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

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

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PEARLS IN ALLERGY AND IMMUNOLOGY

May 2013 – content:


• EVIDENCE MOUNTS THAT VIRUSES DRIVE ATOPIC DEVELOPMENT (Sigua JA, Grayson MH. J Allergy Clin Immunol 2013; 131: 1340-1341).


• INHIBITION OF POLYETHYLENE GLYCOL–INDUCED HISTAMINE RELEASE BY MONOMERIC ETHYLENE AND DIETHYLENE GLYCOL: A CASE OF PROBABLE POLYETHYLENE GLYCOL ALLERGY (Wenande EC, Skov PS, Mosbech H, Poulsen LK, Garvey LH. J Allergy Clin Immunol 2013; 131: 1425-1427).


• PRACTICAL APPROACH TO NUTRITION AND DIETARY INTERVENTION IN PEDIATRIC FOOD ALLERGY (Groetch M, Nowak-Wegrzyn A. Pediatr Allergy Immunol 2013: 24: 212–221).


ALLERGY:


- Allergic reactions during general anesthesia (incidence: 1/1480 to 1/20000) can interrupt surgery. Skin tests to detect culprit drugs are suggested minimum at 4-6 wks after the reaction because of the ‘refractory period’ (consumption of mediators from mast cells and basophils?). But what should be done if surgery is required urgently? Is it useful to perform earlier skin tests?

- Authors studied 44 patients (12–82 yrs old) with hypersensitivity reactions during anesthesia. Skin tests were done at ‘stage 1’ (0-4 days after the reaction) and ‘stage 2’ (4-8 wks after the reaction) → (i) skin tests were positive in 25/44 patients (57%); (ii) 12/25 patients had positive skin tests in both ‘stages’; 3/25 had positive skin tests only in ‘stage 1’; 10/25 had positive skin tests only in ‘stage 2’; (iii) overall agreement between tests at both ‘stages’ was 70.45%; (iv) odds ratio of obtaining a false negative in ‘stage 1’ (compared with ‘stage 2’) was 3.33.

- Author’s commentaries: (i) early skin tests are useful to detect culprit drugs in patients with allergic reactions during general anesthesia, especially when surgery is needed urgently; (ii) early skin tests do not completely replace late skin tests, both should be done.

- Personal commentary: it is important to note that in the current study ‘antihistamines were avoided by the anesthetist in the treatment of the reactions’.

**IgE-MEDIATED ANAPHYLAXIS AND ALLERGIC REACTIONS TO IDURSULFASE IN PATIENTS WITH HUNTER SYNDROME** (Kim J, Park MR, Kim DS, Lee JO, Maeng SH, Cho SY, Han Y, Ahn K, Jin DK. Allergy 2013; 68: 796–802):

- Mucopolysaccharidosis type II (MPS II, Hunter syndrome): rare (0.5/100,000 live births) X-linked genetic deficiency of the lysosomal enzyme iduronate-2-sulfatase; glycosaminoglycans accumulate and damage organs (skeletal deformities, neurologic impairment, cardiomyopathy, airway obstruction); therapy: early replacement with recombinant human idursulfase (Elaprase; Shire Human Genetic Therapies, Cambridge, USA), a purified form of iduronate-2-sulfatase.

- Authors studied 34 patients with MPS II who received intravenous Elaprase (0.5 mg/kg/week) → (i) 3 patients had anaphylaxis, 4 patients had only urticaria/angioedema, no deaths; (ii) anaphylaxis was related to specific IgE antibodies [diagnosis: SPT (2 µg/ml), IDR (0.02 ml at 0.002 µg/ml), ELISA, immunoblotting]; (iii) SPT could predict all 3 cases of anaphylaxis; (iv) the overall sensitivity and specificity of SPT was 66.7% and 100%; (v) the overall sensitivity and specificity of sIgE detection by ELISA was 100% and 22.2%; (vi) patients with anaphylaxis had also specific IgG antibodies; (vii) no risk factors for allergic reactions could be detected.

- Author’s commentaries: (i) 1st report of sIgE against Elaprase in patients with allergic reactions; (ii) immediate allergy to Elaprase seem to be mediated by de novo-produced sIgE (rather than sIgG); (iii) SPT before Elaprase infusion may be used as a screening test for anaphylaxis.

- Specific IgE antibodies have been reported in patients receiving other biologic agents (eg. OKT3 in transplant recipients, laronidase for MPS I, alglucerase for Gaucher disease).

  • Authors present a diagnostic algorithm to evaluate patients with chronic urticaria/angioedema.
  
  • Differential diagnoses of chronic urticaria/angioedema: autoinflammatory disorders (hereditary or acquired), autoimmune diseases, urticarial vasculitis, bradykinin-mediated angioedema (ACEI-induced, hereditary or acquired C1-inh deficiency).


  • Plasmacytoid dendritic cells (pDCs): (i) In a homeostatic environment (no danger signals): poor antigen presentation to CD4+ T cells; high expression of IDO, PD-L1, RALDH enzymes (convert retinol into retinoic acid) and GITRL → suppression of T effector cells, generation of FOXP3+ Treg cells → tolerogenic effects (especially CD8α+β- and CD8α+β+ pDC subtypes). (ii) In an inflammatory environment (viral danger signals): viral nucleic acids activate TLR7 and TLR9 on pDCs → type-I IFN production → antiviral immunity, asthma exacerbations?


  • Skin tests are useful and generally safe to diagnose drug allergy: (i) positive skin tests, when performed correctly, usually confirm drug allergy; (ii) negative skin tests do not exclude drug allergy, further drug challenge is required in most cases.

  • Authors present an ENDA/EAACI position paper that describes: (i) safe and non irritant drug concentrations to perform skin prick and intradermal tests with betalactam antibiotics, perioperative drugs, heparins, platinum salts and radiocontrast media; (ii) the need for multicentre studies to validate protocols for drug skin tests.

  • For most drugs, sensitivity of skin testing is higher in immediate than in nonimmediate allergy.

• **THE CRUX WITH A RELIABLE IN VITRO AND IN VIVO DIAGNOSIS OF ALLERGY** (R. Crameri. Allergy 2013; 68: 693–694):

  • Diagnosis of allergic diseases: clinical history, skin tests, in vitro detection of specific IgE (slgE), provocation tests.

  • Problems related to in vitro and in vivo detection of IgE: (i) extracts may not contain all relevant allergenic epitopes; (ii) extracts may contain cross-reactive carbohydrate determinants (~20% of allergic patients have clinically irrelevant antiglycan IgE); (iii) detection of slgE do not confirm clinical relevance; (iv) negative slgE detection in skin or serum do not exclude local IgE production in mucosal tissues (entopy).
• **Component-resolved diagnosis (CRD)** using hundreds of recombinant allergens could be more sensitive and specific than conventional extracts to diagnose IgE sensitization. However, problems (iii) and (iv) (see last paragraph) are not solved by CRD.

• The practicing allergist must correlate allergologic test results with the clinical history.

**USEFULNESS OF OMALIZUMAB IN TEN PATIENTS WITH SEVERE OCCUPATIONAL ASTHMA**


• Authors report 10 patients (20-57 yrs old) with severe uncontrolled occupational asthma who received therapy with [omalizumab](#) (anti-IgE mAb) according to weight and serum total IgE → (i) 6 patients were sensitive to a high molecular weight (HMW) compound (wheat flour, cat, rabbit, storage mites, Alternaria); 4 patients to a low molecular weight (LMW) chemical (isocyanates, acrylates, tetrachloroethylene); (ii) 9 patients improved during 9 patients improved during omalizumab therapy (↑ asthma control, ↓ asthma exacerbations, ↓ use of corticosteroids); (iii) 7 patients could continue working at the same workplace.

• Omalizumab may improve severe uncontrolled occupational asthma induced by LMW and HMW agents → improvement of quality of life; prevention of employment loss.

**ACUTE GENERALIZED EXANTHEMATIC PUSTULOSIS DUE TO IBUPROFEN**


• Ibuprofen: over-the-counter NSAID in many countries.

• **Acute generalized exanthematic pustulosis (AGEP):** rare delayed drug-induced reaction; most frequently induced by antibiotics; occasionally caused by NSAIDs; **diagnosis:** clinical history, patch tests, lymphocyte transformation tests.

• Authors report the case of a 47-yr-old man with AGEP after intake of ibuprofen 600 mg for foot-ache (multiple painful and itchy pustular lesions with underlying erythema on the neck, trunk, arms, legs and buttocks, followed by desquamation; no fever; suggestive histology; **positive dose-dependent basophil activation test**) → treatment: oral and topical steroids.

• **Author’s commentaries:** (i) it is the 1st time that AGEP is reported as an immediate reaction; (ii) AGEP may include immediate allergic mechanisms.

**EFFICACY OF OMALIZUMAB IN EOSINOPHILIC CHRONIC RHINOSINUSITIS (ECRS) PATIENTS WITH ASTHMA**


• **ECRS:** difficult-to-treat CRS with eosinophil-enriched nasal polyps; associated to severe atopic asthma; ↑ Th2/eosinophil inflammation; ↑ local IgE levels, mainly to S aureus enterotoxin.

• Authors evaluated the efficacy of [omalizumab](#) in 6 ECRS patients (51-78 yrs old) with severe atopic asthma → omalizumab improved rhinological symptoms, sinus CT scores and asthma control after 16 wks of treatment; improvements correlated with ↓ in sputum eosinophil counts and serum periostin levels.

• Omalizumab was effective for ECRS and severe atopic asthma.
• **EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB)** (Pongdee T, Li JT. Ann Allergy Asthma Immunol 2013; 110: 311–315):

  - **EIB**: transient, reversible bronchoconstriction after exercise; occurs in 90% of asthmatics, ~15% of the general population and 50% of elite athletes. **Diagnosis**: clinical history; ↓ 10-15% of FEV1 within 30 min after exercise challenge (exercise at suboptimal intensity/duration or with warm/humid inspired air may cause false-negative results); mannitol challenge.
  - **Mechanisms of EIB** (osmotic theory is more accepted than thermal theory): (i) heating and humidifying large volumes of air in a short period → loss of water from the lower airways → hyperosmolar environment → activation and release of mediators (cysLTs, PGD2, ECP, adenosine, neurokinins, MUC5AC, ↓ PGE2) from mast cells, eosinophils, epithelial cells and nerves → bronchoconstriction; (ii) very intense exercise in athletes → dehydration injury to the airway epithelium → microvascular leak and plasma exudation → bronchoconstriction.
  - A 20-min warm-up at submaximal intensity or 30-sec repeated sprints cause refractoriness to following vigorous exercise (hypothesis: ↓ mast cell mediator stores, ↑ protective PG, desensitization of airway smooth muscle receptors to mediators).
  - **Risk factors for EIB**: dry air, cold air, high ventilation, mouth breathing.


  - Filaggrin (FLG) gene defects have been associated to atopic eczema, bronchial asthma, allergic rhinitis and peanut allergy.
  - Authors show a relationship between a common variant of FLG and food sensitization in 116 Japanese infants (9 to 14 months old), irrespective of concomitant null mutations.
  - **Hypothesis**: FLG dysfunction → skin barrier defect → food sensitization through skin.

• **HYPER IMMUNOGLOBULIN M SYNDROME IN A 15-YEAR-OLD BOY CAUSED BY A GLY219ARG MISSENSE MUTATION** (Katta A, Hong J, Knutsen AP. Ann Allergy Asthma Immunol 2013; 110: 391–393):

  - Hyper immunoglobulin M (HIGM) syndrome: ↓ IgG, ↓ IgA, normal or ↑ IgM; ↓ class switch recombination and affinity maturation in B cells.
  - **CD40L deficiency**: most frequent cause of HIGM syndrome; X-linked inheritance; T-cell defect → combined immunodeficiency, opportunistic infections; HSCT is the only definitive therapy.
  - Authors report the case of a 15-yr-old boy with a ‘mild’ form of HIGM syndrome (recurrent pneumonias, chronic gingivitis, severe varicella, herpes zoster, aplastic anemia at 5 yrs of age, Crohn’s disease at 8 yrs of age, malnutrition; ↓ IgG, normal IgA and IgM; ↓ antibody responses; ↓ T cells, normal total B cell counts, ↓ memory B cells; decreased but not absent CD40L expression and function on activated T cells; ↓ CD40-Ig binding) → **genetic analysis**: ‘leaky’ c.655G>A missense mutation in CD40L gene (this mutation has been found in 1% of healthy population, so pathogenicity is controversial) → patient had good response to IVIG alone.
• Some patients with CD40L deficiency may present with a CVID-like phenotype.


  - 5-10% of patients with asthma remain symptomatic despite guideline-based therapy.
  - **Severe asthma** is associated with: (i) corticoid-refractory eosinophilic inflammation; (ii) neutrophilic inflammation; (iii) irreversible airway remodeling; (iv) features of COPD; (v) ↑ inflammatory markers (LTB4, IL-8, IL-17, TNF-α, MIP, osteopontin, EGFR, etc.).

  How to evaluate airway inflammation in patients with severe asthma? (i) Clinical history and spirometry: frequent inaccurate. (ii) Bronchial biopsies or bronchoalveolar lavage: too invasive to be performed repetitive. (iii) **Other noninvasive methods**: detection of cells and cytokines in induced sputum, FENO, exhaled breath condensate, arachidonic acid metabolites (LT and isoprostanes); diagnostic and prognostic value is not well defined and standardized.

  - **Induced sputum** shows 4 asthma phenotypes: (i) eosinophilic asthma (>3% eosinophils); (ii) neutrophilic asthma (>60% neutrophils); (iii) mixed granulocytic asthma (>3% eosinophils and >60% neutrophils); (iv) paucigranulocytic asthma (<3% eosinophils and <60% neutrophils).

  - **Ideal situation**: determine **asthma phenotype** using specific biomarkers → **personalized therapy** (e.g. eosinophilic asthma may respond better to anti-IL-5).

  - Analysis of **induced sputum** should be available as a routine test in specialized centers to evaluate patients with severe asthma.


  - **Mare (Equus caballus)** milk is used in food supplement pills and cosmetics. Allergy to MM is rare; anaphylaxis to MM has been reported previously.

  Authors report the case of a 44-yr-old woman with: (i) contact dermatitis after using MM-based organic cosmetics (soap and shampoo); (ii) vomiting after eating MM-based dietary supplement pills → SPT, ImmunoCAP, ELISA, Western blot and a lymphoblastic transformation test were positive to MM and/or its derivatives (pills and shampoo) → **diagnosis**: immediate and delayed sensitivity to MM → symptoms resolved after avoidance of all MM-based products.

  - **Cross-reactivities with cow milk**: (i) frequent: goat, sheep; (ii) rare: mare, camel, donkey.


  Authors report the case of a 38-yr-old patient with a steroid-responsive pruritic desquamative dermatitis and hyperkeratosis for 2 yrs; no history of recurrent or opportunistic infections.

  - **Laboratory**: eosinophilia; IgE: 747 kU/L; normal IgG, IgA and IgM; normal antibody response to vaccine antigens; ↓ memory B cells; **almost absent T cells** and CD4 recent thymic emigrants; ↓
TRECs; ↓ lymphocyte proliferation to mitogens, antigens and anti-CD3; positive autoantibodies without evidence of autoimmune disease (dysregulated B cell responses?).

- Genetic analysis: heterozygous mutation (c.256_257delAA, K86VfsX33) in RAG1 gene (this mutation causes SCID or Omenn syndrome (OS) when present as homozygous or compound heterozygous).

- Protein analysis: truncated RAG1 protein; reduced but not absent function.

- Final diagnosis: adult-onset idiopathic T-cell lymphopenia due to RAG1 deficiency.

- Successful treatment: prophylactic antibiotics.

- Patient’s father had the same heterozygous mutation and no clinical abnormality; normal T, B and NK cell numbers → epigenetic, environmental or other genetic factors may influence in RAG1 expression or function.

- Author’s commentaries: (i) genetic defects associated with SCID or OS (eg. RAG1 defects) may present with diverse phenotypes, including milder clinical disease (unlikely to require HSCT; be careful with autoimmunity); (ii) late-onset disease and normal B cell numbers in the patient may be explained by residual RAG1 function; (iii) heterozygous RAG1 mutations may lead to premature immune senescence and T-cell dysfunction; (iv) heterozygous ADA mutations may also present as adult-onset immunodeficiency (immune function also declines over time).


  - Authors present a clinical vignette of a 34-yr-old woman with moderate persistent asthma exacerbated by a viral respiratory infection (↑ cough, ↑ chest tightness, ↑ wheezing, minimal yellow sputum, no fever, normal chest X-rays, ↓ FEV1) → treatment: prednisone and inhaled β-2 agonist; no need for antibiotics, despite frequent use in the past.

  - Asthma: multifactorial disease (genetic, epigenetic and environmental factors).

  - How do microorganisms affect asthma? (i) Viral respiratory infections, especially by RSV, may initiate asthma in an atopic patient. Nearly all children have serologic evidence of RSV infection in their first 2 years of life; only 40% have clinical symptoms of bronchiolitis.

  - (ii) Viral respiratory infections, especially by rhinovirus, are the most frequent infectious cause of asthma exacerbation.

  - (iii) Atypical bacterial infections (M pneumoniae, C pneumoniae) can ↓ asthma control → give macrolides (kill atypical bacteria, ↓ inflammation); therapy duration is not well established, it may require several weeks.

  - (iv) Respiratory allergies are a risk factor for respiratory infections.

  - (v) Type and diversity of microbiota (intestinal and respiratory) favor tolerogenic vs allergic responses: Lactobacillus sp, Bifidobacterium sp and high microbial diversity may ↓ allergy risk; Staphylococcus, Proteobacteria and Acinetobacter sp may ↑ allergy risk.

  - (vi) Probiotics, prebiotics (fiber, SCFA) and microbial particles may be good options to prevent or treat allergic diseases by increasing Treg and Th1 responses.
• (vii) Natural delivery → newborn is colonized by tolerogenic microbiota → ↓ allergy risk.


  • CVID: heterogeneous group of PIDs; diverse etiology; ↓ IgG; susceptibility to infections, autoimmunity and neoplasms; may involve B or T cell defects; it would be useful to classify CVID based on severity and prognostic markers, which will allow more personalized therapies.

  • TREC levels: reflect TCR gene recombination; associated to T-cell neogenesis; most accepted newborn screening test for severe combined immunodeficiencies (SCID).

  • KREC levels: reflect BCR gene recombination (kappa light chain); associated to B-cell neogenesis; newborn screening test for B-cell defects.

  Authors classified 40 CVID patients (2-52 yrs old) based on TREC and KREC levels in 4 groups:

  • (i) Group A: detectable TREC and KREC → low frequency of complications; IVIG therapy had good results; these patients may only have defects in terminal B-cell differentiation.

  • (ii) Group B: detectable TREC only → ↑ autoimmunity and malignancy; some patients may have T-cell defects and should be treated as patients with combined immunodeficiency (CID).

  • (iii) Group C: detectable KREC only → ↓ T cells, markedly ↓ naive T cells; ↑ opportunistic infections, autoimmunity and malignancies; patients should be treated as patients with CID.

  • (iv) group D: undetectable TREC and KREC → markedly ↓ CD4+CD45RA+ naive T cells; ↑ opportunistic infections, autoimmunity and malignancy; one patient died from P jiroveci pneumonia; 2 patients received HSCT for an EBV-related lymphoproliferative disorder; phenotypic similarity to CID; HSCT should be considered in this group of patients.

  Overall, complications (opportunistic infections, autoimmune diseases and malignancies) were highest in group D, followed by group C, B and A. Complications worsened survival.

  • TREC/KREC-based classification: (i) correlates well with clinical severity and survival rate in CVID patients; (ii) may differentiate CVID from CID; (iii) refines therapy for each CVID patient.

• EVIDENCE MOUNTS THAT VIRUSES DRIVE ATOPIC DEVELOPMENT (Sigua JA, Grayson MH. J Allergy Clin Immunol 2013; 131: 1340-1341):

  • Viral respiratory tract infections, especially early-life severe infection by RSV, have been associated with ↑ risk of asthma. Mechanisms and causality are not well defined.

  • TLR7: endosomal pattern-recognition receptor that recognizes single-stranded RNA (ssRNA).

  • Infection by Sendai virus, RSV or influenza in mice → IgE production against: (i) the virus; (ii) an innocuous antigen inhaled during the infection → symptomatic allergy.
Kaiko et al show the following mechanism: TLR7 deficiency in newborn mice → susceptibility to infection by PVM (pneumonia virus of mice, an ssRNA paramyxovirus closely related to RSV) → asthma-like response (TH2 cytokines, airway hyperreactivity, tissue eosinophilia); ↑ IgE levels after repeated infections; IgE production to concomitantly-administered cockroach allergen.

Defects in antiviral immunity might underlie development of post-viral atopy.


Naive and central memory (CM) T cells circulate through lymph nodes (LNs); effector memory (EM) T cells preferentially screen peripheral tissues searching cognate antigen.

ENTRY TO LNs: Interaction of L-selectin (CD62L) on T cells with peripheral node addressins → tethering/rolling along high endothelial venules (HEVs) → interaction of CCR7 and CXCR4 on T cells with CCL19/CCL21 and CXCL12, respectively → LFA-1 conformational change on T cells → interaction of LFA-1 on T cells with ICAM-1 on HEVs → firm adhesion to HEVs → transmigration across endothelium → entry to LN.

EGRESS FROM LNs: Sphingosine-1-phosphate (S1P) gradient → S1P receptor (S1PR)-mediated T-cell migration to cortical sinuses → egress from LN through efferent lymph vessels.

Fingolimod: S1PR antagonist; ↓ LN egress of naive and CM T cells; used for treatment of multiple sclerosis (MS).

Authors studied the effects of Fingolimod in patients with MS: (i) naive CD4+ T cells (CD62L+CD45RA+) started to ↓ in the circulation 2 hrs later; (ii) CM CD4+ T cells (CD62L+CD45RA-) started to ↓ in the circulation 5 hrs later; (iii) naive CD8+ T cells (CD62L+CD45RA+) started to ↓ in the circulation 3 hrs later.

Author’s commentaries: (i) Naive T cells express higher levels of CCR7 and CXCR4 compared to CM T cells → naive T cells are more sensitive to LN-homing chemokines CCL12, CCL19 and CCL21 → naive T cells circulate through LNs more frequently → naive T cells may compete better for antigen and costimulation, surmounting their disadvantage of high activation threshold; (ii) CD4+ T cells enter LNs more often than CD8+ T cells → more access to DCs.


Apoptosis: programmed cell death → ↓ T-cell lifespan.

Autophagy: degradation of cytoplasmic material → ↓ apoptosis → ↑ T-cell lifespan.

The lifespan of T cells, including autoreactive T cells, depends partially on the balance between autophagy and apoptosis.

↑ autoreactive T cells (mainly CD4+CD45RO+ effector T cells) → autoimmune diseases.
• **Hydroxychloroquine (HCQ):** antimalarial drug; also used to treat autoimmune diseases; ↓ production of inflammatory cytokines by macrophages; ↓ antigen presentation.

• **Authors present the following findings and hypothesis:** HCQ (at therapeutic concentrations) → ↓ lysosome acidification and function → ↓ autophagy (determined by accumulation of autophagosomes) → ↑ apoptosis, mainly of CD4+CD45RO+ effector T cells (determined by Annexin V expression) → ↓ autoreactive T cells → ↓ autoimmunity.

• **Author’s commentaries:** (i) CD4+CD45RO+ effector T cells depend more in autophagy to survive, compared to CD4+CD45RA+ naive T cells; (ii) self-reactive T cells in patients with autoimmunity are mainly CD4+CD45RO+ → HCQ will preferentially induce apoptosis in these cells while preserving naive T-cell repertoire; (iii) autophagy is a promising therapeutic target.

• **INHIBITION OF POLYETHYLENE GLYCOL–INDUCED HISTAMINE RELEASE BY MONOMERIC ETHYLENE AND DIETHYLENE GLYCOL: A CASE OF PROBABLE POLYETHYLENE GLYCOL ALLERGY** (Wenande EC, Skov PS, Mosbech H, Poulsen LK, Garvey LH. J Allergy Clin Immunol 2013; 131: 1425-1427):

  • Polyethylene glycols (PEGs) or macrogols: hydrophilic polyethers commonly used in pharmaceutical, cosmetic, food and household products; active ingredient in colonoscopic lavages, solvents, excipients, bulking and dispersing agents; low toxicity and immunogenicity. Nomenclature consists of a number (eg. PEG 4000) that denotes the average molecular weight.

  • Authors report a 27-yr-old atopic woman with allergic reactions after using PEG-containing products: (i) Effexor (venlafaxin containing PEG 400); (ii) Depo-Medrol (methylprednisolone acetate containing PEG 3350) caused anaphylaxis; (iii) Balancid Novum (calcium carbonate magnesium hydroxide containing PEG 6000) caused anaphylaxis; (iv) Helosan (cream containing PEG 100) caused itching.

  • **Diagnostic approach:** (i) SPT, basophil-histamine release/inhibition tests and provocation tests with PEG or PEG-containing products were positive; (ii) normal serum tryptase → low probability of an underlying mast cell disorder; (iii) negative skin and provocation tests to steroid-based products not containing PEG.

  • **Final diagnosis:** probable IgE-mediated allergy to both low- and high-molecular-weight PEGs. Why “probable”? Because there is no commercially available specific IgE assay for PEG.

  • Sensitization to PEG could have occurred during a tattoo procedure that used Vaseline → localized urticaria and palmoplantar pruritus.

  • **Author’s commentaries:** (i) Consider PEG allergy in patients with reactions to PEG-containing substances; (ii) prevalence of PEG allergy may be rising because of its extensive use; (iii) avoidance of PEG-containing products is difficult due to deficient nomenclature and labeling.


  • Genes represent only 2% of the genome.

  • Several transcription factors (Thpok, Runx3, Runx1, Ets1, Tox) and the E proteins E2A and HEB are important for T-cell differentiation into CD4+ or CD8+ T cells.
• CD4+ T cells: (i) normal function: host defense; (ii) excessive function → autoimmunity, allergy.

• CD4+ T cells are grouped in subtypes (Th1, Th2, etc.) according to the "master" transcription factor and main cytokines that they express. There is considerable plasticity between subtypes.

• T-bet → Th1 cells → IFNγ (defence against intracellular microorganisms; autoimmunity); CCR5 and CXCR3 expression.

• GATA3 → Th2 cells → IL-4 (defence against helminths; IgE-mediated allergies); CCR4 and CCR8 expression.

• PU.1 → Th9 cells → IL-9 (defence against helminths; ↑ mucus production in allergies).

• RORγt → Th17 cells → IL-17 (defence against extracellular bacteria and fungi; autoimmunity; neutrophilic asthma); CCR6 expression.

• Antibodies to IL-17 (ixekizumab, secukinumab) may be useful for autoimmune diseases.

• Th22 cells → IL-22 (defence against extracellular bacteria; epithelial regeneration and proliferation; atopic dermatitis).

• Foxp3 → Treg cells → IL-10, TGF-β (tolerance; immune regulation).

• Bl6 → T<sub>FH</sub> cells → IL-21 (help to B cells in germinal centers → CSR, affinity maturation); CXCR5 expression.

• ICOS, SAP or STAT3 deficiency → impaired function of T<sub>FH</sub> → antibody deficiency.

• Examples of T-cell plasticity: (i) ‘signature’ cytokines can be produced by other T-cell subtypes (eg. IL-10 and IL-13 can also be produced by Th1 cells; IFN-γ and IL-10 can also be produced by Th17 cells); (ii) ‘master’ transcription factors can be expressed by different T-cell lineages (eg. the same Th cell can express T-bet and GATA3, or T-bet and Foxp3); (iii) Th cells can change their phenotypes (eg. Th2 or Th17 cells can convert into Th1 cells by type-I IFNs); (iv) additional transcription factors participate in Th cell fate (eg. Hlx, Runx3 and Ets are important for TH1-cell differentiation; (HIF1, Runx1, Aiolos and Fosl2 are important for TH17-cell differentiation); (iv) epigenetics can regulate Th cell fate.

• Th cells could be better classified by ‘transcriptomes’ (global patterns of gene expression).

• Importance of studying T-cell plasticity: (i) to develop better therapies (eg. neutrophilic asthma may respond better to anti-Th17 therapies; reprogramming immune cells in immunotherapy); (ii) to improve research about genetic basis of allergy; (iii) to understand the role of junk DNA and epigenetics; (iv) to develop cellular assays that could predict efficacy of treatments; (v) to study the effects of current therapies in transcriptomes and epigenomes of immune cells.

• T CELLS IN ASTHMA: INFLUENCES OF GENETICS, ENVIRONMENT, AND T-CELL PLASTICITY

(Lloyd CM, Saglani S. J Allergy Clin Immunol 2013; 131: 1267-1274):

• Asthma: high clinical heterogeneity. Pathogenesis: genetic, epigenetic and environmental factors → airway inflammation (TH2 responses predominate, especially in atopic patients; however, not every patient responds to TH2-targeting therapies).

• High T-cell plasticity may explain high phenotypic heterogeneity in asthma.
• Other T cells in asthma: TH17 cells (steroid-resistant neutrophilic asthma); TH22 cells (allergy initiation?); TH9 cells (mast cell activation; ↑ mucous production); Treg cells (asthma control).

• TH cell encounters cognate antigen → TH cell differentiates into a subset (TH1, TH2, etc.) → microenvironment affects TH phenotype even after differentiation (eg. an IL-4-producing TH2 cell can become an IL-17/IL-4-producing ‘dual’ TH cell).

• The IL-17/IL-4-producing dual TH cell could be: (i) a state of transition between TH17 and TH2 subsets; or (ii) a stable ‘dual’ subset. The same principle applies for other ‘dual’ TH cells.

• IL-17 can be produced by: (i) TH17 cells in an inflammatory environment → proinflammatory proneutrophilic role; (ii) γδ T cells in a homeostatic environment → regulatory role. As a consequence, prescribing anti–IL-17 to all patients with high IL-17 levels may result in very different effects.

• Clinical implications of T-cell plasticity for allergic diseases: (i) TGF-β ± retinoic acid ± rapamycin → ↑ FoxP3 expression in antigen-specific TH2 cells → switching into Treg cells → ↓ allergy; (ii) vit D ingestion → ↑ IL-10–secreting CD4+ cells → ↓ allergy.

• Allergen enters airways → 1st contact: epithelial cells → epithelium may have a central role in asthma.

• Asthmatic patients may have ↑ IL-13 → ↓ production of IFN type I from airway epithelial cells → ↓ clearance of respiratory viruses.


  • Egg allergy: 1.6% of children; often resolved by 8 yrs of age; diagnosis: skin tests, IgE detection in vitro, oral food challenges (OFC); treatment: avoidance, epinephrine autoinjectors, oral immunotherapy (IT).

  • OFC with raw egg white (REW): (i) advantages: intact proteins, preserved allergenicity; (ii) disadvantages: bacterial contamination (eg. Salmonella spp).

  • OFC with cooked or baked egg: (i) advantages: ↓ bacterial contamination; (ii) disadvantages: ↓ allergenicity (ovalbumin, lysozyme and ovotransferrin are heat-labile allergens; ovomucoid is a heat-resistant allergen, possibly as a result of its strong disulfide bonds).

  • Dehydrated egg white (DEW): egg white after pasteurization and drying.

  • Authors performed OFC with DEW and REW in 40 egg-allergic patients (2-17 yrs old) to determine correlation between these tests → 10 patients reacted to both DEW and REW (at similar doses); DEW and REW had similar allergenicity (SDS-PAGE and IgE immunoblotting) → DEW is a reliable and microbiologically safer source of allergen to diagnose egg allergy; DEW could be used in egg oral IT.

• **Diagnosis of food allergy:** skin tests, sIgE detection in vitro, oral food challenge (gold standard).

• **How to perform OFC?** (i) open challenges; (ii) single-blinded challenges; (iii) double-blinded placebo-controlled challenges (DBPCFC).

• **Suggestions for DBPCFC:** (i) food should be given in its usual edible form; (ii) total quantity of the food should be similar to a real serving; (iii) food’s taste and consistency should be masked (alternatives: freeze-dried food; concentrated food in capsules; using other foods as ‘maskers’); (iv) food should allow a stepwise increase in dosage (liquid preparations are easier to dose); (v) starting dose depends on the type and severity of previous reactions and eliciting doses.

• As a consequence of these requirements, DBPCFC are hard to standardize.

• Authors present new validated recipes for low-dose DBPCFCs → (i) no sensory differences between active and placebo materials for cow’s milk, hen’s egg, soy, wheat or cod; (ii) taste of the materials was accepted by school-age children; (iii) no side effects related to test materials; (iv) all materials contained the same hypoallergenic liquid vehicle (Elemental 028 extra liquid orange/pineapple flavor), which facilitated preparation and dosing; (v) additional ingredients were added to mask taste; (vi) all foods were used in raw form, except cod (cooked puree).


  • Severe cutaneous adverse drug reactions (SCARs): Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS); typically appear 1–8 wks after initiating the culprit drug; aromatic anticonvulsivants (phenobarbital, phenytoin, carbamazepine) are frequent causal drugs.

  • CYP2C19 (member of cytochrome P450 enzymes): essential role in metabolism of aromatic anticonvulsants; CYP2C19*2 and CYP2C19*3 are poor metabolizing variants; CYP2C19*2 is frequent in Thai individuals.

  • Authors investigated in 40 Thai children (0.5-15 yrs old) the association between: (i) SCARs to aromatic anticonvulsivants; and (ii) genotypes of CYP2C19*1, CYP2C19*2 and HLA-B*1502 → (i) patients with CYP2C19*2 variant had more tendency to develop SCARs compared to CYP2C19 wild type patients; (ii) patients with CYP2C19*2 variant had 4 times more risk of phenobarbital-induced SCARs compared to CYP2C19 wild type patients; (iii) no association was found between HLA-B*1502 and SCARs → CYP2C19*2 variant was a risk factor for phenobarbital-induced SCARs.

  • A previous study showed association between HLA-B*1502 allele and carbamazepine- and phenytoin-induced SJS-TEN in Thai adults.

• **PRACTICAL APPROACH TO NUTRITION AND DIETARY INTERVENTION IN PEDIATRIC FOOD ALLERGY** (Groetch M, Nowak-Wegrzyn A. Pediatr Allergy Immunol 2013: 24: 212–221):

  • Important issues to manage children with food allergy: (i) diagnose correctly food allergy and cross-reactivities; (ii) avoid false labels of ‘food allergy’; (iii) explain thoroughly about food avoidance (avoidance is not simple); (iv) prescribe appropriately epinephrine autoinjectors; (v)
ensure that the patient or guardians know what to do during an allergic reaction; (vi) give written educational material; (vii) avoid extensive unnecessary diets; (viii) avoid food avoidance when allergy to specific foods has not been demonstrated, especially in chronic diseases (eg. atopic dermatitis or eosinophilic esophagitis); (ix) replace the nutrients of avoided foods to meet nutrient requirements and optimize growth (eg. milk-allergic patients require other sources of calcium, riboflavin, phosphorus, pantothenic acid, vit B12, vit D, protein and fat); (x) improve food labeling; (xi) read food-product labels at purchasing and prior to ingestion; (xii) consider food immunotherapy; (xiii) reevaluate the patient periodically to determine development of tolerance (egg, milk, wheat and soy allergies are generally surpassed); (xiii) consider maternal diet in exclusively breastfed infants with suspected food allergy.

• Removing an allergenic-proven food for >2 wks to treat chronic symptoms (eg. egg in atopic dermatitis) may ↑ risk of acute reaction upon reintroduction or accidental ingestion.

• For egg- or milk-allergic patients who tolerate baked products, under-baking may cause allergic symptoms (eg. a frosted cake may have baked milk in the cake but unbaked milk in the frosting; a flavored cracker may contain baked milk in the cracker but unbaked milk in the flavoring).

• Tolerated foods could be contaminated with food allergens during manufacturing → manufacturers often add a preventive label (eg. ‘may contain milk’ or ‘manufactured in a facility that manufactures milk products’); these labels are unregulated, leaving consumers feeling uncertain about the safety of manufactured products.

• Some allergens are not appropriately labeled in manufactured products (eg. sesame or mustard may be hidden in a vague labeling term such as ‘natural flavoring’ or ‘spice’).

• Recommended alternatives to replace milk for cow milk-allergic infants <2 yrs of age: (i) continue breast-feeding with maternal milk avoidance; (ii) use a substitute formula, including fortified soy beverage (other fortified plant-based beverages such as rice, almond and potato ‘milk’ are very low in protein and fat).

• Recommended alternatives to replace milk for cow milk-allergic infants >2 yrs of age: (i) use a substitute formula; (ii) varied diet with calcium supplementation.

• A healthy newborn is able to coordinate sucking, breathing and swallowing; other feeding skills (chewing, taste acceptance) should be learned → breastfed infants with unpleasant experiences or delayed introduction (after 10 months of age) of solid foods may develop food refusal → feeding rehabilitation may be necessary.

• Food protein-induced enterocolitis syndrome (FPIES): commonly starts at <6 months of age and resolves by 3 yrs of age; breast-fed infants with FPIES can typically continue lactating without maternal avoidance; rare cases have been reported in exclusively breast-fed infants.

• Micronutrient supplements: (i) 1 mg iron/kg body weight after 4 months of age; (ii) vit D 400 IU beginning shortly after birth; (iii) some patients require zinc supplements after 4 months of age.

• Elimination diets should be followed by physician-supervised food reintroduction to prove allergenicity.

• We can provide diverse textures with the same tolerated food (eg. a diet of only sweet potato can provide multiple textures: squashed (puree), mashed, soft cooked, fried, etc.).
• Highly refined oils do not contain allergenic proteins → safe option for food-allergic children.


  • Atopic dermatitis (AD): 60% of cases start in infancy; pathogenic factors: (i) ↓ skin barrier, (ii) immune dysregulation, (iii) sensitization to foods, microbes or own antigens; treatment: restore skin barrier, ↓ environmental triggers; ↓ skin inflammation.

  • Malassezia: skin colonizing yeast; colonization occurs immediately after birth; may cause skin infection or IgE-mediated allergy, mainly in AD patients (↓ skin barrier, immune dysregulation).

  • Authors studied 187 infants diagnosed with AD and milk or wheat allergy before 1 yr of age → 10-yr follow-up: (i) 10% of children had ongoing FA; (ii) 27% of children had sIgE to Malassezia mix; (iii) 20% of children had sIgE to M. sympodialis; (iv) sIgE to Malassezia was associated with AD severity (area of affected skin) in infancy; (v) sIgE to Malassezia was associated to FA.

  • Infants with severe AD and FA had increased risk of IgE-sensitization to Malassezia.


  • VODI (OMIM 235550): autosomal recessive (AR) form of combined immunodeficiency (CID) and hepatic sinusoidal obstruction; linked to mutations in the SP110 gene (encodes PML nuclear body protein); pathogenesis is not well understood; clinical presentation: failure to thrive, opportunistic infections (especially P. jiroveci), hepatomegaly, ascites, jaundice; laboratory: severe hypogammaglobulinemia, T- and B-cell immunodeficiency; histology: absent LN germinal centers, absent plasma cells, marked sinusoidal fibrosis, necrosis of pericentral hepatocytes, narrowing and fibrosis of central veins; treatment: supportive care, antimicrobial drugs, IVIG, HSCT (high rates of complications in previous reports).

  • Criteria to diagnose VODI (Roscioli et al): (i) Severe hypogamma with clinical evidence of T-cell dysfunction, including P. jiroveci infection or mucocutaneous candidiasis; (ii) histological evidence of hepatic veno-occlusive disease (hVOD) in the patient or in a 1st-degree relative, not explained by iatrogenic factors; (iii) AR inheritance; (iv) onset before 12 months of age.

  • Hepatic damage in VODI is indistinguishable from hVOD (now called ‘sinusoidal obstruction syndrome’), which follows high-dose myeloablative conditioning during HSCT.

  • When to suspect VODI? Patients with: (i) SCID-like presentation (including normal mitogen response); (ii) signs of hepatic injury.

  • Authors studied 8 Palestinian kindreds with VODI → (i) all had early clinical presentation (<5 months of age); (ii) 4 had P. jiroveci infection; (iii) 6 had clinical hepatic injury; (iv) 2 had liver biopsy consistent with hVOD; (v) 1 had neurologic features (seizures); (vi) frequent cytopenias; (vi) immunological studies: severe hypogamma, normal numbers of T, B and NK cells, normal T-cell proliferation to mitogens, normal TRECsin 3 patients, normal TCR repertoire in 1 patient; (viii) genetics: novel mutation in the SP110 gene; (ix) successful HSCT in 3 out of 5 patients; (x)
mixed chimerism was compatible with adequate immune function and long-term survival; (xi) 1 patient was diagnosed shortly after birth and received IVIG and P. jiroveci prophylaxis until early successful HSCT was done (before development of infectious or veno-occlusive complications).

- **Early HSCT using low-hepatotoxic conditioning** (including treosulfan and prophylactically defibrotide) may correct immune defect and prevent liver disease in patients with VODI.

  - **T-cell defects** may result in different phenotypes: (i) severe combined immunodeficiency, (ii) partial immunodeficiency with immune dysregulation, (iii) predominant autoimmunity.
  - **CD3**: essential molecule for T-cell activation; defects in CD3 γ, ε, δ and ζ chains result in T-cell immunodeficiency (AR inheritance; usual phenotype: T-B+NK+; clinical presentation may be mild [CD3γ defect] or severe [CD3δ, ε, ζ defects]).
  - **CD3γ**: associates with the TCRβ chain; essential for development of the pre-TCR complex and mature TCRαβ–CD3 complex; CD3γ+/— mice have low numbers of T cells and 10-fold lower expression of CD3ε and TCRαβ (or TCRγδ).
  - **CD3γ deficiency**: only 4 cases previously described (recurrent respiratory infections, oral candidiasis, severe diarrhea, peri-anal fistulas, autoimmune hemolytic anemia, Hashimoto’s thyroiditis, vitiligo, autoimmune enteropathy). Treatment: (i) milder cases (more frequent): IVIG, antimicrobial treatment or prophylaxis; (ii) severe cases (rare): HSCT could be considered.
    - **Authors** report 2 female siblings (11 and 30 yrs-old) with autoimmune diseases (Evans syndrome, autoimmune hepatitis, nephrotic syndrome, Hashimoto’s thyroiditis) and no previous history of severe infections → patient 1: ↓ IgG, ↓ IgA, ↓ IgM, ↓ T cells (CD3+, CD4+, CD8+), low TCRαβ expression, low CD25 expression after T-cell stimulation with phytohemagglutinin; patient 2: low TCRαβ expression → genetics: homozygous splicing mutation (IVS2-1G>C) in the CD3γ gene → final diagnosis: CD3γ deficiency presenting only with autoimmunity → successful treatment: IVIG and TMP-SMX prophylaxis for patient 1; observation for patient 2.
    - **Author’s commentaries**: (i) 1st report of Evans syndrome, autoimmune hepatitis and nephrotic syndrome in patients with CD3γ deficiency; (ii) consider CD3γ deficiency in patients with autoimmunity, especially in those with history of infections and family history of autoimmunity; (iii) determination of TCR and CD3 expression may help to diagnose CD3γ deficiency.
  - **Autoimmunity** may be only manifestation in patients with CD3γ deficiency.

  - **Adrenaline**: 1st-line therapy for anaphylaxis; early use of autoinjectors is potentially life-saving; only 20% of individuals use them; adolescents do not use them as expected.
  - **Fatal anaphylaxis** occurs more frequently in adolescents. Why? (i) do not want to carry adrenaline autoinjectors; (ii) fear to use them; (iii) do not know how to use them; (iv) do not use them timely; (v) idea that anaphylaxis will resolve spontaneously; (vi) do not know about their
disease; (vii) do not worry about their disease; (viii) do not follow counsel about allergen avoidance; (ix) do not remember previous allergic reactions.

• How to solve this problem? (i) Discuss thoroughly about disease; (ii) give detailed and didactic education; (iii) explain precise indications for using adrenaline; (iv) revise situation-specific scenarios; (v) work with parents, friends, schools, groups and organizations.