (40-90%) with other atopic diseases (asthma, allergic rhinitis, food allergy, atopic dermatitis); (xiii) often misdiagnosed as GERD.

**Diagnosis of EoE:** (i) clinical history: abdominal pain, vomiting, dysphagia, heartburn, cough, choking, food aversion; (ii) complications: food impaction, failure to thrive, spontaneous esophageal perforation, mental affectation; (iii) esophageal endoscopy: edema, white exudative plaques, mucosal rings (‘trachealization’), strictures, linear furrows, mucosal tearing; (iv) "But knowledge puffs up while love builds up" 1 Corinthians 8:1
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; other findings: superficial layering, microabscesses, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, lamina propria fibrosis; before endoscopy, all patients should be treated with high-dose PPI therapy of 20-40 mg bid in adults and 1 mg/kg bid in children for 8-12 wks to exclude GERD and other forms of PPI-responsive esophageal eosinophilia); (v) allergy testing (SPT, in vitro sIgE detection, patch test) with food and respiratory allergens; (vi) food elimination-reintroduction trials; (vii) 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) topical corticosteroids (most recommended regimen: to swallow viscous budesonide respules mixed into a slurry-type solution with a sucralose-containing artificial sweetener; other regimen: to spray MDI fluticasone without a spacer into the mouth and swallow it; swallowed steroids have low bioavailability and low potential for systemic adverse effects but ↑ risk of local fungal infection); (iii) systemic corticosteroids: effective, severe side effects; (iv) biologic therapies targeting the eosinophil (e.g. anti-IL-5 mAb, anti-IL-5R mAb); (v) esophageal dilation: might provide short-term symptomatic relief, only used if dietary and medical therapy has failed.

• Human esophageal epithelial cells: (i) express TLRs; (ii) produce proinflammatory cytokines in response to both PAMPs and DAMPs; (iii) can produce the eosinophilic and T-cell chemokine RANTES (CCL5); (iv) may function as nonprofessional APCs.

• IL-5: (i) important for the production and early growth of eosinophils; (ii) mature eosinophils lose IL-5 receptors and are more dependent on IL-3 and GM-CSF.

• Activated myofibroblast: (i) exhibits properties of both smooth muscle cells and fibroblasts; (ii) key effector cell in all models of fibrosis (mechanisms: myofibroblast contracts and places tension on the extracellular matrix [ECM] → activation and differentiation of neighboring cells → myofibroblast secretes ECM components to stabilize its new contracted position); (iii) TGF-β stimulates myofibroblast differentiation.

• GOOD SYNDROME AND POLYMYOSITIS (Frith J, Toller-Artis E, Tcheurekdjian H, Hostoffer R. Ann Allergy Asthma Immunol 2014; 112: 478):

• Good syndrome (GS): (i) described by Dr Robert Good in 1954 in an adult patient with thymoma and immunodeficiency; (ii) usual age of onset: 40-70 yrs; (iii) immune abnormalities: low to absent peripheral B cells, hypogammaglobulinemia, defects in cell-mediated immunity; (iv) clinical manifestations: infections, autoimmunity, paraneoplastic disorders; (v) complications: myasthenia gravis, oral lichen planus, red blood cell aplasia, aplastic anemia, macrocytic anemia, autoimmune hemolytic anemia, monoclonal gammapathy, diabetes mellitus, polyarthropathy, myelodysplastic syndromes; (vi) unclear pathogenesis.

• Polymyositis: (i) inflammatory myopathy probably caused by T-cell-mediated cytotoxicity; (ii) clinical presentation: progressive muscle weakness, fatigue, dysphagia, myalgias, arthralgias; (iii) diagnosis: clinical history, serum muscle enzymes, electromyography, muscle biopsy; (iv) treatment: corticosteroids, immunosuppressants, immunomodulators; (v) found in approximately 5% of thymoma cases.
• Author’s report the case of a 65-yr-old man with GS (thymoma, thrush, esophageal candidiasis, onichomycosis, pneumonias, ↓ IgG, ↓ antibody response to Pneumovax, ↓ CD19+ cells, ↓ CD3+ cells, ↓ CD8+ T cells, ↓ response to mitogen and antigen stimulation) who developed polymyositis at 73 yrs of age (proximal muscle weakness, ↑ muscle enzyme levels [CPK, aldolase, GOT], abnormal electromyography and muscle biopsy) → treatment: IVIG 1 g/kg every 4 wks, oral fluconazole every other day → patient eventually died of a pneumonia.

• Author’s commentary: 1st case report of association between GS and polymyositis.

• INFLUENCE OF β2-ADRENOCEPTOR 16 GENOTYPE ON PROPRANOLOL-INDUCED BRONCHOCONSTRICTION IN PATIENTS WITH PERSISTENT ASTHMA (Anderson WJ, Short PM, Manoharan A, Lipworth JLR, Lipworth BJ. Ann Allergy Asthma Immunol 2014; 112: 475-476):

• Polymorphisms in the β2-adrenoceptor (B2ADR) gene: (i) ↓ efficacy of β2-agonist therapy in asthmatic patients; (ii) ↑ susceptibility to propranolol-induced bronchoconstriction.

• PENICILLIN AND CEPHALOSPORIN ALLERGY (Pichichero ME, Zagursky R. Ann Allergy Asthma Immunol 2014; 112: 404-412):

• β-lactams: (i) antibiotic drugs that have the β-lactam ring; (ii) inhibit the synthesis of the bacterial membrane; (iii) include penicillins, 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.

• Penicillin (PNC): (i) discovered by Alexander Fleming from the fungus Penicillium; (ii) core structure: the β-lactam ring with the variable side chain R attached to the amide bridge to the ring carbon 6 atom; (iii) modifications at the R site → PNC-derivative antibiotics (e.g. the aminopenicillins amoxicillin and ampicillin contain an amine group in their side chain).

• IgE-mediated PNC allergy: (i) self-reported in ~10% of the population; (ii) confirmed in <1% of the population; (iii) most common mechanism: hapten-carrier; (iv) incidence of anaphylaxis to PNCs=0.015-0.004% (fatality rate=0.002-0.0015%); (v) major PNC allergen: benzylpenicilloyl determinant (95% of the PNC that is bound to proteins); (vi) minor PNC allergens (minor determinant mixture, MDM): benzylpenicilloate, benzylpenilloate, benzylpenicilloyl-n-propylamine, penicillin G; (vii) diagnosis: clinical history, specific IgE detection by skin tests or in vitro tests, drug challenge; (viii) false-positive diagnosis of PNC allergy → unnecessary use of alternative antibiotics (e.g. quinolones, vancomycin, clindamycin, cephalosporins) that ↑ cost, bacterial resistance (e.g. methicillin-resistant S aureus, vancomycin-resistant enterococcus) and C infection; (ix) reasons for false-positive diagnosis of PNC allergy: assumption that every rash during PNC therapy is caused by PNC allergy, wrong interpretation of skin or in vitro allergy tests; (x) appropriate PNC skin testing can ↓ the rate of false-positive diagnosis of PNC allergy; (xi) there is a 3-fold increased coincidental risk of adverse reactions to unrelated drugs among PNC-allergic patients.

• 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.

- Many drug reactions do not fit into the Coombs and Gell classification: (i) reactions typically initiate after 72 hrs; (ii) occur in 1-4% of patients receiving PNC and cephalosporins; (iii) generally manifest as nonpruritic rashes; (iv) skin and FEIA testing are not valuable for diagnosis; (v) oral challenge may reproduce the reaction, especially if caused by excipients (e.g. dyes, flavoring agents).

- Major educational messages from this article: (i) PNC allergy does not occur in 10% of the population; <10% are true allergies; many patients consider a family history of PNC allergy as applicable to themselves; (ii) PNC allergy is not due to reactions to the β-lactam ring: the PNC β-lactam ring is converted in the body to benzylpenicilloyl (benzylpenicilloyl is attached to polylysine and commercially supplied for allergy testing as penicilloyl polylysine or major antigenic determinant); penicillin G can also be metabolized to other products (minor antigenic determinants: benzylpenicilloylate, benzylpenilloate, benzylpenicilloyl-n-propylamine, penicillin G); the PNC antigenic determinant conformation may involve both the side chain and the β-lactam-thiazolidine backbone; (iii) allergy to PNCs and cephalosporins is caused mainly by reactions to the side chains of the molecules and less commonly to the β-lactam ring; (iv) predictive value of PNC skin testing may ↑ using MDM: 99% of patients with negative skin test results to PNC that include the MDM can safely receive penicillin; (v) 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. cephalexin and ampicillin; cephaloridine and amoxicillin) or similar biosostere properties (e.g. penicillin G and cephalothin); cross-allergy is negligible with 2nd and later generation cephalosporins (distinct side chains from PNCs); (vi) cephalosporin allergy does not cross all cephalosporin generations: cross-reactivity depends on the similarity between the different R1 and/or R2 side chains.

- PNC allergy skin testing panel: penicillin G, penicilloyl polylysine, MDM, ampicillin, cephalosporins (e.g. cefazolin, cefuroxime, ceftriaxone) → if the skin test results are negative, open oral challenges can be performed (typically for 5 days with a selected antibiotic, then a 3-day washout, then a 5-day challenge with a 2nd antibiotic if required, and successively).

- Cross-allergy between PNC and other β-lactams: (i) carbapenems: cross-allergy with PNCs and cephalosporins is very unlikely or absent; (ii) monobactams: cross-allergy with PNCs and cephalosporins is exceptional (e.g. aztreonam with ceftazidime, which share an identical side chain); (iii) β-lactamase inhibitors: they can be β-lactams themselves (e.g. clavulanic acid).
THERAPY OF CHRONIC URTICARIA: A SIMPLISTIC, MODERN APPROACH (Kaplan AP. Ann Allergy Asthma Immunol 2014; 112: 419-425):

- Chronic urticaria (CU): (i) definition: recurrent wheals for >6 weeks (concomitant angioedema may occur in ~50% of CSU cases); (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 are ‘autoimmune’ [IgG1/IgG3 to FcεRIα or IgE]; wheals usually last between 4 and 24 hours), inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise; wheals usually last <2 hours after stimuli ceases, except for delayed pressure urticaria [similar to CU wheals]); (v) wheals vary from a few mm to 15 cm in diameter; (vi) 1st-line treatment: non-sedating 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 therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A (only FDA-approved immunosuppressant drug for CSU; side effects: ↑ blood pressure, renal damage; renal function reverts to normal within 4 to 6 weeks 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) 25-30% of AU patients benefit with placebo; (x) prognosis: 50% of cases may resolve spontaneously within 1 year; 75% of cases within 5 years; (xi) although 25% of CSU patients may have ↑ antithyroid antibodies (e.g. anti-TPO, anti-TG), most have normal thyroid function; (xii) positive ANA test occurs in ~25% of CSU patients, mostly with no clinical significance; (xiii) a prominent nonnecrotizing perivascular inflammatory infiltrate (TH0 or mixed TH1/TH2 lymphocytes, eosinophils, monocytes, basophils) is observed in CSU (not seen in inducible urticarias, except delayed pressure); (xiv) angioedema: longer duration than hives (up to 3 days for complete resolution), less pruritic than hives (fewer itch-mediating nerve endings in the deep skin); (xv) the autologous serum skin test generally (but not perfectly) reflects the presence of anti- FcεRIα antibodies; (xvi) ANA, C3, C4, cryoglobulin and C1q binding assay for circulating immune complexes should be requested for urticarial vasculitis.

- 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-week period; (v) suggested maximum dose: 750 mg every 4 weeks; (vi) rate of anaphylaxis in patients with severe refractory asthma receiving omalizumab=1/1000; (vii) protocols recommend patient observation of 2 hours for the first 3 doses and 30 minutes for each subsequent dose; (viii) efficacy has also been documented in mastocytosis, anaphylaxis (idiopathic; exercise-induced), eosinophilic chronic rhinosinusitis, atopic dermatitis.

“But knowledge puffs up while love builds up” 1 Corinthians 8:1
• **Omalizumab for chronic urticaria/angioedema (CUA):** (i) several observational studies and RCTs (>900 patients) show that omalizumab can be beneficial and safe for patients with antihistamine-refractory CUA (mainly spontaneous CUA; weaker evidence for inducible CUA); (ii) response rate in antihistamine- and LTRA-refractory CUA=65% (40% of patients are completely free of hives as long as therapy is continued); (iii) 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; (iv) benefit can be observed within days of therapy onset; (v) some patients have complete remission of symptoms; (vi) serious adverse events are rare; (vii) dosing has followed the asthma scheme, a fixed regimen or an individualized algorithm; (viii) limitations for routine use: cost, availability; (ix) areas of uncertainty: biomarkers to predict response (not all patients improve), mechanism of action, optimal dosing, optimal duration of treatment; (x) only cyclosporine can match the response rate to omalizumab (excluding steroids), but adverse effects are greater (↑ blood pressure, ↓ renal function).

• **Therapeutic approach for CU:** 4x nonsedating antihistamines (45% response rate) → omalizumab (additional 65% response rate [65% of the remaining 55% is an additional 36%; combined response rate=81%]) → cyclosporine (additional 60% response rate [60% of the remaining 19% is an additional 11%; total response rate=92%]) → consider sulfasalazine, methotrexate and low-dose systemic steroids (start at 10-15 mg/day [prednisone equivalent], then taper by 1 mg/wk) for the refractory patients (8%).
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**JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:**

  - Dedicator of cytokinesis 8 (DOCK8) deficiency: (i) autosomal recessive hyper-IgE syndrome (AR-HIES) with features of combined immunodeficiency; (ii) clinical features: skin viral infections, fungal and bacterial infections, pneumonias, severe allergies, cancer susceptibility (e.g. squamous cell carcinoma, lymphoma); (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ dendritic cell migration, ↓ production of antiviral cytokines, lymphopenia, ↓ T-cell priming, ↓ T-cell chemotaxis, ↓ T-cell survival, ↓ T-cell and B-cell memory, ↓ T-cell activation, ↓ 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: inhibition of 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) 3 previous reports showed IFN-α efficacy to treat HPV and molluscum contagiosum virus infections in patients with clinically defined AR-HIES.
  - Authors report the case of a 17-yr-old girl with DOCK8 deficiency → previous history: consanguineous parents, early-onset eczema, food allergies, asthma, bacterial pneumonias, skin infections, cerebral artery vasculitis, eosinophilia (peak at 11,033 cells/µL), ↑ IgE (peak at 25,987 IU/mL) → genetic analysis: homozygous DOCK8 mutation (c.3120+1g>t → skipped exon 25) → current disease: severe left eyelid ectropion; no response to systemic acyclovir, vancomycin, rifampicin, oral methylprednisolone, IVIG, ofloxacin eye drops and clobatesole propionate ointment; eyelid biopsy: ulcerative dermatitis with strong inflammatory response, no epithelial dysplasia or malignancy; quantitative PCR of biopsy material: ↑ HSV type 1 DNA (150,000 geq/mL) → successful therapy: subcutaneous pegylated IFN-α 2b (starting dose=0.6 µg/kg/wk, followed by 1 µg/kg/wk; clinical response started within 24 hrs after the 1st dose, ectropion was substantially reduced 96 hrs later; adverse effect: fever up to 37.5ºC).
  - Author's commentaries: (i) IFN-α may improve viral host defense in patients with DOCK8 deficiency; (ii) continuous IFN-α treatment may benefit DOCK8 patients ineligible for HSCT.

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

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• **Combined immunodeficiency (CID):** genetic defects causing ↓ in T-cell function → ↓ cellular and humoral immunity → severe infections (including opportunistic), usually fatal course if not treated (HSCT, gene therapy, enzyme replacement therapy).

• **Transcription factor nuclear factor-κB (NF-κB):** (i) chief regulator of lymphocyte activation, survival and proliferation; (ii) assembly of the CARMA1–BCL10–MALT1 (mucosa-associated lymphoid tissue lymphoma translocation gene 1) signalosome complex is an essential step in regulating NF-κB activation.

• Authors report the case of a 15-yr-old Kurdish girl with CID → clinical history: consanguineous parents; short stature and low weight since 2 yrs of age; severe eczematous rash from 2 wks of age; skin infections by S aureus, VZV and HSV-1; severe inflammatory GI disease since infancy (requiring Nissan fundoplication, esophageal stricture dilatation and elemental formula feeding via jejunostomy); multiple pneumonias (including by S aureus, S pneumoniae and CMV); chronic inflammatory lung disease; bronchiectasis; nail clubbing; bone fractures (femur, both tibiae) after low-impact injuries; chronic granulation tissue involving the vocal cords, larynx and external auditory canal; severe periodicontal disease; multiple nonspecific dysmorphic facial features; widespread excoriated and lichenified dermatitis; chronic cheilitis resulting in microstomia; inflammation of the oral mucosa; delayed bone age; very low bone mineral density.

  → immunologic analysis: normal serum IgG, IgA and IgM levels; ↑ serum IgE (maximum=9,856 IU/mL); normal antibody response to antigens (e.g. tetanus, diphtheria, measles, mumps, rubella, VZV); normal isohemagglutinins; normal total lymphocyte counts; CD3+ T cells=97%; CD4+ T cells=75% (2,610/µL); CD19+ cells=1% (50/µL); abundant IgD+IgM+CD27- naive B cells; absent IgD+IgM+CD27+ marginal zone B cells; ↓ IgD-IgM+CD27+ switched memory B cells; normal CD4+CD25+CD127lowFoxP3+ Treg cell counts; normal NK-cell counts; ↓ lymphoproliferation and IL-2 secretion with phytohemagglutinin → histologic analysis: atypical, nonspecific chronic CD3+ T-cell lymphocytic infiltration in the skin and GI tract interfering with the normal epithelial maturation sequence → genetic analysis: homozygous mutations in MALT1 (NM_006785:c.1739G>C; NP_006776.1:p.Trp580Ser) → protein analysis: very low expression of MALT1 protein, ↓ MALT1 paracaspase activity, ↓ MALT1 scaffold function, ↓ NF-κB degradation, ↓ NF-κB p56 subunit phosphorylation (rescued by cell transfection with a normal MALT1 transcript).

• **Other recent reports:** (i) AR SCID due to inactivating mutations in CARD11 (encoding CARMA1): hypogammaglobulinemia, normal B-cell numbers with developmental arrest at the late transitional stage; (ii) fatal CID due to homozygous missense mutations in MALT1.

• **When to suspect MALT1 deficiency?** (i) CID with normal T-cell numbers, ↓ T-cell proliferation and ↓ NF-κB activation after TCR signaling; (ii) defective B-cell development is likely to be a defining feature (unifying phenotype of the Malt1-/-, Card11-/-, and Bcl10-/- mice).

• **EFFECTS OF ANTIOXIDANT SUPPLEMENTS AND NUTRIENTS ON PATIENTS WITH ASTHMA AND ALLERGIES (Moreno-Macias H, Romieu I. J Allergy Clin Immunol 2014; 133: 1237-1244):**

  • Allergic diseases: (i) rising prevalence → public health concern; (ii) pathogenesis: complex interactions between genetic and environmental factors; (iii) origins of asthma and allergy might be in fetal life or early childhood; (iv) oxidative stress (local and systemic) can ↑ inflammation and allergy; (v) low dietary intake of antioxidants can be related to ↑ allergy prevalence; (vi) antioxidants may contribute to allergy prevention (no high-quality evidence supports it); (vii) specific antioxidants from diet or vitamin supplements might improve asthma control andlung

PEARLS IN ALLERGY AND IMMUNOLOGY

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function in children or adults (large RCTs are required to confirm it); (viii) antioxidant vitamin supplementation to prevent cancer has shown to ↑ overall mortality; (ix) responses to antioxidants might be modified by life stage, genetic susceptibility and environmental sources of oxidative stress; (x) research with vitamin supplementation might be more relevant in vulnerable populations with deficiency in dietary antioxidants, poor access to dietary antioxidants or high exposure to environmental sources of oxidants (e.g. air pollution); (xi) best recommendation: supplement the diet with fresh fruits and vegetables.

- **Fluid lining the lungs** contains several low-molecular-weight antioxidants (e.g. vit C, vit E, reduced glutathione, uric acid) and antioxidant enzymes (e.g. catalase, superoxide dismutase).
- **Concentration of antioxidants** in the upper and lower respiratory tracts are markedly different.
- **What is still unknown?** (i) how oxidants interact with molecules in the cells, tissues and epithelial lining fluid of the lungs; (ii) protective mechanisms of different types of antioxidants on the lung; (iii) the extent to which antioxidants in blood act as oxidants in the lungs; (iv) the effects of specific antioxidants on asthma and allergies; (v) how antioxidants in the diet or supplements can be used to prevent or control asthma and allergies.


- **Food allergy (FA)** affects up to 5% of children and 4% of adults in some countries.
- **Atopic dermatitis (AD):** (i) known risk factor for FA (hypothesis: sensitization to food allergens through a disrupted and inflamed skin); (ii) human AD skin lesions are associated with ↑ TSLP expression and basophil infiltration.
- **Skin barrier defect → pruritus and skin inflammation (including ↑ TSLP production) → entry of food allergens through disrupted skin → activation of TSLP-elicited basophils → TH2 responses, IgE sensitization → development of FA.
- **TSLP-basophil axis:** novel target to prevent and treat FA.


- **Schaflen (SLFN) genes:** control cell-cycle progression; virulence factors in orthopoxviruses.
- Authors report the case of a 65-yr-old female with cutaneous Merkel cell carcinoma of the left thigh (positive histology for Merkel cell polyoma virus [MCPyV] DNA), severe EBV infection (lymphadenopathy, skin rash, weight loss, night sweats, fatigue, high EBV-DNA copy numbers in peripheral blood, EBV-positive B-cell blasts in the disturbed lymph nodes, T-cell lymphoma) and extremely high quantity of Torque teno virus (TTV) in the plasma → previous history: unremarkable history of infections → immunologic analysis: mild hypogammaglobulinemia;

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moderate lymphopenia; intact proportions of T, B and NK cells; ↑ CD8+ TEMRA cells; ↓ T-cell proliferation and IFN-γ production after stimulation with MCPyV (intact IL-10 production); abnormal T-cell proliferation via CD3/CD28; ↑ T-cell apoptosis; premature entry of T cells into cell-cycle S-phase on activation; similar immune features to the Elektra phenotype in Slfn2 mutated mice → genetic analysis: heterozygous deletion of the SLFN gene region (chromosomal band 17q12, encompassing the SLFN11, SLFN12, and SLFN13 genes; also found in healthy subjects); homozygosity for a missense variant in the schlafen-like gene 1 (chromosome 1p34.2: exon2:c.G431C:p.R144T; likely to be pathogenic); an heterozygous missense substitution in the schlafen-like gene 1 (c.C1047A:p.D349E); no abnormalities in genes known to cause susceptibility to EBV (AP3B1, BIRC4, FCGR3A, CD27, CORO1A, GATA2, HPLH1, ITK, LG4, LRBA, LYST, MAGT1, PIK3CD, PRKCD, PRF1, RAB27A, SH2D1A, STX11, STXBP2, TRAC, UNC13D, WAS).


  - Allergic diseases are usually multifactorial (several genetic and environmental factors).
  - Monogenic causes of allergic disease and inherited mast cell disorders: (i) Kazal type 5 (SPINK5) mutations in patients with Netherton syndrome; (ii) STAT3 mutations in AD hyper-IgE syndrome; (iii) DOCK8 mutations in AR HIES; (iv) phospholipase C, gamma 2 (PLCG2) mutations in familial cold urticaria; (v) KIT mutations in mastocytosis.
  - Some connective tissue syndromes (Loeys-Dietz, Marfan and Ehlers-Danlos syndromes) have been associated with atopic disease.
  - Authors report subjects from 9 families (dominant inheritance pattern) with persistent high basal serum protryptase levels (mean=21.6±1.4 ng/mL), symptoms of mast cell mediator release (urticaria, flushing, cramping abdominal pain, fecal urgency, diarrhea, asthma, anaphylaxis; spontaneous or triggered by heat, exercise, vibration, stress, foods or minor physical trauma) and additional nonatopic features (eosinophilic GI disease, GERD, irritable bowel syndrome, hypermobility, chronic musculoskeletal pain, autonomic dysfunction, neuropsychiatric symptoms) → no evidence of mast cell clonal disorders (bone marrow biopsy: significant ↑ in mast cell numbers, no mast cell aggregates, no aberrant expression of CD2/CD25, no KIT D816V mutations; impaired basophil activation in vitro) → additional genetic study is ongoing.


  - Allergic rhinitis (AR): (i) definition: symptomatic disorder of the nose induced after allergen exposure by IgE-mediated inflammation; (ii) prevalence: >500 million people worldwide.
  - Allergen avoidance: (i) essential issue in AR management; (ii) difficult to implement; (iii) nasal filters might be useful (potential advantages: efficacy, safety, comfortableness, low visibility).
  - Rhinix (Rhinix ApS, Aarhus, Denmark): (i) a new nasal filter; (ii) consists of a membrane that is placed in each nostril’s anterior vestibule and kept in place by a copolymer frame; (iii) can
benefit adults with seasonal allergic rhinitis, mainly through its effect on itching and sneezing; (iv) did not ↑ tendency to breathe orally (minimal air resistance); (v) acceptable to wear.

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PEDIATRIC ALLERGY AND IMMUNOLOGY:

  
  - Human papilloma virus (HPV) infection: pathogenic factor for cervix cancer.
  - Vaccination against HPV (e.g. quadrivalent vaccine Gardasil): (i) main objective: reduce incidence of cervix cancer; (ii) severe neurologic adverse effects have been reported (e.g. Guillain–Barré syndrome, demyelinating diseases, acute disseminated encephalomyelitis).
  - Authors report the case of a previously healthy 11-yr-old girl with rapid-onset persistent neurologic symptoms (generalized choreic movements, facial grimaces, ataxic gait, dysarthria) 1 month after receiving the 2nd dose of Gardasil (1st dose=February 25th 2013; 2nd dose=April 8th 2013) → laboratory analysis: normal CBC, liver enzymes, renal testing, cardiac testing, autoimmune panel, brain MRI and CSF analysis → common causes of chorea in children were excluded (e.g. rheumatic chorea, SLE, Wilson disease) → suggestive diagnosis: autoimmune chorea after Gardasil vaccine → successful treatment (complete resolution of symptoms within 1 wk): oral methylprednisolone (2 mg/kg/day for 4 wks, then gradual tapering).
  - Author’s commentaries: (i) Gardasil vaccine may trigger immune-mediated neurologic disease (proposed mechanism: molecular mimicry); (ii) the target population for the wide HPV immunization program (girls in pubertal age) is per se predisposed to autoimmune reactions.

  
  - Food allergy: (i) IgE-mediated: urticaria, angioedema, bronchospasm, GI symptoms, anaphylaxis; (ii) non-IgE-mediated: enterocolitis, proctocolitis, celiac disease, contact dermatitis, Heiner syndrome; (iii) IgE- and cell-mediated: atopic dermatitis, eosinophilic GI diseases.
  - Food protein-induced enterocolitis syndrome (FPIES): (i) non-IgE-mediated allergy to food proteins; (ii) usually starts in the 1st yr of life; (iii) clinical history: vomiting, diarrhea, dehydration, hypotension, shock, acidemia, methemoglobinemia (2-6 hrs after eating the culprit food); (iv) frequent culprits: cow’s milk, soy, grains; (v) diagnosis: clinical history, OFC; (vi) differential diagnosis: sepsis, metabolic diseases; (vii) treatment: allergen avoidance; (viii) prognosis: typically resolves by 3-5 yrs of age (OFCs are usually performed to confirm resolution); (ix) breast-fed infants with FPIES can usually continue lactating without maternal diet (FPIES is very rare in exclusively breast-fed infants); (x) egg white-induced FPIES has been reported.
  - Authors report the case of a 9-month-old boy with 3 episodes of FPIES (vomiting, diarrhea, pallor, weakness, irritability, hypotension, loss of consciousness) 2-3 hrs after ingesting egg yolk (boiled egg yolk; cake containing whole egg) → laboratory analysis: normal CBC, liver function tests, renal function tests, serum albumin and aminoacid levels in serum and urine; total IgE=4.33 kU/l; negative SPT and specific IgE to egg white and yolk → diagnosis: positive OFC with boiled hen’s egg yolk at 12 months of age (vomiting, diarrhea, pallor, irritability, weakness) → successful management: avoidance of egg yolk.
  - Author’s commentary: 1st reported case of FPIES triggered by hen’s egg yolk.
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.


- **Neutropenia**: (i) absolute neutrophil count <1,000/µL in infants (≤1 yr of age) and <1,500/µL thereafter (lower cutoff values should be used in black populations due to shorter neutrophil life); (ii) acute: ≤3-6 months, chronic: >3-6 months; (iii) usually benign (e.g. infection-induced or autoimmune); (iv) occasionally life-threatening (e.g. severe congenital neutropenia [SCN]).

- Author’s studied retrospectively 104 children with recently detected neutropenia (patients with neutropenia due to chemotherapy, proliferative disorders and myelodysplastic syndromes were excluded) → (i) 66 patients (63.5%) had chronic neutropenia (most frequent forms: chronic idiopathic neutropenia [CIN], autoimmune neutropenia [AIN]); (ii) congenital neutropenia was identified in 6 patients (3 cases of SCN; 1 case of CD40L deficiency; 1 case of methylmalonic aciduria); (iii) acute neutropenia was mainly post-infectious; (iv) among patients with AIN and CIN, ~50% recovered within 7-46 months and ~25% had significant infections during follow-up.


- Allergic diseases have dramatically increased (probably due to environmental and lifestyle factors; unlikely due to genetic causes). Risk factor: ↓ exposure to pathogens during childhood → insufficient maturation of regulatory immunity.

- Helminths: (i) metazoan parasites that can ↓ host’s immunity to prevent their elimination and ↓ severe pathology in the host; (ii) infect ~1 billion people worldwide; (iii) risk factors for infection: living in tropical regions, poverty, poor sanitation; (iv) immune response to helminths depends on the infected tissue and the type of helminth (e.g. TH2 vs T regulatory responses).

- Relationship between helminth infections and allergic diseases: (i) helminth infections may protect, promote or have no effect on allergic sensitization/disease (recombinant allergen technology may help to clarify this relationship); (ii) contributing factors: type of helminth, site of infection, host’s characteristics; (iii) antihelmintic therapy may either worsen or relieve allergic sensitization and disease; (iv) helminth infections can induce IgE cross-reactivity (often clinically irrelevant) against allergen proteins (e.g. tropomyosin, paramyosin, glutathione S-transferase) or glycans (e.g. xylose, core-3-linked fucose); (v) a prominent feature of helminth infection consists in high levels of IgE against allergens without SPT reactivity; (vi) helminth products have been used as therapies to promote immune tolerance and treat inflammatory conditions (e.g. Trichuris suis eggs to treat allergies and IBD); (vii) further research is necessary.


- IL-4: (i) essential cytokine for TH2 immune responses; (ii) actions: TH2-cell differentiation, B-cell switching to IgE production, ↑ MHC-II expression on mast cells (also basophils?); (iii) therapeutic target for allergic diseases.

- Sources of IL-4: (i) TH2 lymphocytes; (ii) innate lymphoid cells type 2; (iii) basophils.

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• **IL-4-expressing non-T cells**, particularly basophils, might play an essential role in the early development of food allergy.

  - Mothers of food-allergic children, but not children themselves, had increased levels of anxiety and stress, especially when there was a history of poorly controlled asthma and anaphylaxis.
  - Hepatitis A, Toxoplasma gondii and salmonella infections did not have significant association with allergic sensitization to food and aeroallergens.
  - Childhood neutropenia has diverse etiologies (benign causes are more frequent [e.g. post-infectious, autoimmune or idiopathic neutropenia]; severe causes can occur [e.g. severe congenital neutropenia or metabolic disease]).

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

• IgE-mediated cow’s milk (CM) allergy: (i) prevalence: 1-2% of children; (ii) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (iii) ~70% of children outgrow CM allergy spontaneously by 8 yrs of age; (iv) up to 75% of children with CM allergy tolerate baked CM products (in this children consumption of baked CM accelerates tolerance to raw CM); (v) some children recover tolerance to CM incompletely (e.g. some children tolerate minimal quantities of CM but react to ‘normal’ intake; others react to CM only when cofactors are present [e.g. infections, exercise]); (vi) CM oral immunotherapy (OIT) can restore tolerance to CM.

• **OIT** for FA is under active investigation; potential benefits: long-lasting acquisition of tolerance, ↑ QoL, ↓ danger of accidental food exposure.

• Main limitations of OIT: (i) lack of evidence of long-lasting efficacy (RCTs with cow’s milk, egg and peanut OIT have reported successful desensitization in 33–90% of subjects; however, ability of OIT to induce long-lasting tolerance remains uncertain); (ii) allergic reactions during OIT, including reactions to previously tolerated doses (common triggers: concurrent infection, physical activity within 2 h, poorly controlled asthma, empty stomach, pollen season, menses); (iii) OIT should be performed by expert physicians in an appropriate environment; (iv) patient and family should collaborate actively.
Mechanisms of OIT: (i) ↑ specific T regulatory cells; (ii) ↑ IL-10–secreting B regulatory cells (BR1 cells [CD25^{high}, CD71^{high}, CD73^{low}]); (iii) deletion, suppression and anergy of effector T cells (TH2, TH1, TH17); (iv) ↑ specific IgG4 and IgA; (v) ↓ specific IgE (poor correlation with clinical improvement); (vi) very early desensitization of mast cells and basophils (within hours; mediated by upregulation of histamine 2 receptors?); (vii) ↓ migration and activation of allergy effector cells (eosinophils, basophils, mast cells).

Authors studied 32 children (6-17 yrs of age) with CM allergy (26 children who successfully completed OIT; 6 children who discontinued OIT due to adverse reactions) → (i) children who achieved desensitization after OIT: IgE binding to CM peptides decreased, IgG4 binding increased, IgE and IgG4 antibodies more often recognized the same epitopes; (ii) children who discontinued OIT due to adverse reactions: quantity and affinity of epitope-specific IgE antibodies increased, diversity of IgE and IgG4 binding increased, IgE and IgG4 antibodies less often recognized the same epitopes; (iii) IgE affinity to CM epitopes may discriminate children who will complete OIT successfully from those who will have to discontinue therapy.

Author’s commentary: detailed analysis of IgE and IgG4 binding to CM peptides may help to predict whether CM OIT will be tolerated successfully.

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