September 2013

General considerations:

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

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

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

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

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September 2013 – content:


- **CONTACT DERMATITIS TO VITAMIN K1 IN AN EYE CREAM** (Lopez-Lerma I, Vilaplana J. Ann Allergy Asthma Immunol 2013; 111: 227–228).


- **IMMUNOTHERAPY FOR MOUSE BITE ANAPHYLAXIS AND ALLERGY** (Bunyavanich S, Donovan MA, Sherry JM, Diamond DV. Ann Allergy Asthma Immunol 2013; 111: 233–234).


- **TREATMENT OF PATIENTS WHO PRESENT AFTER AN EPISODE OF ANAPHYLAXIS** (Lieberman P. Ann Allergy Asthma Immunol 2013; 111: 170–175).

- **USE OF VACCINES IN THE EVALUATION OF PRESUMED IMMUNODEFICIENCY** (Ballow M. Ann Allergy Asthma Immunol 2013; 111: 163–166).

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- EDITOR’S CHOICE (Pediatr Allergy Immunol 2013; 24: 511).
ALLERGY:


  - **Food allergy**: increasing prevalence worldwide; **impact**: mortality, ↓ QoL; **treatment**: avoidance, epinephrine autoinjectors, immunotherapy.
  - **Food allergenicity** can be changed by **processing** (e.g. 60% of egg- or milk-allergic patients may tolerate baked egg or milk, respectively; cooking can ↑ allergenicity of **seafood**).
  - **Tree nuts**: highly nutritive food; major cause of food allergy; cross-reactivity with birch pollen (PR-10 proteins).
  - Authors performed a **systematic review** (32 articles) to assess the effects of processing on the allergenicity of tree nuts → (i) thermal processing (e.g. roasting) reduced allergenicity of PR-10 proteins in hazelnut and almond; (ii) thermal processing did not affect allergenicity of nsLTPs and seed storage proteins in hazelnut, almond, cashew nut, Brazil nut, walnut, pecan nut and pistachio nut.
  - **Author’s commentaries**: (i) patients with allergy to PR-10 proteins in hazelnut or almond may tolerate thermally-processed forms; (ii) oral food challenges (OFCs) with roasted hazelnut or almond may give false-negative results in patients with allergy to PR-10 proteins → OFCs to hazelnut and almond should be performed with raw food.


  - **Proton pump inhibitors (PPIs)**: most potent drugs for suppressing gastric acid secretion; hypersensitivity reactions are rare; several anaphylactic reactions have been reported.
  - Authors performed a prospective study in **65 patients** (22–78 yrs old) with a suggestive history of immediate hypersensitivity to PPIs → (i) suspected culprit PPI: lansoprazole (n= 52), esomeprazole (n=11), pantoprazole (n=9), rabeprazole (n=2), omeprazole (n=1); (ii) **sensitivity**, **specificity**, **NPV** and **PPV** of skin tests with PPIs = 58.8%, 100%, 70.8%, 100%, respectively.
  - **Author’s commentaries**: (i) **skin testing** may help in the diagnosis of immediate hypersensitivity to PPIs; (ii) **skin testing** may help to evaluate cross-reactivity among PPIs; (iii) **oral drug challenges** to PPIs should be performed in patients with negative skin tests.
  - **Solutions for skin prick tests**: (i) smashed oral preparations (omeprazole capsule 20 mg, lansoprazole capsule 30 mg, pantoprazole tablet 40 mg, rabeprazole tablet 20 mg, esomeprazole tablet 20 mg) diluted in 1 ml of 0.9% NaCl; (ii) 1/10 and 1/1 dilutions of **injectable preparations** (omeprazole 4 mg/ml, pantoprazole 4 mg/ml, esomeprazole 8 mg/ml).
  - **Solutions for intradermal tests**: 1/1000, 1/100 and 1/10 dilutions of **injectable preparations** (omeprazole 4 mg/ml, pantoprazole 4 mg/ml, esomeprazole 8 mg/ml).
• **Oral drug challenges** (increasing doses at 30-min intervals): (i) omeprazole capsule: 5, 10, 20 mg; (ii) lansoprazole capsule: 7.5, 15, 30 mg; (iii) pantoprazole tablet: 5, 10, 20 mg; (iv) rabeprazole tablet: 5, 10, 20 mg; (v) esomeprazole tablet: 5, 10, 20 mg.


  • **Atopic eczema (AE):** common chronic skin disease (3% of adults, 20% of children); impact: ↓ QoL, ↑ predisposition to skin infections (bacterial, viral) and other allergies (asthma, allergic rhinitis).

  • **Pathogenic factors for AE:** (i) skin barrier defects: scratching, ↓ synthesis of epidermal proteins (e.g. filaggrin, loricrin, involucrin, corneodesmosin, S100 proteins, proteases, antiproteases [e.g. LEKTI], tight junction proteins [e.g. claudin-1]) due to genetic mutations or TH2-cytokine influence → increased entry of allergens through skin.

  • (ii) innate immune dysregulation: ↑ inflammatory dendritic cells, altered TLR signalling, ↓ production of antimicrobial peptides (e.g. cathelicidin, defensins), ↑ keratinocyte production of cytokines that promote TH2 environment (e.g. TSLP, IL-25, IL-33).

  • (iii) adaptive immune dysregulation (determined by genetic factors [e.g. polymorphisms in IL4RA] and environmental factors [e.g. Staphylococcal superantigens, low vit D]): ↑ TH2 inflammation (IL-4, IL-13, IL-5, IgE, IL-31 → promote skin barrier dysfunction and pruritus), ↑ TH17 inflammation (promotes acanthosis), altered TH1 responses (predisposition to viral and bacterial infections), altered TH17 responses (predisposition to bacterial and fungal infections), ↓ 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 AE patients (staphylococcal enterotoxins induce polyclonal T-cell and B-cell activation).

  • Several pathogenic factors are probably combined and may result in varied clinical phenotypes.

  • Filaggrin: important role in the integrity of skin barrier; expressed by keratinocytes; not expressed by nasal, bronchial or esophageal epithelium; loss-of-function genetic mutations occur in 30% of AE patients (however, 8% of healthy subjects also carry those mutations).


  • **Asthma:** high prevalence worldwide (20% of children, 10% of adults); mainstay of treatment: inhaled corticosteroids, inhaled β2-agonists. Many patients do not respond to standard therapy → new therapeutic options are needed.

  • **Macrolides:** (i) antibacterial action (including against *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*); (ii) immunomodulatory/antiinflammatory effects (e.g. ↓ IL-8).
• Previous studies and case reports have shown beneficial effects of macrolides in chronic inflammatory lung diseases (e.g. asthma, COPD, bronchiectasis, cystic fibrosis, diffuse panbronchiolitis, post-transplant bronchiolitis obliterans).

• Authors performed a metaanalysis (12 RCT) to assess the effects of prolonged macrolide treatment (≥3 wks) in patients (children and adults) with asthma → (i) no effect on FEV1 (8 RCT, 381 subjects); (ii) significant ↑ in PEF (4 RCT, 419 subjects); (iii) significant improvements in symptom scores (8 RCT, 478 subjects), airway hyper-reactivity (2 RCT, 131 subjects) and QoL (5 RCT, 346 subjects).

• Author’s commentaries: (i) macrolides may be beneficial as an adjunct asthma therapy, particularly in certain phenotypes (e.g. noneosinophilic or neutrophilic asthma); (ii) consider the risk of increasing bacterial resistance to macrolides.

• MANY WAYS LEAD TO ROME: A GLANCE AT THE MULTIPLE IMMUNOLOGICAL PATHWAYS UNDERLYING ATOPIC DERMATITIS (Bieber T. Allergy 2013; 68: 957-958):

  • Atopic dermatitis (AD) cannot simply be qualified as a TH2 disease.

  • Multiple pathogenic factors in AD (genetic, epigenetic, environmental): (i) skin barrier defects, (ii) innate immune dysregulation, (iii) adaptive immune dysregulation, (iv) exaggerated immune responses to self and non-self antigens, (v) abnormal skin colonization by microbes.

  • Several pathogenic factors are probably combined and may result in varied clinical phenotypes.

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


  • Authors present the history of the naissance and evolution of the term ‘allergy’.

  • Clemens von Pirquet used for the 1st time the term ‘allergy’ in 1906 (from the Greek allos [‘other or different’] and ergia [‘energy or action’], in the sense of ‘change in reactivity of the immune system after the 1st encounter with an antigen’) → at that time the term ‘allergy’ included both protective immunity and hypersensitivity reactions.

  • Currently, the term ‘allergy’ is limited to describe only hypersensitivity conditions.

  • In the general population the term ‘allergy’ is also used as synonymous of antipathy or rejection.

• UTILIZING METABOLOMICS TO DISTINGUISH ASTHMA PHENOTYPES: STRATEGIES AND CLINICAL IMPLICATIONS (Reisdorph N, Wechsler ME. Allergy 2013; 68: 959–962):

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

  • Diagnostic tools to precisely distinguish asthma phenotypes are lacking.

  • Metabolomics: study of chemical processes involving metabolites; valuable tool to discover biomarkers and to elucidate mechanisms of disease (e.g. metabolomic analysis of exhaled breath concentrate [EBC], BALF, serum or urine in patients with asthma).
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- **Ibrahim et al** (Allergy 2013; 68: 1050–1056): metabolomic analysis (using nuclear magnetic resonance spectroscopy) of EBC samples could: (i) discriminate asthmatic adults from nonasthmatic adults; (ii) distinguish sputum neutrophilia and use of inhaled corticosteroids; (iii) not distinguish eosinophilia and asthma control.

  - Influence of serum vit D levels and vit D supplementation on the development of allergic diseases during childhood is controversial.
  - Gold standard to diagnose food allergy: oral food challenge.
  - Vit D deficiency in pregnancy has been strongly associated with low birth weight.

- **A CASE OF ANAPHYLAXIS TO ERYTHRITOL DIAGNOSED BY CD203c EXPRESSION-BASED BASOPHIL ACTIVATION TEST** (Sugiura S, Kondo Y, Ito K, Hashiguchi A, Takeuchi M, Koyama N. Ann Allergy Asthma Immunol 2013; 111: 222–223):
  - Food or drug additives occasionally cause allergic reactions.
  - Erythritol (a sugar alcohol): widely used food and drug sweetener (sweet, low calorie content, chemical inert, nontoxic); adverse reactions are rare (4 previous reports of allergic reactions).
  - PAL SWEET Calorie Zero (PSCZ): artificial sweetener containing 99% erythritol.
  - Authors report the case of an 8-yr-old girl with recurrent anaphylaxis to erythritol (as an ingredient of snacks, chewing gum, milk and milk tea containing PSCZ) → diagnosis: negative serum specific IgE to 82 types of food, latex and gelatin; positive oral food challenge to PSCZ; positive skin prick test to PSCZ (100 mg/mL dissolved in normal saline); positive basophil activation test with erythritol (concentration-dependent manner; basophil activation was reduced when surface IgE was removed).
  - Author’s commentaries: (i) allergy to food additives should be considered when a patient has reacted to several ‘non-related’ foods; (ii) BAT with food additives could be a useful diagnostic test, even if the detection of specific IgE antibodies is not feasible.

  - Asthma: chronic respiratory disease (airway inflammation, bronchial hyperreactivity, reversible airway obstruction, variable remodeling); typical symptoms: cough, wheezing, breathlessness, chest tightness; atypical presentations can occur (e.g. cough variant asthma [only chronic cough]).
  - Authors report 24 patients (10 men, 14 women, mean age=34.5 yrs) with ‘chest tightness variant asthma (CTVA)’: (i) recurrent chest tightness was the only symptom; (ii) no cough or wheezing on auscultation; (iii) no alternative causes of chest tightness (e.g. cardiac disease, inhalation of toxic substances, hematologic disease, hyperthyroidism, neurological disease, myopathy); (iv) abnormal lung function tests (18 patients had positive methacholine test and PEF variability, 6 patients had reversible airflow limitation after bronchodilator inhalation); (v)
histological findings consistent with asthma (in 6 patients who agreed bronchoscopy with biopsy); (vi) good response to either ICS or ICS+LABA.

- **Author’s commentary:** asthma should be considered in patients with recurrent chest tightness as their sole complaint in the absence of other recognized diseases.

**ONTACT DERMATITIS TO VITAMIN K1 IN AN EYE CREAM** (Lopez-Lerma I, Vilaplana J. Ann Allergy Asthma Immunol 2013; 111: 227–228):

- **Eyelid allergic contact dermatitis:** frequently caused by cosmetic ingredients (dyes, fragrances, resins, preservatives, vehicles) applied on the face, hair or fingernails.

- **Uses of vit K1 (phytonadione):** (i) **systemic use:** bleeding prophylaxis in patients with hypoprothrombinemia, antidote to warfarin (coumadin); (ii) **topical use:** cosmetics to improve skin lightening, dark eyed circles, bruising, spider veins, varicose veins, actinic purpura, traumatic purpura.

- Authors report the case of a 23-yr-old woman with eyelid eczema after a 2-month use of an antiwrinkle eye cream containing vit K1 → diagnosis: positive patch test to vit K1 (all cream ingredients were tested, including urea, ubiquinone, parabens, fragrance and other additives; 20 healthy controls did not react to vit K1 patch testing) → successful treatment: topical steroids, cream withdrawal.


- **FEF25-75** (mid-expiratory flow between 25% and 75% of forced vital capacity) is more reflective of small airways than FEV1 (forced expiratory volume in the 1st second).

- Impaired FEF25-75 (<65% of predicted) may suggest: (i) affection of small airways (including the ‘small airways asthma phenotype’); (ii) early bronchial affection in patients with recent onset of allergic rhinitis; (iii) severe bronchial hyperreactivity in patients with asthma or rhinitis; (iv) positive response to bronchodilation test in patients with asthma; (v) bronchial inflammation as assessed by FeNO measurement; (vi) significant association with adiposity, (vii) significant association with breathlessness perception in children with asthma, (viii) significant association with symptom duration and sensitization to perennial allergens in patients with rhinitis; (ix) significant association with asthma control.

- **Author’s commentary:** do not underestimate an impaired FEF25-75, even in patients with normal FEV1.

**IMMUNOTHERAPY FOR MOUSE BITE ANAPHYLAXIS AND ALLERGY** (Bunyavanich S, Donovan MA, Sherry JM, Diamond DV. Ann Allergy Asthma Immunol 2013; 111: 233–234):

- **Allergy to laboratory animals:** affects 11-44% of laboratory animal workers; mainly allergic rhinoconjunctivitis and asthma; treatment: avoidance, use of protective gear.

- **Allergy to mice:** 3 main allergens (Mus m 1, Mus m 2, albumin), variably present in mouse hair, dander, urine and serum.

- Authors report the case of a 55 yr-old laboratory worker (personal history of rhinitis while working with mice; financially dependent on this employment) with anaphylaxis (urticaria,
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angioedema, chest and throat tightness, dizziness, mild hypotension [94/59 mmHg]) minutes after a bite (on his 3rd digit) of a laboratory mouse → diagnosis confirmation (6 wks after the reaction): positive SPT for mouse epithelium, ↑ serum sIgE for mouse epithelium (6.17 kU/L) and mouse urinary protein (0.41 kU/L) → treatment: subcutaneous immunotherapy with mouse antigen (change of employment was not possible) → rhinitis symptoms resolved 14 months after initiation of immunotherapy, patient has not been bitten again.

• Author’s commentary: immunotherapy to occupational allergens should be considered in high-risk patients who cannot avoid exposure.

• LIPID MEDIATORS AND ALLERGIC DISEASES (Fanning LB, Boyce JA. Ann Allergy Asthma Immunol 2013; 111: 155–162):

  • Lipid mediators (e.g. prostaglandins [PG], leukotrienes [LT], thromboxanes [TX], lipoxins [LX]): bioactive molecules generated from cell membrane phospholipids; clinical significance: (i) important roles in physiologic and pathologic cell processes, including inflammatory/immune responses (e.g. proallergic effects of LT, PGD2 and TXA2; antiallergic effects of PGE2 and PG12); (ii) diagnostic markers of disease (e.g. urinary LTE4, urinary TXA2, LT in exhaled breath concentrate); (iii) therapeutic targets (e.g. cysteinyl LT receptor type 1 [CysLT1R] antagonists, 5-lipoxygenase inhibitors, CRTH2 [PGD2 receptor] antagonists, TX receptor antagonists, EP [PGE2 receptors] agonists).

  • Synthesis of lipid mediators: (1) phospholipase A2 release arachidonic acid from membrane phospholipids → (2) arachidonic acid is oxidatively metabolized → (3) cyclooxygenase pathway converts arachidonic acid into PG and TX; lipoxygenase pathway converts arachidonic acid into LT and LX.

  • COX inhibition generally results in increased allergic inflammation.

  • In vivo and in vitro studies suggest that signalling through CysLT2R inhibits CysLT1R expression and function.

  • LTB4 is strongly chemotactic for neutrophils and eosinophils.

• TREATMENT OF PATIENTS WHO PRESENT AFTER AN EPISODE OF ANAPHYLAXIS (Lieberman P. Ann Allergy Asthma Immunol 2013; 111: 170–175):

  • Anaphylaxis: severe allergic reaction due to the liberation of mast cell and basophil mediators.

  • Allergists/immunologists must know: (i) how to treat acute anaphylaxis (may occur after immunotherapy application, skin testing or food/drug challenges); (ii) how to evaluate and manage a patient with a suspected history of anaphylaxis (confirm diagnosis, determine the etiology, give a treatment plan to prevent and treat further episodes).

  • Approach to a patient with a history of anaphylaxis: (i) evaluate all potential triggers (e.g. food, drugs, insect stings, exercise [or food + exercise], temperature changes, menstruation) within 6 hrs before symptom onset (idiopathic anaphylaxis can account for 60% of adult cases); (ii) take a thorough history of all signs and symptoms (place and time of onset, duration, recurrence, response to treatment); (iii) exclude differential diagnosis (e.g. mastocytosis, mast cell activation disorder, carcinoid syndrome, neuroendocrine tumors, drug-induced flush [niacin, nicotine, ACE inhibitors, corticosteroids, cathecolamines], alcohol related flush [alone or
in combination with drugs such as disulfiram, griseofulvin or cephalosporins], acute coronary syndrome, pulmonary embolism, postprandial syndromes [ingestion of monosodium glutamate or sulfites, scombroidosis], hereditary angioedema, vocal cord dysfunction syndrome, panic attack, somatoform disorder; (iv) perform proper laboratory tests (serum tryptase, plasma histamine, urinary histamine metabolites, serum PAF, serum PGD2, in vivo and in vitro allergy tests, oral challenges, tests to exclude differential diagnosis [e.g. imaging studies if suspicion of neuroendocrine tumors, neuropeptide levels if suspicion of carcinoid syndrome, bone marrow biopsy if suspicion of mastocytosis]); (v) give detailed written indications to prevent and quickly-treat further anaphylaxis episodes (e.g. trigger avoidance, use of identification, use of autoinjectable epinephrine [2 injections are needed in up to 30% of episodes], quickly assume recumbent position with feet elevated until complete CV recovery, avoidance of some drugs [β-blockers can ↓ epinephrine action; ACE inhibitors can ↓ angiotensin effect and ↑ bradykinin levels, MAO inhibitors can interfere with epinephrine effect]).

- **NIAID/FAAN criteria to diagnose anaphylaxis** → sensitivity=96.7%, specificity=82.4%.
- **Anaphylaxis** can present without cutaneous signs (urticaria or angioedema) in >20% of patients.
- Median times to cardiovascular and/or respiratory collapse during anaphylaxis: (i) 10 min for iatrogenic events, (ii) 15 minutes for field insect stings, (iii) 30 minutes for food.

### USE OF VACCINES IN THE EVALUATION OF PRESUMED IMMUNODEFICIENCY (Ballow M. Ann Allergy Asthma Immunol 2013; 111: 163–166):

- Assessment of antibody responses is very important in the evaluation of patients with suspected primary immunodeficiency (PID).
- **Importance of evaluating antibody responses:** (i) to diagnose specific antibody deficiency; (ii) to diagnose common variable immunodeficiency; (iii) to indicate replacement therapy with immunoglobulin.
- In 2012 a working group of the AAAAI published a must-read report about the use of vaccine responses in the evaluation of patients with suspected PID (J Allergy Clin Immunol 2012; 130 (suppl): S1-S24).
- **Common vaccines currently used to measure antibody responses:** (i) T-cell dependent: Haemophilus influenzae type b conjugate, meningococcal conjugate, pneumococcal conjugate (e.g. Prevnar 13), rabies, tetanus; (ii) T-cell independent: meningococcal polysaccharide, pneumococcal polysaccharide (e.g. Pneumovax 23).
- **How to assess antibody response in patients who are already using immunoglobulin replacement therapy?** (i) stop immunoglobulin for some months and then assess antibody responses (sometimes it is not feasible because of patient’s risk); (ii) use novel vaccines or neoantigen vaccines (e.g. meningococcal vaccines, rabies vaccine, tickborne encephalitis virus vaccine, bacteriophage ΦX174).
- **Important points of vaccine use in patients with confirmed or suspected PID:** (i) live viral vaccines should be avoided in patients with severe PIDs; (ii) patients with severe PIDs do not need vaccine challenges to confirm defective immunity (little additional value); (iii) unconjugated polysaccharide vaccines should not be used for the routine investigation of antibody deficiency in children <18 months of age; (iv) immediate repeat booster with unconjugated polysaccharide
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Vaccines is not recommended and might promote hyporesponsiveness; (v) protective response to each pneumococcal polysaccharide serotype = antibody titer ≥1.3 mg/mL; (vi) for those serotypes with a prevaccine antibody titer ≥1.3 mg/mL, a 2-fold response is considered an adequate response; (vii) normal response to unconjugated pneumococcal polysaccharide vaccine in children between 2 and 5 yrs of age = conversion of ≥50% of the serotypes tested and/or ≥2-fold increase in titer for those serotypes already ≥1.3 mg/mL at baseline; (viii) normal response to unconjugated pneumococcal polysaccharide vaccine in subjects between 6 and 65 yrs of age = conversion of ≥70% of the serotypes tested and/or ≥2-fold increase in baseline titers; (ix) specific antibody deficiency = deficient response to pneumococcal polysaccharide vaccine + normal responses to protein or conjugate vaccines + normal serum immunoglobulin levels (some patients may have ↓ serum IgG subclass levels).

  • Recognition of Candida by innate immune cells → phagocytosis, secretion of TH17-inducing cytokines (IL-6, IL-23, IL-18), antigen presentation to naive T cells → differentiation of Candida-specific TH17 cells → secretion of TH17 cytokines (e.g. IL-17A, IL-17F, IL-22) → attraction of neutrophils, synthesis of antimicrobial peptides → elimination of Candida.
  • Genetic defects in TH17 immunity (e.g. IL-17F deficiency, IL17RA deficiency, STAT3 deficiency, STAT1 gain-of-function mutations, APECED, CARD9 deficiency) → recurrent infections with Candida albicans → chronic mucocutaneous candidiasis (CMC).
  • Authors report the case of a 59-yr-old woman with isolated CMC (for >33 yrs) → genetic analysis: heterozygous G821A mutation in the coiled-coil domain of STAT1 → successful treatment: intravenous GM-CSF (leucomax) 800 µg twice a week for 3 yrs (rapid complete clinical remission, ↑ monocyte and neutrophil functions), then switched to subcutaneous G-CSF (filgrastim) 400 µg (5 µg/kg) twice a week for the last 16 yrs (keeping WBC ≤15,000/mm³ with 80-90% granulocytes) → suspension of G-CSF was attempted but CMC recurred within 4 wks → resumption of G-CSF resulted in complete clinical remission within 2 wks.
  • Effects of G-CSF therapy in the patient: (i) ↑ proportion of TH17 cells; (ii) ↑ production of TH-17 cytokines (e.g. IL-17A, IL-17F, IL-22, IL-6); (iii) ↑ expression and phosphorylation of STAT3; (iv) ↑ expression of SOCS 1 (which inhibits STAT1).
  • Hypothesis: G-CSF → ↑ production of IL-6 → ↑ expression of STAT3, ↓ expression of STAT1 → ↑ TH17 cell development.
  • Author’s commentaries: (i) G-CSF therapy may achieve complete clinical remission in patients with isolated CMC due to STAT1 gain-of-function mutations; (ii) G-CSF therapy may benefit patients with other genetic defects causing isolated CMC.

• DEVELOPMENT OF A VALIDATED BLOOD TEST FOR NICKEL SENSITIZATION (Pacheco K, Barker L, Maier L, Erb S, Sills M, Knight V. J Allergy Clin Immunol 2013; 132: 767-769):
  • Reasons for joint implant failure: delayed allergy to metals, infection, biomechanical mismatch.
  • Diagnosis of delayed allergy to metals: patch test (gold standard), lymphocyte proliferation test (non validated method).
• Authors report the development and validation of a blood lymphocyte proliferation test to diagnose nickel sensitization → sensitivity: 68%, specificity: 98%, PPV: 93%, NPV: 90% (compared to patch test).

  - Urticarial vasculitis (UV): (i) Clinical manifestations: urticarial rash (individual lesions last >24 hrs, may cause burning/pain rather than pruritus, often resolve with hyperpigmentation or purpura); systemic involvement (e.g. joints, respiratory tract, GI tract, kidneys) can be found, especially in hypocomplementemtic UV patients. (ii) Histology: findings of leukocytoclastic vasculitis. (iii) Etiology: unclear in most cases (may associate with connective tissue disorders, drugs, infections, hematologic disorders). (iv) Pathophysiology: autoinflammatory/autoimmune disease, IL-1 may have an important pathogenic role. (v) Treatment: not standardized (based mainly on case reports), depends on severity; includes antihistamines, NSAIDs, colchicine, immunomodulators (hydroxychloroquine, dapsone), immunosuppressives (corticosteroids, cyclosporine A, azathioprine, cyclophosphamide, methotrexate), anakinra (IL-1R antagonist), anti-IL6 mAb.
  - Authors report an open-label pilot study in 10 patients with active UV (only 1 with hypocomplementemic UV) who were treated with a single dose (300 mg subcutaneously) of canakinumab (long-acting fully humanized anti–IL-1β mAb) → (i) ↓ mean total UV activity score; (ii) ↓ global disease activity (physician-based and patient-reported); (iii) ↓ inflammatory markers (CRP and ESR); (iv) ↓ serum IL-6 levels; (v) ↑ QoL; (vi) complete clinical and laboratory remission in 2 of 10 patients; (vii) no serious adverse effects.
  - Author's commentaries: (i) canakinumab may be an effective and safe therapy for patients with UV; (ii) larger studies are required, especially in patients with hypocomplementemtic UV.

• LONG-TERM FOLLOW-UP OF ORAL IMMUNOTHERAPY FOR COW'S MILK ALLERGY (Keet CA, Seopaul S, Knorr S, Nairsety S, Skripak J, Wood RA. J Allergy Clin Immunol 2013; 132: 737-739):
  - Food allergy: increasing prevalence worldwide, high economic and health impact; conventional treatment: avoidance (does not prevent accidental exposure), epinephrine autoinjectors, follow-up (to assess for spontaneous resolution).
  - Oral immunotherapy (OIT) for food allergy is under active investigation; potential benefits: long-lasting acquisition of tolerance, ↑ QoL, ↓ danger of accidental food exposure; limitations: severe allergic reactions during treatment, potential lack of efficacy (short- or long-term).
  - Authors report the follow-up (3 to 5 yrs after treatment) of 32 children who received cow milk [CM] OIT (from 2 well-designed trials) → (i) only 31% of subjects were tolerating full servings of CM with minimal or no symptoms; (ii) 19% of subjects reported anaphylaxis in recent follow-up; (iii) 22% of patients limited CM consumption because of symptoms, 9% because of symptoms, 13% because of taste; (iv) some subjects with initial successful OIT reported recurrence of symptoms over time (1 subject reported epinephrine use at least twice per month) → long-term outcomes after CM OIT were mixed, some subjects lost desensitization over time.
Author’s commentaries: (i) OIT for food allergy is far from ready for clinical practice; (ii) more research into the long-term outcomes of OIT for food allergy is necessary.


Severe combined immunodeficiency (SCID): genetic defects causing near-absence of T cells → marked failure of cellular and humoral immune responses → severe infections (including opportunistic), fatal course if not treated (HSCT or gene therapy).

X-linked SCID (X-SCID): most frequent SCID (44-46%); etiology: IL2RG gene mutations → deficient common gamma chain → deficient signalling of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 → markedly ↓ production of T and NK lymphocytes.

Authors report the case of a 9-month-old boy with X-SCID → genetic mutation: p.R226C (IL2RG gene) → massively parallel sequencing: maternal somatic IL2RG mosaicism (frequencies for the mutated allele oscillating from 7.7% to 20.2%); no mutation in the patient’s maternal grandparents (supporting the de novo nature of the mother’s somatic mosaicism) → successful treatment: HLA-matched unrelated HSCT (37 wks of follow-up).

Author’s commentaries: (i) Somatic mosaicism can play a role in the pathogenesis of PIDs (e.g. ALPS, NOMID, X-SCID); (ii) 13-56% of X-SCID patients are diagnosed with ‘de novo’ IL2RG mutations (some of them could actually be a consequence of unidentified maternal mosaicism) (ii) mosaicism detection is important for genetic counseling (de novo mutation → virtually zero risk of affected siblings) (mosaicism detection → potential risk of affected siblings).

NATURAL KILLER CELL DEFICIENCY (Orange J. J Allergy Clin Immunol 2013; 132: 515-525):

Functions of NK cells: (i) direct cytotoxicity; (ii) secretion of protective cytokines (e.g. IFN-γ); (iii) immune regulation.

Defects in NK cells may occur: (i) as part of broader genetic immune defects (e.g. X-linked SCID, ADA-SCID, reticular dysgenesis); (ii) as the major immune defect (‘NK cell deficiency’).

At least 46 known single-gene PIDs include an NK cell defect.

NK cell deficiency (NKD): (i) classic NKD subtype 1 (GATA2 defect, autosomal dominant inheritance): ↓ CD56dim NK cell numbers, ↓ CD56bright NK cell numbers, ↓ NK cell function, susceptibility to VZV, HSV, CMV, HPV and mycobacteria; (ii) classic NKD subtype 2 (MCM4 defect, autosomal recessive inheritance): ↓ CD56dim NK cell numbers, normal CD56bright NK cell numbers, ↓ NK cell function; (iii) functional NKD subtype 1 (FCGR3A defect, autosomal recessive inheritance): normal NK cell numbers, ↓ NK cell function.

Features of NKD: (i) NK cell deficiency represents the major immunologic abnormality; (ii) defect is stable over time; (iii) secondary causes are excluded (e.g. drugs, malignancy, HIV infection, severe physiologic or emotional stress); (iv) broader PIDs that include an NK cell defect are excluded; (v) NK cells are evaluated as CD3-/CD56+ cells; (vi) in patients with classical NKD, NK cells are ≤1% of peripheral blood lymphocytes; (vii) abnormal functional evaluations are repeatable.
• **NATURAL KILLER CELLS IN PATIENTS WITH ALLERGIC DISEASES** (Deniz G, van de Veen W, Akdis M. J Allergy Clin Immunol 2013; 132: 527-535):

  • **NK cells:** (i) kill tumor cells or virus-infected cells; (ii) regulate the function of other immune cells through cytokine/chemokine secretion or cell-cell contact; (iii) 4 subtypes: NK1 cells (favor TH1 immunity), NK2 cells (favor TH2 immunity), regulatory NK cells (regulate immune responses), NK22 cells (protect epithelial cell barriers?); (iv) important roles in viral infection, cancer, autoimmunity, transplantation and pregnancy; (v) role in allergic diseases is not well defined.

  • NK cells respond to several chemoattractants (e.g. CXCL12-CXCR4 chemokine signaling).

• **THE EDITOR’S CHOICE** (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2013; 132: 545-546):

  • **Asthma** may represent a collection of diseases with similar clinical manifestations.

  • 2 subphenotypes of children with persistent wheeze: (i) persistent troublesome wheeze: major airway obstruction and hyperreactivity, high atopy levels, high rates of severe exacerbations and health care use; (ii) persistent controlled wheeze: lower rates of severe exacerbations.

  • Predictors of subsequent troublesome symptoms among 3-yr-old wheezers: large skin test responses, history of previous exacerbations, ↓ lung function, eczema.

  • Tetratricopeptide repeat domain 7A (TTC7A) deficiency → combined immunodeficiency (intrinsic defect of T cells or defect of the thymic stroma?) with multiple intestinal atresias (small bowel, large bowel or both).

  • TTC7A is abundantly expressed in a subset of thymic epithelial cells and, to a lower extent, in thymocytes.

  • Currently, there is no effective specific therapy for severe immune reactions mediated by cytotoxic T lymphocytes (e.g. SJS/TEN, GVHD).

  • Wang et al (J Allergy Clin Immunol. 2013; 132: 713-722) developed a nucleic acid–based molecule (using siRNA) to specifically target cytotoxic T lymphocytes → ↓ cytotoxicity in the in vitro models of SJS/TEN and GVHD; advantages: specificity, low immunogenicity, low toxicity.

  • Natural birth delivery, breastfeeding, ↑ sibship size → promotion of beneficial microbiota (e.g. ↓ clostridia) → ↓ risk of allergy.


  • Proteases regulate WASP–driven F-actin assembly.

  • WASP activation (phosphorylation following TCR signalling) is essential for F-actin assembly and T-cell function; WASP regulation (ubiquitination, degradation by proteases) is essential to prevent pathologic excessive F-actin assembly.

• **ALLERGIC REACTIONS TO VACCINES** (Wood RA. Pediatr Allergy Immunol 2013; 24: 521–526):

  • Vaccines: ↓ morbidity and mortality of many infectious diseases (eg. eradication of smallpox).
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.

- **Adverse reactions to vaccines:** (i) **immediate allergy** (minutes to hours): IgE-mediated; (ii) **delayed allergy** (hours to days): usually not IgE-mediated (e.g. serum sickness, polyarthritis, erythema nodosum); (iii) **non immunologic**.

- **Immediate hypersensitivity to vaccines** range from 1 per 50,000 doses for DTP to about 1 per 500,000–1,000,000 doses for most other vaccines.

- **Anaphylaxis to vaccines:** rare but possible (reported for nearly every vaccine); most often due to vaccine constituents (e.g. gelatin, egg, milk, chicken, preservatives, antibiotics, yeast, latex) rather than the microbial components; in many cases the specific culprit is not detected.

- **Important considerations regarding adverse reactions to vaccines:** (i) **confirm the adverse reaction** (fever and local reactions are very common, generally self-limited, and usually do not contraindicate further doses); (ii) evaluate if the patient needs further doses of the culprit vaccine or similar vaccines (some patients mount adequate immune responses after fewer than the recommended vaccine doses); (iii) if the clinical history suggests an IgE-mediated reaction, perform *in vivo* and *in vitro* tests to detect specific IgE (sIgE) against the vaccine or its components; (iv) patients with **negative vaccine skin tests** will usually tolerate the vaccine; (v) patients with **positive vaccine skin tests** might tolerate the vaccine (if benefits outweigh risk the vaccine should be administered gradually); (vi) it is prudent to **observe** the patient 30 min after vaccination; (vii) it is prudent to be prepared for **anaphylaxis**; (viii) if an IgE-mediated reaction to the vaccine is confirmed, try to detect the **specific culprit allergen** because other vaccines could contain the same allergen (e.g. a patient with gelatin allergy may react to MMR, varicella or influenza vaccines); (ix) in most cases, patients with **suspected allergy to vaccines** can receive subsequent vaccinations safely; (x) some vaccines might be more important than others (e.g. measles is a potential fatal disease; influenza infection is usually less life-threatening).

- **How to confirm an IgE-mediated allergy to a vaccine?** (i) **Suggestive clinical history:** manifestations of mast cell degranulation within 4 hrs after immunization; (ii) **specific IgE detection by skin testing** (use the same vaccine brand that caused the reaction; falsely positive results may occur; “normal” delayed responses are common [most likely represent prior immunity]): SPT (usually with undiluted vaccine, consider using dilutions when there is a history of severe reaction), *intradermal test* with 1/100 diluted vaccine (nonirritating concentration).

- **How to confirm an IgE-mediated allergy to a vaccine component?** (i) **Suggestive clinical history:** signs of mast cell degranulation within 4 hrs after exposure to a vaccine component (e.g. egg, gelatin, yeast, latex, chicken, antibiotics); (ii) **specific IgE detection to the vaccine component:** SPT, *in vitro* testing; (iii) **allergen challenge**.

- **Gelatin:** (i) **stabilizer** (µg to mg quantities) of many vaccines (e.g. MMR, varicella, influenza, Japanese encephalitis); (ii) bovine or porcine origin (extensively cross-reactive); (iii) most frequent culprit allergen in vaccines.

- **How to diagnose gelatin allergy?** (i) **Clinical history:** ask for reactions after gelatin ingestion, a negative history does not exclude gelatin allergy; (ii) sIgE detection *in vitro*; (iii) SPT with an **office-made extract** (not approved by the FDA): dissolve 1 teaspoon of sugared gelatin powder (any flavor) in 5 mL of normal saline (unsugared gelatin tends to gel at room temperature).

- **How to approach a patient with IgE-mediated gelatin allergy?** Perform **skin testing with gelatin-containing vaccines** → (i) **negative results** → vaccinate the patient, observe 30 min afterward,
be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

- **Egg protein (ovalbumin):** (i) very low amounts in influenza, MMR and rabies vaccines (usually no risk for egg-allergic patients); (ii) higher amounts in yellow fever vaccine (be careful with egg-allergic patients).

- **How to diagnose egg allergy?** (i) Clinical history: ask for reactions after egg ingestion; (ii) sIgE detection by skin and serum tests; (iii) oral food challenge.

- **How to approach a patient with IgE-mediated egg allergy who needs influenza vaccine?** (i) Administer an entire dose without previous skin tests, even in patients with anaphylaxis to egg; (ii) observe 30 min after vaccination; (iii) be prepared to manage anaphylaxis; (iv) injectable trivalent vaccine is preferred over nasal live attenuated vaccine because its safety in egg-allergic patients has been studied more extensively; (v) 2 egg-free influenza vaccines were recently approved for patients ≥18 yrs of age (Optaflu [Flucelvax] and Flublok).

- **How to approach a patient with IgE-mediated egg allergy who needs yellow fever vaccine?** Perform skin tests with the vaccine → (i) negative results → vaccinate the patient, observe 30 min afterward, be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

- **Yellow fever vaccine** may contain chicken proteins → follow the same approach (see last paragraph) when vaccinating chicken-allergic patients.

- **Yeast protein** (Saccharomyces cerevisiae; common baker’s or brewer’s yeast): present in hepatitis B vaccines (up to 25 mg per dose) and quadrivalent human papillomavirus vaccine (<7 µg per dose); yeast allergy is rare.

- **How to diagnose yeast allergy?** (i) Clinical history: ask for reactions after yeast ingestion; (ii) sIgE detection by skin and serum tests to Saccharomyces cerevisiae.

- **How to approach a patient with IgE-mediated yeast allergy?** Perform skin testing with yeast-containing vaccines → (i) negative results → vaccinate the patient, observe 30 min afterward, be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

- **Natural rubber latex:** present in the packaging of many vaccines (vial stopper, syringe plunger); very low risk of vaccine contamination with latex → minimal risk of allergic reactions in patients with IgE-mediated latex allergy.

- **How to diagnose latex allergy?** (i) Clinical history: ask for immediate reactions after exposure to latex; (ii) sIgE detection by skin and serum tests.

- **How to approach a patient with IgE-mediated latex allergy?** (i) Use a vaccine without latex stopper; (ii) if not possible, remove the stopper and take the vaccine directly from the vial; (iii) if latex packaging cannot be avoided (e.g. a prefilled syringe), vaccinate and observe the patient 30 min afterward, be prepared to treat anaphylaxis.

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- Pertussis vaccines (DTaP or Tdap) may contain trace amounts of casein → be careful when vaccinating egg-allergic children (the vast majority of patients with even severe milk allergy tolerate these vaccines well).

- Vaccines commonly contain traces of antimicrobial agents (e.g. neomycin, polymyxin B, streptomycin) → be careful when vaccinating patients with allergy to these compounds (not including contact dermatitis).

- Vaccines commonly contain preservatives (e.g. thimerosal, aluminum, phenoxyethanol), which may cause delayed-type hypersensitivity reactions (including contact dermatitis).


- This paper updates management of chronic pruritus associated with dermatologic diseases in pediatric patients, mainly atopic dermatitis (AD) and chronic spontaneous urticaria (CSU).

- Pruritus: usually unpleasant sensation that causes an intense desire to scratch; lifetime prevalence=22%; possible triggers: sweating, xerosis, temperature, stress, emotions, food, exercise, drugs, infections, tumor antigens, toxic substances, toxic metabolites; pathophysiology: production of pruritic substances (e.g. histamine, proteases, gastrin-releasing peptide [GRP], mu opioids, substance P, IL-31) by several types of cells (e.g. T cells, eosinophils, mast cells, keratinocytes, neurons) → activation of 'pruritic' nerve fibers.

- Chronic pruritus (>6 wks): (i) most bothersome symptom of many diseases; (ii) affects QoL; (iii) clinical history should include localization, severity, presence/absence of skin lesions, age of onset, duration, evolution over time, triggers, alleviating factors, associated symptoms; (iv) differential diagnosis should include systemic diseases (e.g. kidney disease, liver disease, cancer) and mental disorders; (v) treatment should be guideline-based (skin barrier restoration, antiinflammatory treatments, rapid-acting antipruritic therapies, psychological interventions, etc.); (vi) treatment should be as specific and safe as possible.

- Chronic pruritus can be classified in 3 groups: (i) pruritus on primarily inflamed skin (includes patients with underlying dermatologic diseases); (ii) pruritus on primarily non-inflamed skin; (iii) pruritus with chronic secondary scratch lesions, such as prurigo nodularis (groups ii and iii include patients with systemic diseases, pregnancy and psychiatric diseases).

- Proteinase-activated receptor (PAR-2) seems to mediate pruritus in AD (a histamine-independent pathway) → antihistamines are usually not effective.

- Methylprednisolone aceponate: 4th generation, non-halogenated corticosteroid; rapid and effective action in children/infants with AD; low incidence of topical and systemic side effects.

**DEVELOPMENT OF FOOD ALLERGIES IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD) TREATED WITH GASTRIC ACID SUPPRESSIVE MEDICATIONS** (Trikha A,

- **Food allergy**: increased prevalence worldwide → which are the reasons?

- **Gastric acid digestion** ↓ the potential of food proteins to bind specific IgE.

- Authors performed a study to determine the association between use of **gastric acid suppressive (GAS) medications** (proton pump inhibitors or type 2 histamine receptor blockers) and occurrence of **food allergies in children with GERD** (0-18 yrs old) → children with GERD who received GAS (n=4724) had a greater risk of food allergy compared to children with GERD who were untreated (n=4724) and children without GERD who were untreated (n=4724).

- Author’s commentary: use of GAS medications in children may ↑ risk of food allergy (apparently independent of GERD diagnosis).

- **Hypothesis**: GAS medications → ↓ gastric acid → altered degradation of food allergens → ↑ food allergy risk.

**EDITOR’S CHOICE** (Pediatr Allergy Immunol 2013; 24: 511):

- Abrahamsson et al (Pediatr Allergy Immunol 2013; 24: 556–561) report the follow up of children who received probiotics (**Lactobacillus reuteri**) for eczema prevention (↓ eczema incidence at 2 yrs of age) → at 7-yr follow up there was **no protective effect on the risk of respiratory allergies**.

- **Increased intestinal permeability** may be an intrinsic trait in a subset of food allergic children. **Hypothesis**: ↑ intestinal permeability → ↑ entry of food allergens through gut epithelium → abnormal TH2 immune responses → ↑ risk of food allergy.

- **Maternal allergy**: risk factor for allergic disease in children.

- Infants of allergic mothers had higher levels of surface-bound IgE on cord blood basophils compared to infants of non-allergic mothers (no difference in cord blood serum IgE levels). Unclear if: (i) the basophil-bound IgE is maternal or fetal in origin; (ii) IgE loading of fetal basophils impacts allergy development.


- **Normal gut epithelium** → (i) absorption of small molecules; (ii) exclusion of larger molecules.

- Most common method to assess **intestinal permeability (IP)**: ingest lactulose (L) and mannitol (M) → measure urinary levels of L and M, calculate the L/M ratio (↑ IP → ↑ L/M ratio).

- Children with **food allergy** may have ↑ IP → which is first? (Allergic inflammation increases IP or IP predisposes to food allergy?).

- Authors evaluated 131 asymptomatic food (cow’s milk and/or egg) **allergic children** (3–17 yrs old) during an elimination diet → (i) 38% of children had ↑ IP; (ii) ↑ IP was associated with shorter stature.
• **Author's commentaries:** (i) ↑ IP may be an intrinsic trait in a subset of food allergic children; (ii) Hypothesis: ↑ intestinal permeability → ↑ entry of food allergens through gut epithelium → abnormal TH2 immune responses → ↑ risk of food allergy; (iii) larger studies are necessary to determine the role of impaired IP in food allergy.


  • Authors report the follow up of 232 children who received probiotics for eczema prevention (oral supplementation with *Lactobacillus reuteri* during the last month of gestation and through the 1st year of life reduced IgE-associated eczema incidence at 2 yrs of age) → (i) at 7 yrs of age there was no protective effect on the risk of respiratory allergies (asthma and allergic rhinoconjunctivitis); (ii) at 7 yrs of age there were no long-term side effects.

  • **Author's commentaries:** (i) the beneficial effect of *L. reuteri* on sensitization and IgE-associated eczema at 2 yrs of age did not lead to a lower prevalence of respiratory allergic disease at 7 yrs of age; (ii) the effect of *L. reuteri* on the immune system seems to be transient.

• **ORAL IMMUNOTHERAPY AND TOLERANCE INDUCTION IN CHILDHOOD** (Tang MLK, Martino DJ. Pediatr Allergy Immunol 2013; 24: 512–520):

  • **Food allergy:** increasing prevalence worldwide; impact: significant morbidity, ↓ QoL, mortality risk; conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors; optimal treatment: restore tolerance to allergens (immunotherapy).

  • **Desensitization:** no reactivity to a food while ingesting regular doses; mediated by lowering the reactivity of effector cells (mast cells, basophils); ingestion of the food after 2-4 wks of discontinuation results in an acute allergic reaction.

  • **Tolerance:** no reactivity to a food after a large period of discontinuation (months or yrs); mediated by reprogramming immune response (development of Tregs, allergen-specific anergy and/or clonal deletion).

  • **Oral tolerance:** antigen-specific tolerance induced in gut-associated lymphoid tissues (GALT).

  • **Factors associated to food allergy:** (i) ↑ intestinal inflammation; (ii) ↓ gut epithelial barrier; (iii) use of gastric acid suppressive drugs; (iv) ↑ proinflammatory microbiota (e.g. *Clostridium, Staphylococci*); (v) ↑ TH2 responses (including IgE production).

  • **Factors that promote oral tolerance:** (i) ↑ tolerogenic microbiota (*Lactobacillus, Bifidobacterium*); (ii) ↑ tolerogenic dendritic cells (CD103+ DCs migrate to mesenteric lymph nodes, CX3CR1+ DCs remain within the gut); (iii) ↑ T regulatory responses (CD4+CD25+ iTregs, Th3 cells, Tr1 cells, CD8+ Tregs); (iv) ↑ TH1 responses; (v) ↑ tolerogenic molecules (retinoic acid, TGF-β, TSLP, indoleamine-2,3-dioxygenase, IL-10, IgG4, IgA).

  • **Main limitations of oral immunotherapy (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 of a dose, taking a dose on an empty stomach, poorly controlled asthma, pollen season, menses).

- **How to increase 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.