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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February 2014 – content:


• **NEW APPROACHES TO THE PREVENTION OF CHILDHOOD ATOPIC DERMATITIS** (Flohr C, Mann J. Allergy 2014; 69: 56–61).

• **NEW INSIGHTS INTO THE EPIDEMIOLOGY OF CHILDHOOD ATOPIC DERMATITIS** (Flohr C, Mann J. Allergy 2014; 69: 3–16).


• **SYSTEMIC THERAPY FOR ATOPIC DERMATITIS** (Simon D, Bieber T. Allergy 2014; 69: 46–55).


• **ASPIRIN ALLERGY IN PATIENTS WITH MYOCARDIAL INFARCTION: THE ALLERGIST’S ROLE** (McMullan KL. Ann Allergy Asthma Immunol 2014; 112: 90-93).

• **BIOLOGIC TARGETED THERAPY IN ALLERGIC ASTHMA** (Bice JB, Leechawengwongs E, Montanaro A. Ann Allergy Asthma Immunol 2014; 112: 108-115).


• **EFFECT OF VITAMIN D ON T-HELPER TYPE 9 POLARIZED HUMAN MEMORY CELLS IN CHRONIC PERSISTENT ASTHMA** (Keating P, Munim A, Hartmann JX. Ann Allergy Asthma Immunol 2014; 112: 154-162).

• **MICE MATTER** (Kelly BT, Grayson MH. Ann Allergy Asthma Immunol 2014; 112: 87-89).


• ADVANCES IN ALLERGIC SKIN DISEASE, ANAPHYLAXIS, AND HYPERSENSITIVITY REACTIONS TO FOODS, DRUGS, AND INSECTS IN 2013 (Sicherer SH, Leung DYM. J Allergy Clin Immunol 2014; 133: 324-334).


• INFECTION-INDUCED WHEEZING IN YOUNG CHILDREN (Beigelman A, Bacharier LB. J Allergy Clin Immunol 2014; 133: 603-604).


ALLERGY:

  - **Athy**: predisposition to develop IgE-mediated allergic diseases (e.g. allergic rhinitis, allergic asthma, atopic dermatitis).
  - **Atopic dermatitis (AD)**: (i) common chronic skin disease (3% of adults, 20% of children); (ii) impact: ↓ QoL, high costs, ↑ predisposition to skin infections (bacterial, viral) and other allergies (~1/3 of AD patients develop asthma, ~2/3 develop allergic rhinitis); (iii) multiple pathogenic factors (genetic, epigenetic, environmental); (iv) varied clinical phenotypes (extrinsic, intrinsic, autoallergic); (v) normal-looking skin of AD patients may have invisible inflammation and barrier defect → ‘proactive therapy’ is encouraged (long-term, low-dose, intermittent anti-inflammatory therapy to previously affected skin + continuous moisturizing of unaffected skin).
  - **Atopic march**: atopic dermatitis (± food allergy) → asthma and allergic rhinitis.
  - Important points about atopic march: (i) skin barrier defect is proposed as the primary pathogenic mechanism (skin barrier defect → pruritus and skin inflammation → allergen penetration (food and respiratory allergens) → immune dysregulation → TH2 responses, IgE sensitization → development of other allergies); (ii) it usually occurs in childhood; (iii) appearance of diseases may not follow the same order (e.g. asthma can precede AD); (iv) all diseases do not always occur (e.g. some patients do not develop food allergy or asthma); (v) environmental factors can modify the atopic march (e.g. antibiotic use, microbiota disruption, exposure to pollutants and allergens); (vi) it is important to promote behaviors and therapies that may prevent or stop the atopic march (e.g. allergen immunotherapy, appropriate skin hydration, ↓ exposure to house dust mite, use of probiotics/prebiotics); (vii) there is no definitive proof that the atopic march is causal.

  - **Omalizumab**: (i) recombinant humanized anti-IgE mAb → binds to free IgE → ↓ IgE binding to its receptors, ↓ expression of IgE receptors → ↓ IgE-mediated inflammation; (ii) approved for [uncontrolled asthma + serum IgE levels between 30 and 700 IU/mL + sensitization to perennial allergens]; (iii) dose is calculated in a chart, based on body weight and pretreatment IgE levels (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) efficacy has also been documented in nonallergic asthma, chronic urticaria, atopic dermatitis, mastocytosis, eosinophilic chronic rhinosinusitis, idiopathic and exercise-induced anaphylaxis.
  - **Filaggrin**: (i) important protein for normal skin barrier; (ii) expressed by keratinocytes; (iii) not expressed by nasal, bronchial or esophageal epithelium; (iv) main source of pyrrolidone carboxylic acid [PCA] and urocanic acid [UCA] (components of the natural moisturizing factor); (v) loss-of-function FLG gene mutations occur in 30% of AD patients (also associated to asthma, chronic rhinosinusitis and food allergy); (vi) TH2 cytokines ↓ filaggrin synthesis.
• Authors prospectively studied 20 adults with moderate-to-severe AD who received omalizumab → (i) 4 patients had very good response (↓ in SCORAD ≥50%), 4 patients had satisfying results (↓ in SCORAD 25–50%), 5 patients had no relevant response (↑ or ↓ in SCORAD <25%), 7 patients had disease worsening (↑ SCORAD); (ii) responders were characterized by the absence of FLG mutations and high serum levels of various glycerophospholipids (hypothesis: immunodysregulative features, rather than skin barrier defects, may predominate in AD patients who respond to omalizumab).

• **NEW APPROACHES TO THE PREVENTION OF CHILDHOOD ATOPIC DERMATITIS** (Flohr C, Mann J. Allergy 2014; 69: 56–61):
  
  • *Immune tolerance*: (i) definition: nonresponsiveness of the adaptive immune system or active Treg response to antigens; (ii) mechanisms: anergy or deletion of reactive lymphocytes, generation of Treg cells.

  • 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. skin barrier defect → allergen entry through skin → TH2/TH22 inappropriate responses → atopic dermatitis [AD]).

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

    • Ideas to induce immune tolerance and prevent AD, especially in high-risk infants (positive family history, early wheezing): (i) improve skin barrier (e.g. using emollients, avoiding early use of soap and detergents, upregulating FLG expression); (ii) promote early tolerance to food and respiratory allergens (rather than avoiding allergen exposure during pregnancy or infancy).

    • Ideas to induce early tolerance to foods and aeroallergens: (i) adequate breastfeeding, (ii) early exposure to foods, (iii) use of probiotics and prebiotics during pregnancy and infancy, (iv) use of cow’s milk hydrolysates when indicated, (v) use of bacterial lysates, (vi) vit D supplementation, (vii) supplementation with n-3 long chain polyunsaturated fatty acids from fatty fish and fish oil.

• **NEW INSIGHTS INTO THE EPIDEMIOLOGY OF CHILDHOOD ATOPIC DERMATITIS** (Flohr C, Mann J. Allergy 2014; 69: 3–16):

  • Atopic dermatitis (AD): (i) common chronic skin disease (3% of adults, 20% of children); (ii) prevalence has ↑ globally; (iii) proposed risk factors: genetic susceptibility (e.g. skin barrier defects), Cesarean delivery, ↓ breastfeeding, “Western” diet, early use of broad-spectrum antibiotics, ↓ farm exposure, ↓ helminth infections, ↓ tolerogenic gut microbiota, ↑ exposure to pollutants, irritants and allergens, ↓ exposure to UV light, obesity, ↓ exercise; (iv) impact: ↓ QoL, high costs, ↑ predisposition to skin infections and other allergies.

• Atopic eczema has been associated with: (i) ↓ risk of glioma, meningioma and acute lymphoblastic leukemia; (ii) ↑ risk of attention-deficit hyperactivity disorder.

• Atopic eczema was not associated with diabetes mellitus type 1 or multiple sclerosis.

• Prospective studies with better methodological quality are needed to evaluate nonallergic comorbidities of atopic eczema.

**SYSTEMIC THERAPY FOR ATOPIC DERMATITIS** (Simon D, Bieber T. Allergy 2014; 69: 46–55):

• Therapy of atopic dermatitis (AD): (i) trigger avoidance; (ii) emollients; (iii) topical corticosteroids (advantages: potent antiinflammatory effect, ↑ expression of filaggrin and loricrin; disadvantages: ↓ restoration of the stratum corneum, ↓ expression of involucrin and small proline-rich proteins); (iv) topical calcineurin inhibitors (advantages: do not impair skin restoration; disadvantages: milder antiinflammatory effect compared to corticosteroids); (v) systemic therapies (see below); (vi) research therapies: H4R blockers (↓ pruritus, ↓ skin inflammation), topical PPARα activators, cannabinoids, inducers of FLG synthesis.

• Most patients with AD respond well to topical therapy. Some patients require systemic therapy.

• Systemic therapy for AD: (i) indicated for patients with severe disease refractory to adequate topical treatment (atopic lid eczema and blepharoconjunctivitis often require systemic therapy to ↓ lid damage and ectropium); (ii) most therapies are not approved for AD (except cyclosporin in some European countries); (iii) drug election depends on patient’s age, disease severity, localization, complications, concomitant diseases, drug availability, costs and doctor’s experience; (iv) clinical and laboratory work-up is mandatory before starting immunomodulatory therapies, including exclusion of underlying active infections (e.g. hepatitis B or HIV); (v) adverse effects of systemic therapy must be monitored.

• Systemic therapeutic options for AD: systemic corticosteroids, cyclosporine (do not combine with phototherapy due to ↑ risk of skin cancer), azathioprine (risk of myelosuppression is higher in patients with thiopurine methyltransferase [TPMT] deficiency), mycophenolate mofetil, methotrexate, alitretinoin (be careful with teratogenicity), intravenous immunoglobulin (IVIG 2 g/kg per month for 6 cycles), omalizumab (anti-IgE mAb), rituximab (anti-CD20 mAb), mepolizumab (anti-IL-5 mAb), anti-IL-6 therapy (↑ risk of infections), anti-TNF-α therapies (do not seem effective), interferon-gamma (does not seem effective), antibiotics (to eradicate S aureus), antivirals (e.g. in eczema herpeticum), antifungals (e.g. to eradicate Malassezia sp), immunoabsorption, allergen-specific immunotherapy, phototherapy, vit D, antihistamines (H1R blockers).

• Omalizumab + IVIG + rituximab has been applied to patients with severe AD resulting in drastic clinical improvement and long-term effects.

• ‘Futuristic’ therapy of AD: determine specific AD phenotypes and endotypes using clinical, laboratory, histologic and genetic biomarkers → individualize therapy.

**TH17 CELLS AND TISSUE REMODELING IN ATOPIC AND CONTACT DERMATITIS** (Simon D, Aeberhard C, Erdemoglu Y, Simon H-U. Allergy 2014; 69: 125–131):

• Eczematous lesions in atopic dermatitis (AD), allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) look clinically similar.
• **Classical concepts:** (i) AD results from exaggerated TH2 responses to allergens, microbial molecules or autoantigens; (ii) ACD results from exaggerated TH1 responses to haptens; (iii) ICD results from epidermal damage and inflammation caused by chemicals.

• Authors evaluated acute eczematous skin lesions of AD, ACD and ICD → (i) IL-17, IL-21, IL-22 and remodeling markers (MMP-9, procollagen-3, tenasin C) were expressed in all skin lesions; (ii) IL-22+ T cell numbers correlated with eosinophil numbers; (iii) IL-17+ T cell numbers correlated with tenasin C-expressing cells and MMP-9+ eosinophils.

• Author’s commentaries: (i) IL-17 and IL-22 may promote tissue remodeling and eosinophil recruitment, respectively → promising therapeutic targets in eczema; (ii) hypothesis: TH17 responses in the skin → production of IL-17, IL-21, IL-22 and IL-23 → eosinophil recruitment and activation → secretion of pro-fibrotic cytokines (TGF-β, IL-11) → skin remodeling.

• **Pathogenic factors in AD:** (i) **Skin barrier defects:** scratching, ↓ synthesis of epidermal barrier proteins (e.g. filaggrin, loricrin, involucrin, corneodesmosin, S100 proteins, desmoglein 1, antiproteases [e.g. LEKTI], tight junction proteins [e.g. claudin-1]) due to genetic mutations or TH2 cytokine influence (e.g. histamine action) → increased entry of allergens through skin, ↑ susceptibility to skin infections (e.g. eczema herpeticum).

• (ii) **Innate immune dysregulation:** ↑ inflammatory dendritic cells, altered TLR signalling (e.g. TLR2 gene polymorphism), ↓ production of antimicrobial peptides (e.g. cathelicidin, defensins), ↑ keratinocyte production of cytokines that promote a TH2 environment (e.g. TSLP, IL-25, IL-33), ↑ production of neuropeptides (AD is usually associated with stress).

• (iii) **Adaptive immune dysregulation** (determined by genetic factors [e.g. polymorphisms in IL4RA, hypomethylation of FcεRIγ-chain DNA]) and environmental factors [e.g. Staphylococcal superantigens, allergens, low vit D]): ↑ TH2 inflammation (IL-4, IL-13, IL-5, IgE, IL-31 → skin barrier dysfunction and pruritus), ↑ TH22 inflammation (promotes acanthosis), altered TH1 responses (predisposition to viral and bacterial infections [e.g. eczema herpeticum]), altered TH17 responses (predisposition to bacterial and fungal infections; ↑ TH17 responses correlated with AD severity; IL-17 and IFN-γ can induce T-cell-mediated keratinocyte killing in an antigen-independent manner), ↓ Treg responses.

• (iv) **Exaggerated immune responses** to food allergens (e.g. milk, egg), aeroallergens (e.g. house dust mites), microbial molecules (e.g. from S aureus or Malassezia sp) or self antigens (e.g. human thioredoxin).

• (v) **Abnormal skin colonization by microbes:** S aureus colonizes the skin in 90% of AD patients (staphylococcal enterotoxins induce polyclonal T-cell and B-cell activation; staphylococcal extracellular vesicles induce inflammation); Malassezia sp colonize frequently the skin of AD patients.


• IgE-mediated food allergy: (i) increasing prevalence worldwide (6% of children and 4% of adults in the westernized world); (ii) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (iii) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soybeans,
seafood; (iv) diagnosis: specific IgE detection by skin prick test (SPT) or in vitro testing (slgE, component-resolved testing), basophil activation test, food challenge (DBPCFC is the gold standard); (v) conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling, follow-up to check for spontaneous development of tolerance; (vi) optimal treatment: restore tolerance by exposing patients to gradually increasing doses of allergen (immunotherapy).

- Authors performed a systematic review and metaanalysis (24 studies, 2831 participants) to investigate the accuracy of diagnostic tests for food allergy (SPT, slgE, component-resolved diagnosis [CRD], atopy patch test [APT]) → (i) evidence was limited and weak; (ii) overall, SPT and slgE appear sensitive but not specific for diagnosing IgE-mediated food allergy (test performance may differ between foods); (iii) APT may have poor sensitivity but good specificity (limited evidence); (iv) more evidence is needed.


- Authors performed a systematic review and metaanalysis to investigate the epidemiology (incidence, prevalence, time trends, risk factors, prognostic factors) of food allergy (FA) in Europe → (i) most studies had moderate risk of bias; (ii) lifetime prevalence of self-reported FA=17.3%; (iii) point prevalence of self-reported FA=5.9%; (iv) point prevalence of food challenge-confirmed FA=0.9%; (v) point prevalence of sensitization to ≥1 food=10.1% (by specific IgE), 2.7% (by skin prick test); (vi) FA incidence appears stable over time but prevalence may be increasing; (vii) no consistent risk or prognostic factors for the development or resolution of FA were identified (sex, age, country of residence, familial atopy and personal atopy seem to be important); (viii) more evidence is necessary.


- Important relationships between atopic dermatitis (AD), allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD): (i) children and adults with AD are frequently sensitized to contact allergens, including topical therapies (e.g. lanolin, corticosteroids), metals (due to compromised chelation in the stratum corneum) and airborne haptens (plants and fragrances) → patch testing can be useful to confirm it; (ii) patients with AD are predisposed to ICD; (iii) ‘false-positive’ patch test readings to certain contact allergens (especially metals) are higher in patients with AD; (iv) haptens/contact allergens stimulate TH2 responses in patients with AD (compared to TH1 responses in normal controls); (v) exposure to haptens and irritants at early life may predispose to AD; (vi) excessive and prolonged chemical exposure appears to exacerbate quiescent AD.
ANNALS OF ASTHMA, ALLERGY & IMMUNOLOGY:

• AEROALLERGEN BOTANY (Weber RW. Ann Allergy Asthma Immunol 2014; 112: 102-107):
  • Plants: important source of allergens (e.g. airborne pollens from anemophilous plants).
  • Authors explain: (i) the evolution of pollination techniques, (ii) the characteristics of anemophilous plants (plants that pollinate through wind), floristic regions and respirable pollen particles, (iii) the impact of meteorologic parameters and climate change on pollen dispersal.
  • Wind pollination has survival benefit in regions where vectors (e.g. insects) are scarce.
  • Important points about climate: (i) climate is determined by long-term weather conditions, including seasonal changes; weather represents the daily occurrences of climate; (ii) T° has ↑ 0.7°C in the past 100 yrs and is projected to ↑ by 1.8-5.0°C from 1999 to 2099 in US; (iii) main reason for global warming: greenhouse gas concentrations (CO₂, methane and nitrous oxide reflect infrared radiation back to the earth); (iv) greenhouse gases remain in the atmosphere → even if emissions were abruptly stopped, global warming would likely persist for decades.
  • Climate changes (rain, humidity, wind, T°, sunshine) can affect pollen concentration and distribution. Examples: (i) ↑ humidity is associated with ↓ pollen counts (e.g. pollen-releasing grass anthers close when humidity rises); (ii) rainfall trap pollen grains and mold spores (especially sustained little raindrops [~0.2 mm]) → ↓ pollen allergy; (iii) thunderstorms can suddenly ↑ pollen and spore counts → dramatic epidemics of asthma.
  • Symptoms of ragweed hay fever can persist for days after intact airborne pollen is no longer detectable (hypothesis: persistence of fragmented pollen grains in submicron particles).

• ASPIRIN ALLERGY IN PATIENTS WITH MYOCARDIAL INFARCTION: THE ALLERGIST’S ROLE (McMullan KL. Ann Allergy Asthma Immunol 2014; 112: 90-93):
  • Drug desensitization (DS): (i) induction of transient tolerance in a drug-allergic patient; (ii) used when the drug is obligatorily needed and no reasonable alternative therapy exists (e.g. penicillin-allergic pregnant women with syphilis); (iii) mainly performed in IgE-mediated reactions but also seems to work for non-IgE reactions; (iv) 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); (v) DS is usually a risky procedure; (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 immunocytotoxic reactions, vasculitis or bullous skin diseases.
  • Drug graded challenge: (i) procedure aimed to confirm or rule out drug hypersensitivity; (ii) does not modify immune response.
  • It is thought that graded challenges of >4-5 steps may induce DS → there is a gray area determining crossover from a graded challenge to DS → it is proposed that graded challenge protocols should have ≤4 steps and DS protocols ≥6 steps.
• Acetylsalicylic acid (ASA): (i) antiinflammatory and antiplatelet drug; (ii) essential therapy in patients with coronary artery disease [CAD] (other antiplatelet drugs should be additions, not substitutions).

• Hypersensitivity to NSAIDs: (i) Intolerance: pharmacologic mechanism (inhibition of cyclooxygenase-1 [COX-1]); cross-reactivity between COX-1 inhibitors; reactions include respiratory and/or cutaneous manifestations (e.g. aspirin-exacerbated respiratory disease [AERD]); higher prevalence than allergy. (ii) Allergy: immunologic mechanisms (e.g. IgE- or T-cell-mediated); selective reactivity; less frequent than intolerance.

• Management of intolerance to NSAIDs: (i) avoidance of COX-1 inhibitors; (ii) use of selective COX-2 inhibitors as alternative antiinflammatory drugs (usually well tolerated; useless as antiplatelet therapy); (iii) DS to ASA (frequently effective but requires continuous therapy; tolerance disappears within 2-5 days after NSAID discontinuation).

• ASA hypersensitivity occurs in a significant % of CAD patients and hampers antiplatelet therapy → ASA DS is usually needed (efficacy >80%; ASA 81 mg/day usually maintains DS; it is unknown if β-blockers should be stopped before DS; premedication with anti-H1 and corticosteroids is not recommended because it can mask early signs of hypersensitivity).

• Authors present several protocols for ASA DS in patients with CAD → benefits of DS in ASA-hypersensitive patients with CAD (especially myocardial infarction) usually outweigh risks.

• Protocols for ASA DS may differ between patients with only AERD and those with AERD + CAD → (a) DS for only AERD is somewhat combined with graded challenge since a critical goal of the procedure is to demonstrate a mild respiratory reaction, thus confirming the hypersensitivity and placing the patient in a refractory state to complete DS. (b) Graded challenge can be dangerous in a patient with AERD + CAD, so allergists usually go straight to DS.

• In patients with CAD + ASA-induced acute urticaria/angioedema (intolerance), it is not defined if ASA graded challenges are safe or allergists should go straight to ASA DS.

• In patients with ASA-induced chronic urticaria and angioedema, flares of urticaria and angioedema usually persist despite ASA DS.

• BIOLOGIC TARGETED THERAPY IN ALLERGIC ASTHMA (Bice JB, Leechawengwongs E, Montanaro A. Ann Allergy Asthma Immunol 2014; 112: 108-115):

• ~10% of patients with asthma do not benefit with conventional therapy (inhaled corticosteroids, LABA, antileukotrienes) → it is important to develop new therapies based on asthma pathogenesis (e.g. biologic targeted therapy).

• Pathogenesis of allergic asthma: (i) disruption of airway epithelial tight junctions and activation of epithelial cells by allergens (e.g. house dust mite proteases, fungal spores, pollen germination), pollutants (e.g. cigarette smoke) and virus (e.g. respiratory syncytial virus) in a genetically susceptible subject → (ii) entry of allergens through the disrupted epithelium or intact epithelial cells (transcytosis) → (iii) secretion of TSLP, IL-25 and IL-33 from activated epithelial cells → (iv) activation of type 2 innate lymphoid cells (ILCs) by TSLP, IL-25 and IL-33 → (v) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from type 2 ILCs → (vi) activation of dendritic cells (DCs) by cytokines (TSLP, IL-25, IL-33) and PRR-mediated signalling → (vii) maturation of DCs (expression of TH2-favoring costimulatory molecules [OX-40L]; secretion of
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TH2-attracting cytokines [CCL17, CCL22]; presentation of allergen-derived peptides in MHC-II molecules → (viii) attraction and differentiation of TH2 cells via antigen presentation, costimulatory molecules (OX40L, CD80/CD86) and cytokine signalling (IL-4) → (ix) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from TH2 lymphocytes → (x) IgE production from B cells; attraction and activation of effector allergy cells (mast cells, eosinophils, basophils); mucus secretion by epithelial cells → (xi) airway inflammation, epithelial injury, bronchoconstriction, air trapping, airway remodeling (goblet cell hyperplasia, thickening of the reticular basement membrane, subbasement fibrosis, smooth muscle hypertrophy/hyperplasia, angiogenesis).

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

• Examples of biologic therapies for asthma: (i) anti-IgE mAb: omalizumab (the only FDA-approved biologic to treat asthma), (ii) anti-IL-4Rα mAb: dupilumab (blocks IL-4 and IL-13 pathways), AMG-317; (iii) IL-4Rα antagonist: pitrakinra (blocks IL-4 and IL-13 pathways); (iv) IL-4 trapping agent: altrakincept; (v) anti-IL-5 mAb: mepolizumab, reslizumab; (vi) anti-IL-5R mAb: benralizumab (reduce eosinophil and basophil count); (vii) anti-IL-13 mAb: lebrikizumab, tralokinumab, anrulkinzumab; (viii) anti-TNF-α therapies: etanercept, infliximab, adalimumab, golimumab (risk of severe side effects); (ix) antagonists of CRTH2: AMG-853, OC000459 (block PGD2 action on TH2 cells, eosinophils and mast cells); (x) TLR7 agonists: imiquimod, resiquimod; (xi) TLR9 agonist: QbG10.

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

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

• Monoclonal antibodies can be conjugated with cytotoxic chemotherapeutic or radiotherapeutic agents to affect cellular targets (e.g. tositumomab [anti-CD20] for non-Hodgkin lymphoma; brentuximab [anti-CD30] for anaplastic large cell lymphoma).


  • Galactose-α-1,3-galactose [α-Gal]: major blood group oligosaccharide of nonprimate mammals.

  • Allergy to α-Gal: (i) develops after tick bites (α-Gal is present within the GI tract of the ticks Amblyomma americanum and Ixodes ricinus) → production of specific IgE to α-Gal (frequently accompanied by ↑ total IgE); (ii) clinical manifestations: delayed allergic reactions (3-6 hrs) after ingestion of red meat containing α-Gal (beef, pork, lamb), severe immediate allergic reaction to the 1st infusion of cetuximab (a chimeric mouse-human mAb that blocks EGFR; it contains the α-Gal epitope on the Fab portion); (iii) diagnosis: specific IgE detection by in vitro testing (skin testing appears inaccurate); (iv) allergy to α-Gal can rarely remit spontaneously after tick bite avoidance for 1 to 2 yrs; (v) IgE to α-Gal is not associated with rhinitis or asthma.
• It seems that oral exposure to α-Gal in a “naive” subject results in specific IgG2 production and immune tolerance.

• Bovine- and porcine-derived gelatin can be considered a potential occult food allergen because exposure is ubiquitous (gelatin can be present in colloids, tablets, capsules, vaccines, confectioneries [e.g. marshmallows], food thickeners, glazes, yogurt, mayonnaise, ice cream, sausage coatings, salami, fruit juice, wine, “hydrolyzed protein” in shampoo, collagen implants, “catgut” sutures).

**EFFECT OF VITAMIN D ON T-HELPER TYPE 9 POLARIZED HUMAN MEMORY CELLS IN CHRONIC PERSISTENT ASTHMA** (Keating P, Munim A, Hartmann JX. Ann Allergy Asthma Immunol 2014; 112: 1548-162):

- 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) ↓ production of TH1 and TH17 cytokines; (vi) ↑ differentiation of Treg cells; (vii) ↓ function of B-lymphocytes; (viii) ↓ production of IgE; (ix) ↑ IL-10 production by mast cells.

- Hypovitaminosis D has been associated (frequently but not uniformly) with ↑ occurrence or severity of allergy (allergic sensitization, recurrent wheezing, asthma, allergic rhinitis, food allergy, atopic dermatitis).

- T-helper type 9 (TH9) cells: (i) differentiate in the presence of TGF-β and IL-4; (ii) transcription factors: PU.1, IRF4; (iii) secrete IL-9 predominantly; (iv) actions: ↑ mucus secretion, ↑ mast cell activation; (v) can play a role in defense against helminths and asthma pathogenesis.

- Authors show that vitamin D and dexamethasone can ↓ TH9 responses in patients with chronic persistent asthma.

**MICE MATTER** (Kelly BT, Grayson MH. Ann Allergy Asthma Immunol 2014; 112: 87-89):

- Some types of research cannot be performed in human subjects due to ethical issues → animal models are important.

- Arguments that favor the use of mouse models for medical research: (i) mice are easy to manipulate due to small size, (ii) mice reproduce easily; (iii) mouse genes can be easily knocked out; (iv) mouse models have aided in the advancement of medicine for many years.

- Arguments against the use of mouse models for medical research: (i) mice and humans differ in many aspects of physiopathology; (ii) many therapies that work in mice do not work in humans.

- The utility of mouse models lies in their ability to identify potential mechanisms that may underlie human disease, not in directly mimicking human disease.

**OROLINGUAL ANGIOEDEMA ASSOCIATED WITH OLMESARTAN USE AFTER RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR TREATMENT OF ACUTE STROKE** (Wang S, Bi X, Shan L, Zhou Y. Ann Allergy Asthma Immunol 2014; 112: 175-183):

- Angiotensin-converting enzyme inhibitors (ACEI): (i) ↓ bradykinin metabolism → frequent cause of bradykinin-induced angioedema (RR=13.6); (ii) time to angioedema onset: 1 day to 11 yrs (typically >1 yr) after initiating ACEI therapy.
• **Angiotensin receptor blockers (ARBs):** (i) good substitute antihypertensive drugs for patients who do not tolerate ACEI; (ii) can rarely cause angioedema (2-17%) in patients with previous history of ACEI-induced angioedema.

• **Recombinant tissue plasminogen activator (rt-PA):** (i) thrombolytic therapy; (ii) can activate complement and kinin pathways; (iii) may cause angioedema, especially in patients using ACEI.

• Authors report the case of an 80-yr-old woman who developed angioedema (dyspnea, throat pain, swelling of the tongue, uvula and lips; normal serum levels of C3, C4 and C1 inhibitor) few minutes after rt-PA infusion for acute stroke → angioedema partially resolved with systemic corticosteroids but persisted after using olmesartan (20 mg/d) → angioedema completely resolved when olmesartan was discontinued.

• **Author’s commentary:** 1st report of angioedema associated with the use of olmesartan after rt-PA administration.


  • **Chronic urticaria (CU):** (i) definition: recurrent wheals for >6 wks (concomitant angioedema may occur); (ii) lifetime prevalence: 1-20% of the population; (iii) impact: significant morbidity, ↓ QoL (similar to angina pectoris), high costs; (iv) main classification: spontaneous (no clear triggers; 50% of cases are ‘autoimmune’), inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise); spontaneous and inducible urticaria can co-occur in the same patient; (v) 1st-line treatment: anti-H1 at usual dosing (50% of patients may not respond); (vi) 2nd-line treatment: up to quadruple dose of anti-H1 (50% of patients may not respond → antihistamine-refractory CU); (vii) other reported therapies: mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A, sulfasalazine, chloroquine, dapsone, calcineurin inhibitors, mycophenolate, pseudoallergen-free diet, anticholinergic agents, androgens, selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants; (viii) prognosis: 50% of cases may resolve spontaneously within 1 yr; 75% of cases within 5 yrs.

  • **Omalizumab:** (i) recombinant humanized anti-IgE mAb → binds to free IgE → ↓ IgE binding to its receptors, ↓ expression of IgE receptors → ↓ IgE-mediated inflammation; (ii) approved for uncontrolled asthma + serum IgE levels between 30 and 700 IU/mL + sensitization to perennial allergens; (iii) dose is calculated in a chart, based on body weight and pretreatment IgE levels (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) efficacy has also been documented in chronic urticaria, mastocytosis, anaphylaxis (idiopathic, exercise-induced), eosinophilic chronic rhinosinusitis, atopic dermatitis.

  • Authors evaluated the effect of omalizumab 150 mg/month in 68 patients with severe difficult-to-treat CU in a real-life setting → (i) 61 patients had spontaneous CU, 6 had cold urticaria, 1 had urticarial vasculitis; (ii) patients were followed up for 25 months; (iii) ~70% of patients achieved complete remission; (iv) urticaria-activity score and corticosteroid use were markedly ↓; (v) all patients with cold urticaria became symptom free; (vi) omalizumab maintenance doses could be given every 6-12 wks; (vii) no serious adverse events were reported during the study.
• Author’s commentary: omalizumab 150 mg can be an effective and safe therapy for patients with severe difficult-to-treat CU.
**JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:**

- **A NOVEL MUTATION IN IFN-γ RECEPTOR 1 PRESENTING AS MULTISYSTEM MYCOBACTERIUM INTRACELLULARE INFECTION** (Rose DM, Atkins J, Holland SM, Infante AJ. J Allergy Clin Immunol 2014; 133: 591-592):
  - Mendelian susceptibility to mycobacterial disease (MSMD): (i) monogenic disorders that share susceptibility to BCG and nontuberculous mycobacteria; (ii) many patients are also susceptible to intracellular bacteria (most frequently Salmonella), fungi (Histoplasma, Coccioidiodes) and virus (VZV, CMV); (iii) to date, mutations in 9 genes (IFNGR1, IFNGR2, STAT1, IL-12β p40 [IL12B], IL12RB1, NEMO, ISG15, IRF8, GATA2) have been associated with MSMD.

- Interferon-γ receptor 1 (IFNGR1) deficiency has 2 inheritance patterns: (i) recessive IFNGR1 deficiency: loss of function of both IFNGR1 alleles → loss of expression of IFNGR1 on the cell surface → usually complete loss of response to IFN-γ [more severe] (partial deficiency has also been described [less severe]); (ii) dominant negative heterozygous IFNGR1 mutations: a mutant IFNGR1 allele generates nonfunctional IFNGR1 molecules that stay in the cell surface and interfere with the function of the wild-type IFNGR1 allele (less severe phenotype).

- Authors report the case of a 15-month-old boy with disseminated *Mycobacterium intracellulare* infection causing multifocal osteomyelitis (ribs, long bones, skull) and pneumonia → genetic diagnosis: novel heterozygous frameshift mutation (805delT) in the IFNGR1 gene, causing a dominant negative effect (↑ IFNGR1 [CD119] expression in the cell surface) → successful treatment: antimycobacterial therapy (isoniazid, rifampin, ethambutol, azithromycin) followed by antimycobacterial prophylaxis.

- **ADVANCES IN ALLERGIC SKIN DISEASE, ANAPHYLAXIS, AND HYPERSENSITIVITY REACTIONS TO FOODS, DRUGS, AND INSECTS IN 2013** (Sicherer SH, Leung DYM. J Allergy Clin Immunol 2014; 133: 324-334):
  - Authors review important research advances in anaphylaxis, allergic skin diseases, and hypersensitivity reactions to foods, drugs and insects that were reported in the Journal of Allergy and Clinical Immunology in 2013.

  - Advances in anaphylaxis: (i) may affect at least 1.6% of adults in US; (ii) most frequent triggers: drugs (35%), foods (32%), insect stings (19%); (iii) use of antihypertensive drugs (β-blockers, ACE-inhibitors, diuretics), high PAF levels, older age, pre-existing lung disease and drug triggers were reported as risk factors for severe anaphylaxis; (iv) epinephrine autoinjectors are underprescribed and underused; (v) agonists of the sphingosine-1-phosphate receptor 2 could be novel therapeutic agents for anaphylaxis.

  - Advances in atopic dermatitis (AD): (i) defects in skin barrier proteins (filaggrin, hornerin, etc.) are involved in AD pathogenesis; (ii) *Tmem79* deficiency contributed to AD development; (iii) *IL-10* polymorphisms may influence Treg cell activity and AD development; (iv) a functional IL-6 receptor variant has been identified as a risk factor for persistent AD; (v) most AD patients have ↑ TH2 and TH22 activity → atopy, lack of epithelial differentiation; (vi) increased IL-13 and IL-22 expression was found in AD skin; (vii) atopic fibroblasts can downregulate terminal differentiation of epidermal keratinocytes (fibroblast-derived factors might be new therapeutic targets for AD); (viii) patients with intrinsic AD may have ↑ TH17 activity (but weaker than psoriasis); (ix) normal-looking skin of AD patients may present invisible inflammation; (x) the
clinical AD phenotype is influenced by multiple factors, including pollution, pet exposure, endogenous antigens (e.g. sweat antigens) and gut microbiota; (xi) an updated practice parameter to manage AD was published; (xii) meta-analysis support a role for allergen-specific immunotherapy in AD management; (xiii) patients with AD can have significant mental health comorbidity; (xiv) AD might predispose to development of contact dermatitis.

- **Advances in urticaria:** (i) a polymorphism in the thromboxane A1 synthase gene was related to NSAID-induced acute urticaria; (i) D-dimer might be a useful biomarker for antihistamine-resistant chronic urticaria; (ii) omalizumab was safe and effective for antihistamine-resistant chronic urticaria; (iv) canakinumab (anti–IL-1 mAb) ↓ disease activity of urticarial vasculitis.

- **Advances in food allergy:** (i) ~7% of people reports food allergy (many of them are not really allergic); (ii) food allergy ↑ risk of asthma hospitalization; (iii) severe eczema and filaggrin deficiency are risk factors for food allergy (hypothosis: eczema → skin barrier dysfunction → ↑ food allergen entry through skin → sensitization to food); (iv) peanut allergen is found distributed throughout the home in relation to household consumption; (v) use of specific hydrolyzed formulas in comparison with cow’s milk might ↓ eczema rate in high-risk children; (vi) earlier introduction of wheat, rye, barley, oat, fish and egg was associated with protection from asthma, allergic rhinitis and atopic sensitization at age 5 yrs; (vii) earlier egg exposure did not ↑ egg allergy; (viii) a “healthy diet” (fruits and vegetables) and vit D sufficiency might protect against food allergy; (ix) AAAAI recommends exclusive breast-feeding for ≥4 months, use of hydrolyzed formula for infants unable to breast-feed, and early introduction of complementary foods; (x) food elimination diet (avoiding milk, egg, cereals, fish/shellfish, peanut/legumes and soy) can be effective in adults with EoE; (xi) “baked milk” can be tolerated in a subset of patients with milk-induced EoE; (xii) the mast cell–eosinophil–IL-9 axis is important for EoE inflammation; (xiii) EoE had ↑ prevalence among patients with connective tissue disorders (e.g. Marfan, Ehlers-Danlos and Loeys-Dietz syndromes), possibly involving an altered TGF-β pathway; (xiv) ondansetron can ↓ vomiting during FPIES reactions; (xv) production of IgE to galactose-alpha-1,3-galactose (α-Gal) is associated with B-negative blood groups; (xvi) gelatin candies and gelatin-derived medicinal products might have α-Gal; (xvii) pork immediate allergy can be attributable to sensitization to cat albumin; (xviii) wheat-associated, exercise-induced anaphylaxis can be triggered by the use of facial soaps containing acid-hydrolyzed wheat; (xix) a murine model elucidated a strong relationship between food allergy and the gut microbiome; (xx) immune response to food allergens can be affected by the type of fats in the diet (affect allergen absorption); (xxi) allergen component testing is an important tool for food allergy diagnosis (e.g. specific IgE to Ara h 2 is a good predictor of peanut allergy); (xxii) 95% predictive values for allergic reactions during OFCs in infants: egg (SPT wheal >4 mm; sIgE >1.7 kU/A/L), peanut (SPT wheal >8 mm; sIgE >34 kU/A/L), sesame (SPT wheal >8 mm); (xxiii) calculators to predict milk allergy occurrence and resolution were developed (the latter is available at www.cofargroup.org); (xxiv) OFC is required for diagnosis in many patients with food allergy (the procedure must include the form of the food that will be eaten after testing); (xxv) children with wheat allergy might tolerate whole-grain wheat cereal biscuits; (xxvi) factors that might predict the resolution of milk allergy include specific IgE level, SPT wheat size and AD severity; (xxvii) peanut sublingual immunotherapy (SLIT) safely induced a modest level of desensitization in a majority of subjects; (xxviii) oral immunotherapy (OIT) produce better responses but more side effects than SLIT; (xxix) the larger question is whether food IT can induce permanent tolerance; (xxx) food IT is not yet ready for clinical practice; (xxxi) combining OIT + omalizumab may facilitate desensitization; (xxxii) murine models suggest novel IT
strategies using allergen and IgG Fcγ1, and desensitization strategies using anti-FceRIα mAb; (xxxii) studies of allergen threshold might result in opportunity to improve ingredient labels; (xxxiv) vaccination with injectable influenza is safe in patients with egg allergy.

- **Advances in drug allergy:** (i) false-positive *in vitro* specific IgE tests to penicillin can occur; (ii) serum procalcitonin levels could differentiate drug hypersensitivity vs bacterial infection (best cutoff value=1.67 ng/mL); (iii) most patients with self-reported drug allergy are really not allergic; (iv) a high incidence of delayed-type hypersensitivity reactions to heparin was noted among pregnant women; (vi) immediate allergy to quinolones was associated with neuromuscular blocking agent sensitization.

- **Advances in hypersensitivity to stinging insects:** (i) mast cell disease and baseline serum tryptase are risk factors for *Hymenoptera* venom anaphylaxis (mast cell load did not correlate with anaphylaxis risk); (ii) venom immunotherapy is safe and effective in patients with systemic mastocytosis; (iii) the conventional yellow jacket venom ImmunoCAP might have reduced sensitivity because of incomplete capture of *Ves* v 5–reactive IgE; (iv) cross-reactive carbohydrate determinants may not interfere with serum testing for paper wasp allergy.


  - Clinical characteristics and biological mechanisms of disease can no longer be addressed separately.

  - 2 ways to link biological information and clinical phenotyping: (i) hypothesis-dependent approach: most common method, research is based on "known" biological pathways (which might be erroneous); (ii) unbiased approach: not based on a priori hypotheses, allows discovery of new biological networks in disease, can be performed by high-throughput "-omics" analysis of complex matrices (e.g. blood, sputum, exhaled air).

  - -omics: molecular fingerprints at the genetic (genomics), transcriptional (transcriptomics), protein (proteomics) or metabolic level (metabolomics), in relation to clinical disease features.

  - Asthma is a clinical syndrome with multiple endotypes and phenotypes (e.g. TH2-high asthma, TH2-low asthma).

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

- **FOOD ALLERGY: EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSIS, AND TREATMENT** (Sicherer SH, Sampson HA. *J Allergy Clin Immunol* 2014; 133: 291-307):

  - Authors present an excellent extensive review about advances in the epidemiology, pathogenesis, diagnosis and treatment of food allergy.

  - Food allergy (FA): (i) IgE-mediated: urticaria, angioedema, bronchospasm, anaphylaxis; (ii) non-IgE-mediated: food-protein mediated enterocolitis and proctocolitis, Heiner syndrome, celiac disease; (iii) IgE- and cell-mediated: atopic dermatitis, eosinophilic gastroenteropathies; (iv) cell-mediated: allergic contact dermatitis.
• Important points about FA: (i) increasing prevalence: up to 10% of the population; (ii) several genetic and environmental factors play a role in FA pathogenesis; (iii) diagnosis depends on clinical history and appropriate allergy testing; (iv) food allergen sensitization does not imply clinical reactivity and vice versa; (v) sensitization to food allergens can occur by nonoral routes (e.g. allergy to α-gal after tick bites, allergy to peanut after sensitization through skin); (vi) component-resolved diagnosis (CRD) is a promising diagnostic tool that adds sensitivity and specificity; (vii) management of FA depends on the clinical syndrome; (viii) a “personalized medicine” approach to diagnose and treat FA is likely required but remains elusive.

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

• Factors associated with FA: (i) genetic susceptibility; (ii) ↑ intestinal inflammation; (iii) ↓ gut epithelial barrier; (iv) use of gastric acid suppressive drugs; (v) ↑ ‘proinflammatory’ microbiota (e.g. Clostridium, Staphylococcus); (vi) ↓ ‘tolerogenic’ microbiota (e.g. Lactobacillus, Bifidobacterium); (vii) ↑ TH2 responses (including IgE production); (viii) food sensitization through skin; (ix) vitamin D insufficiency; (x) unhealthful dietary fat; (xi) obesity; (xii) increased hygiene; (xiii) “inappropriate” timing of 1st exposure to foods.

• Oral immunotherapy (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 (RCT with cow’s milk, egg and peanut OIT have reported desensitization in 33–90% of subjects; however, ability for 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) it should be performed by expert physicians in an appropriate environment; (iii) patient and family should collaborate actively.

• How to ↑ efficacy and safety of OIT? (i) adding omalizumab (anti-IgE mAb); (ii) using modified allergens (baked food, recombinant allergens, peptides), (iii) adding immune response modifiers (monophosphoryl lipid A [TLR-4 agonist], CpG containing DNA [TLR-9 agonist], probiotics); (iv) personalized OIT schemes.

• **Food allergy (FA):** increasing prevalence, life-threatening potential, high costs → public health concern.

• **Animal models of FA:** important tool to identify potential pathogenic mechanisms and hypothesize therapies; may not reflect human disease appropriately.

• Authors review insights into the etiology, treatment and prevention of human FA based on research in murine models.

• Improved understanding of FA from the study of animal models + human studies = novel strategies to prevent and treat FA.

• **INFECTION-INDUCED WHEEZING IN YOUNG CHILDREN** (Beigelman A, Bacharier LB. J Allergy Clin Immunol 2014; 133: 603-604):

  • **Wheezeing during early childhood:** (i) common condition (~50% of children have ≥1 wheezing episode before 6 yrs of age, most of them do not continue wheezing at school age); (ii) 80-90% of episodes are associated with viral infections (especially respiratory syncytial virus [RSV] and human rhinovirus [HRV]); (iii) factors that affect wheezing severity: age, genetic background, basal lung function, atopic status, exposure to pollutants (e.g. cigarette smoke); (iv) clinical syndromes: acute viral bronchiolitis, recurrent viral-induced wheezing, viral-induced asthma.

  • **Viral bronchiolitis:** (i) definition: initial episode of virus-induced lower respiratory tract infection (RTI) in a child <1-2 yrs of age; (ii) 2 major culprit viruses: RSV and HRV; (iii) other culprit viruses: human metapneumovirus, parainfluenza virus; (iv) leading cause of hospitalization during winter among young children; (v) major role in the development of wheezing and asthma (especially for severe RSV-induced bronchiolitis and outpatient HRV-induced wheezing); (vi) it remains uncertain whether severe bronchiolitis is a cause of asthma ["the first hit"] or a marker for asthma susceptibility; (vii) the best treatment for acute bronchiolitis is undefined (β2-agonists, oral corticosteroids [OCSs], inhaled corticosteroids [ICSs], montelukast and antibiotics have not shown consistent benefit; nebulized 3% saline or [nebulized epinephrine + oral dexamethasone] may help); (viii) how to prevent asthma and recurrent wheezing after severe bronchiolitis is undefined (ICSs and montelukast have not shown consistent benefit; systemic corticosteroids may help).

  • **Virus-induced recurrent wheezing:** (i) 2 categories, which may overlap: children who wheeze exclusively during viral infections (episodic viral wheeze), and children who wheeze after multiple triggers (e.g. virus, allergens, exercise); (ii) early treatment with high-dose ICSs or montelukast might be beneficial during upper RTIs to prevent severe wheezing episodes (benefit of OCSs is undefined).

  • **Asthma:** (i) usually presents before 5 yrs of age; (ii) frequently underdiagnosed or misdiagnosed in early childhood (inappropriate labels: chronic bronchitis, wheezy bronchitis, reactive airway disease, recurrent pneumonia, recurrent upper RTIs, GERD); (iii) not every wheezing infant will develop asthma (40% of children wheeze within 1st yr of life but only 30% of preschoolers with recurrent wheezing will have asthma at 6 yrs); (iv) there is no accurate single screening test to predict which young children with recurrent wheezing will develop asthma.

  • It is difficult to diagnose asthma in children <5 yrs old because at this age: (i) clinical manifestations are variable, nonspecific and difficult to describe; (ii) differential diagnosis is broad (e.g. acute viral wheeze, cystic fibrosis, ciliary dyskinesia, primary immunodeficiency,
vascular ring, tracheomalacia, congenital heart disease, parasitic disease, foreign-body aspiration); (iii) it is difficult to assess airflow limitation and airway inflammation (e.g. routine lung function tests are difficult to perform).

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

- Young children with frequent wheezing (≥3 times/yr), wheezing without colds and no alternative diagnosis → give a therapeutic trial with ICSs for 3 months.

  - IgE: (i) important role in defense against some parasitic infections; (ii) its production is dysregulated in allergic diseases; (iii) total IgE concentrations can be affected by several factors (age, geographic location, diet, climate).
  - Authors measured total IgE in 1376 healthy children (6 months-17 yrs old) and 128 adults (19-69 yrs old) by the ImmunoCAP 1000 instrument (Phadia, Uppsala, Sweden) → reference intervals were considerably higher on the upper end than those reported previously.

  - The Primary Immune Deficiency Treatment Consortium (PIDTC): network of 33 centers in North America that study the treatment of rare and severe PIDs (severe combined immunodeficiency [SCID], Wiskott-Aldrich syndrome [WAS], chronic granulomatous disease [CGD]).
  - Authors present the current PIDTC goals and activities (including research): (i) research protocols to address the natural history of patients treated for SCID, WAS and CGD; (ii) programs and grants to promote training of junior investigators; (iii) partnerships with international colleagues; (iv) collaboration with patient advocacy groups to promote community awareness; (v) further research to determine optimal therapies for severe PIDs.

  - IgE-mediated food allergy (FA): (i) increasing prevalence worldwide (6% of children and 4% of adults in the westernized world); (ii) impact: significant morbidity, ↓ QoL, mortality risk; (iii) >170 foods have been reported to cause allergic reactions; (iv) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soybeans, seafood; (v) diagnosis: specific IgE detection by skin prick test (SPT) or in vitro testing (sIgE, CRD), basophil activation test, food challenge (DBPCFC is the gold standard); (vi) conventional treatment: allergen avoidance (does
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.

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).

- **Food immunotherapy (IT):** (i) potential benefits: acquisition of long-lasting tolerance, ↓ danger of accidental exposure, ↑ QoL; (ii) limitations: severe allergic reactions during treatment (most IT protocols have excluded subjects with severe FA), potential lack of efficacy (short- or long-term); (iii) 3 routes under active investigation: oral (OIT), sublingual (SLIT), epicutaneous (EPIT); (iv) despite active research and promising results, IT is not ready for routine clinical use.

- **OIT:** advantages: more efficacy than SLIT, largest evidence (including multiallergen OIT); limitations: more adverse effects than SLIT or EPIT (anaphylaxis, induction of EoE), including reactions to previously tolerated doses (common triggers: concurrent infection, physical activity within 2 h of a dose, poorly controlled asthma, empty stomach, pollen season, menses).

- **SLIT:** advantages: less adverse effects than OIT; limitations: less efficacy than OIT.

- **EPIT** (using patches): advantages: less adverse effects than OIT; limitations: less evidence.

- **How to ↑ efficacy and safety of IT?** (i) adding omalizumab (anti-IgE mAb); (ii) using modified allergens (heated allergen [egg, milk], recombinant allergens, peptides), (iii) adding immune response modifiers (monophosphoryl lipid A [TLR4 agonist], CpG containing DNA [TLR-9 agonist], probiotics); (iv) using plasmid DNA-encoded vaccines; (v) using fusion proteins.


  - **Hematopoietic cell transplantation (HCT):** (i) procedure that can cure many severe combined immunodeficiencies (SCID); (ii) 10-yr survival rates have improved progressively; (iii) immune reconstitution after HCT may vary depending on the molecular defect (e.g. T-cell reconstitution is better in B+ SCID than in B- SCID; functional B-cell reconstitution is better if there is donor B-cell engraftment in case of X-linked and JAK-3 SCID); (iv) few studies have investigated the details of long-term clinical and immunologic function in SCID patients post-HCT.

  - There is a lack of consensus about: (i) optimal conditioning regimens before HCT (no or minimal conditioning is desired but graft rejection or loss may occur), (ii) the definition of graft failure, (iii) the indication for delivery of a “boost” (additional graft from the same donor without conditioning), (iv) the indication for retransplantation (additional graft from either the same or a different donor with conditioning).

  - Authors conducted a survey among 20 North American and 5 European transplant centers to study the approaches to retransplantation for patients with SCID → despite some trends, there is a lack of consensus on criteria to define graft failure or indications for retransplantation in patients with typical SCID who attain poor immune reconstitution.

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

• **Diagnosis of PIDs can be difficult because:** (i) >170 different PID-causing genes have been described; (ii) clinical and laboratory presentation of PIDs can be very variable (e.g. RAG mutations can present with SCID, Omenn syndrome or hyper-IgM syndrome; WASP mutations can present with Wiskott-Aldrich syndrome, X-linked thrombocytopenia or X-linked neutropenia); (iii) current PID diagnostic approach is often dominated by phenotypic and functional characterization (time-consuming); (iv) genetic diagnosis is classically performed by Sanger sequencing (laborious, time-consuming, not available for several genes).

• **Next-generation sequencing (NGS):** (i) rapid, accurate, low-cost, high-throughput sequencing technology that has successfully identified mutations in novel PID-causing genes; (ii) useful diagnostic tool for complex PIDs, particularly for patients with atypical disease presentation.

• Authors report a robust, time-effective and cost-effective NGS-based diagnostic method that facilitated accurate simultaneous detection of mutations in 161 of 170 known PID-related genes, including point mutations (sensitivity and specificity >99% in covered regions) and exonic deletions (100% sensitivity and specificity).