November-2012

- NOVEL INSIGHTS INTO MECHANISMS OF FOOD ALLERGY AND ALLERGIC AIRWAY INFLAMMATION USING EXPERIMENTAL MOUSE MODELS (Corazza N, Kaufmann T. Allergy 2012; 67: 1483–1490).
- SYSTEMIC CONTACT DERMATITIS TO CORTICOSTEROIDS (Baeck M, Goossens A. Allergy 2012; 67: 1580–1585).


ALLERGY:

• **ATOPIC DERMATITIS 2.0: FROM THE CLINICAL PHENOTYPE TO THE MOLECULAR TAXONOMY AND STRATIFIED MEDICINE** *(Bieber Th. Allergy 2012; 67: 1475–1482):*
  
  • Futuristic information about diseases: (i) *genotype*, including epigenotypic information; (ii) *endophenotype*, including biomarkers; (iii) *clinical phenotype*.

  • **Atopic dermatitis**: high degree of *pathophysiological* (skin barrier defect, Th2 inflammation, autoreactivity, microbial influence) and *clinical heterogeneity*.

  • Clinical heterogeneity in AD can be summarized along two main axes:
    1) Age of onset of the disease: early onset (60% of patients; AD start <2 years old; 65% resolve at 11 years old; 50% develop allergic airway diseases); late onset (in adolescence, less IgE sensitization); geriatric onset.
    2) Severity of inflammation (from simply dry skin with minimal itching to erythrodermic severe AD).

  • ‘*Intrinsic*’ AD: often late onset, affects more often women, non-IgE-associated, not associated with atopic asthma.

  • *Phenotype of AD* = complex gene-gene + gene-environment interactions.

  • **Complex genetic basis for AD**: a) Genes involved in the *epidermal barrier function*: SPINK5/LEKTI, filaggrin, claudin 1, etc. b) Genes involved in the *regulation of innate and adaptive immunity, including IgE sensitization*: TLR2 (associated with severe AD and susceptibility to S. aureus), TLR9 (associated with intrinsic AD), IL-4, IL-4RA, IL-13, STAT6, IL-31, FCERIA, FCERIB, FCERIG.

  • Examples of *biomarkers* for AD: *total IgE* value (predicts severity in ‘extrinsic’ AD; cord blood IgE may predict AD at 6 months of age); sIgE against food, aeroallergens, S. aureus superantigens, Malassezia sympodialis, autoallergens; expression of FcεRI on Langerhans cells; expression of CCL17/TARC (thymus and activation-regulated chemokine) in the stratum corneum.

  • **Biomarker-driven approach to treat diseases** → optimal personalized therapeutic strategies; better primary and secondary prevention.

  • **Hypothetic example**: infant with mild eczema of the cheek → genotyping: FLG mutation, IL-4 mutation → we can predict an early onset of AD associated with disturbed epidermal barrier function, IgE sensitization and atopic march → personalized treatment.

  
  • Most common reason for *recurrent wheals*: chronic spontaneous urticaria.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **Autoinflammatory diseases**: excessive activation of the innate immune system. Skin manifestations are among the earliest and most prominent symptoms.

- **Urticaria in autoinflammatory diseases**: concomitant systemic symptoms (recurrent fever, arthralgia, arthritis, fatigue, etc.); no response to antihistamines; chronic complications such as amyloidosis.

- **When should allergists be aware of autoinflammatory diseases?** Uveitis (eye redness and pain), periorbital oedema, arthralgia, arthritis, myalgia, ulcers, aphthae, pustules, serositis, abdominal pain, diarrhoea, meningeal inflammation, CNS involvement, lymphadenopathy, recurrent fever.

- **Laboratory work-up for autoinflammatory syndromes**: CRP, ESR, CBC (neutrophils are often elevated in autoinflammatory disorders), antinuclear antibodies (to rule out autoimmune diseases), urinalysis (screening for proteinuria and amyloidosis).

- **NOVEL INSIGHTS INTO MECHANISMS OF FOOD ALLERGY AND ALLERGIC AIRWAY INFLAMMATION USING EXPERIMENTAL MOUSE MODELS (Corazza N, Kaufmann T. Allergy 2012; 67: 1483–1490):**

  - **Advances in food tolerance**: a) importance of antigen exclusion through polymeric antibodies (dimeric IgA and pentameric IgM, especially IgA); b) intestinal tolerogenic DCs favor Treg and Th1 responses; c) intestinal T regs are induced and activated early in life through commensal flora.

  - **Immune exclusion of foreign antigens through secretory antibodies + anti-inflammatory tolerance mechanisms → protection of mucosal epithelia.**

  - **CD11c+CD103+ DC phagocyte antigens in the intestinal mucosa → migration to mesenteric lymph nodes → production of retinoic acid and TGFβ → induction of Foxp3+ regulatory T cells → tolerance.**

  - **Intestinal epithelial lymphocytes (γδ T cells represent a large proportion):** located in the paracellular space between intestinal epithelial cells (IECs); mediate crosstalk between IECs and immune cells in the lamina propria; first line of defense against luminal antigen; important in oral tolerance induction.

  - **Intestinal flora** promotes immune homeostasis in the intestine and at other sites in the organism. It prevents pathologic mucosal iNKT accumulation in the gut of mice models.

  - **Advances in allergic airway inflammation**: a) Extracellular ATP release in asthmatic airways → ATP targets P2Y2R receptor in myeloid DCs → migration to sites of lung inflammation → Th2 polarization.

  - **b) Inflammasome activation** in myeloid DCs may be fundamental for their maturation (how an allergen can trigger the activation of the inflammasome?)
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **c)** IL-33 induces production of Th2 cytokines → therapeutic target in allergies.
- **d)** Targeting TNFα may be beneficial in severe corticoid-unresponsive asthma.
- **e)** Enhancing local GC production in the lung of asthma patients may be effective and safe.
- **f)** Insulin-like growth factor 1 (IGF-1) → stimulation of hypoxia-inducing factor 1 alpha (HIF-1α) → upregulation of VEGF → inflammation. Those 3 molecules are therapeutic targets in allergic airway inflammation.
- **g)** Stimulation of eosinophil death with FasL (CD95L) is a therapeutic target.
- **Balb/c mice strain** is a strain of choice in allergy research because of its tendency to develop Th2 immune responses.
- **Mouse asthma models** induce acute airway inflammation, but fail to induce chronic inflammation → difference with human asthma (chronic disease).

**SYSTEMIC CONTACT DERMATITIS TO CORTICOSTEROIDS (Baeck M, Goossens A. Allergy 2012; 67: 1580–1585):**

- Authors report 16 patients with delayed allergic skin manifestations after systemic administration of corticosteroids.
- The main route of sensitization was skin. There was a high frequency of cross-reactions.
- All patients presented with generalized eruption (eczema or maculopapular rash) a few hours or days after the first dose of corticosteroids. 3 of them also presented flare-up (recall) reactions at previously affected skin sites.


- Growing on farms → exposure to a greater microbial diversity (endotoxin, muramic acid) → lower risk of developing asthma.
- Environmental microbiota influences commensal skin, respiratory and digestive microbiota.
- Intestinal microbiome: at least 500–1000 different bacterial species. Newborn gut microbiota depends on type of delivery; further changes in microbiota are influenced by diet. Dysbiosis of gut microbiota can underlie several diseases.
- Future therapy of allergies may include strategies to target microbiome for better immunotherapy.
- Endogenous GC production has been reported in the intestine, skin and lungs. Does altered lung GC synthesis contribute to the pathogenesis of asthma?
Pharmacological induction of local GC synthesis may have considerable advantages over current modalities of systemic and topical steroid treatment.

- **PARP-1** inhibits calpain-mediated cleavage of STAT-6 → ↑ GATA-3 expression. Inhibition of PARP-1 ↓ allergen-induced inflammation in animal models.

- **Hypoxia-inducible factor (HIF)-1** affects gene expression in multiple tissues in response to hypoxia. HIF-1 plays a role in allergic airway inflammation.

- A combination therapy that blocks **histamine receptor 1 (H1R) and H4R** might be effective in allergic inflammation and pruritus.

- **IL-31** mediates pruritus by activating sensory neurons, epithelial and immune cells. Expression of IL-31 and IL-31R in immune and non-immune cells can be stimulated by microbes (eg. *Staphylococcal superantigens*).

- **Basophils**: defense against parasites; IL-4 secretion and antigen presentation → Th2 response.

- AD patients with **filaggrin mutations**: impaired skin barrier function, higher transepidermal water loss (TEWL), higher skin pH levels, altered expression of ceramides in the stratum corneum.

- Genotype and environment (inflammation) affects expression of **filaggrin** and its degradation products.

- Filaggrin breakdown products: urocanic acid (**UCA**), pyrrolidone carboxylic acid (**PCA**) → maintain acidic pH in the skin → inhibit staphylococcal growth.

- **Staphylococcus aureus**: extracellular vesicles with pathogenic proteins (alpha-haemolysin, cysteine protease); enterotoxins acting as superantigens and stimulating IgE responses → contribution to AD.

- Endogenous or exogenous **proteases** → activation of **PAR-2** receptors in the keratinocytes → keratinocytes release TSLP → Th2 responses.

- Mast cells express **dectin-1**, a recognition receptor for fungi.

- **How to restore skin barrier (ceramides, lipids?)** Topical emollients; dietary sphingolipids and n-3 long-chain polyunsaturated fatty acids.

- **Calcineurin inhibitors** and topical corticosteroids may normalize epidermal differentiation and expression of filaggrin and loricrin in AD skin. The problem with corticosteroids is that they also reduce the expression of antimicrobial peptides, involucrin, small proline-rich proteins and lipid-synthesizing lipids.
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:


  • Problem: ~45,000 adults die each year from vaccine-preventable disease.
  
  • Physician recommendation is effective in improving vaccination rates.
  
  • Adults ≥65 years should receive a Tdap dose in place of a single Td vaccine. Tdap is recommended to pregnant women after 20 weeks’ gestation.
  
  • Quadrivalent HPV vaccination (HPV4) targets HPV types 16 and 18 (implicated in ~70% of cervical cancer), and HPV types 6 and 11 (implicated in >90% of genital warts).
  
  • Female who receive HPV4 should be observed for 15 minutes, owing to an observation regarding syncope after HPV4 vaccination.
  
  • Zoster vaccine contains the same viral strain as VZV (Oka strain), but at least 14 times more potent. Zoster vaccine can be given at any time relative to administration of blood products (in other live attenuated viral vaccines, including VZV and MMR, a 3- to 11-month wait time is indicated).
  
  • Only 41% of health care professionals strongly recommended zoster vaccination when indicated. Zoster vaccination is not currently recommended for individuals who have received VZV.
  
  • PCV13 may be administered to 6-18 years-old individuals who have not been previously vaccinated. PPSV23 contains all of the serotypes included in PCV7. Serotype 6A is unique to PCV13 and not included in PPSV23.
  
  • More than 2 PPSV23 doses are no recommended in any situation.
  
  • Cigarette smoking is the strongest risk factor for invasive pneumococcal disease in healthy adults 18-64 years of age.
  
  • Anti-HBsAg ≥10 mIU/mL → protection after HVB vaccine.
  
  • One-dose HBV vaccine → 50% responsiveness in healthy ≤40 years-old individuals. 3-doses HBV vaccine → 90-95% responsiveness.
  
  • Routine 3-shot series in infants → 90% had protective titers 6 months later; 40% had protective titers at 60 months. Considering anamnestic booster responses, 80% remain protected 22 years after completion of primary series.
  
  • How to improve response against HBV in immunocompromised patients, including end-stage renal disease? Early administration of the vaccine schedule, higher dosing (40 μg/dose for 4 doses).
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **Titer interpretation** after vaccinations is difficult in many circumstances.


  - Higher serum level of 25(OH) vit D \(\rightarrow\) better responses to house dust mite IT (more reduction in asthma symptoms score, more steroid-sparing effect, higher TGF-β production, higher Foxp3 induction).
  - 25(OH)D >30 ng/mL may facilitate the optimal effect of IT. Should vit D be supplemented in patients with 25(OH)D insufficiency before SIT?
  - **Limitations**: retrospective study, small sample size, inconclusive cause-effect relationship between vit D levels and IT effectiveness \(\rightarrow\) a RCT is needed.

- **INDUCTION OF TOLERANCE IN A PATIENT WITH A HISTORY OF EXFOLIATIVE DERMATITIS TO TRIMETHOPRIM-SULFAMETHOXAZOLE** (Rabbat JC, Lin MY, Moy JN. *Ann Allergy Asthma Immunol* 2012; 109: 360–361):
  - **When to consider induction of drug tolerance?** IgE- or non–IgE-mediated drug hypersensitivity; no acceptable alternative drugs.
  - **Case report**: 53-year-old woman with psoriatic arthritis and several joint surgeries including arthroplasty; HIV-negative; recurrent MRSA infections, susceptible to vancomycin, linezolid and TMP-SMX. She needed chronic suppressive therapy with TMP-SMX. The 2\(^{nd}\) day of therapy she presented exfoliative dermatitis. A 10-day protocol of tolerance induction failed. As MRSA infections continued, a 266-day protocol of tolerance induction was attempted with success. At the time of publication, the patient has remained on 160 mg TMP-800 mg SMX for 9 months, with no invasive MRSA infections.

  - **Cow’s milk or egg allergy** \(\rightarrow\) avoidance affects quality of life and nutritional status. At teenage, most children have outgrown milk or egg allergy. Few ones persist, especially those with sIgE >50 kIU/L.
  - The majority of cow’s milk and egg allergic children tolerate these ingredients in extensively heated (baked) forms. Development of tolerance to unheated
milk and egg can be accelerated by ingesting baked products, compared to avoidance (16 times more likely for milk, 14.6 times more likely for egg).

- **Be careful with:** undercooked baked products, baked products not fully cooked in the middle, store-bought baked goods with milk protein ingredients listed as the 1st and 2nd ingredient, baked goods with milk chocolate chips.

- **RAPID INTRAVENOUS DESENSITIZATION TO COLISTIN** *(Tosi MF, Konstan MW, Paschall VL. Ann Allergy Asthma Immunol 2012; 109: 361–362):*

  - **Case report:** 17-year-old boy with cystic fibrosis and advanced lung disease; respiratory exacerbation by *Pseudomonas aeruginosa*, only susceptible to colistin. Patient had a previous immediate hypersensitivity reaction to colistin, confirmed by challenge. Skin testing (prick and intradermal) to colistin was negative. Successful rapid intravenous desensitization was performed. Patient completed the protocol and received IV colistin for 6 weeks without hypersensitivity reactions, but he succumbed to his advanced lung disease.


  - **Vitamin D:** secosteroid with immunoregulatory functions. Optimal level for bone health >30 ng/mL. Level for optimal immune system homeostasis: not established.

  - **Case report:** 58-year-old man with osteopenia, vit D deficiency (25-OH vit D = 4.7 ng/mL; normal >30 ng/mL), and chronic urticaria (CU) partially responsive to fexofenadine. He was receiving cholecalciferol 400 IU for 10 years. Because of worsening osteopenia, endocrinologist increased cholecalciferol dose to 2,000 IU daily. Coincidently, CU resolved! The patient continues taking daily cholecalciferol and has not had a recurrence of symptoms.

  - Clinicians may consider screening CU patients for vit D deficiency if standard therapy fails. Vit D deficiency $\rightarrow$ vit D supplementation with subsequent monitoring of serum 25(OH)D levels.

  - A RCT regarding vit D supplementation as a therapy in CU should be done.
JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:


  • CVID: failure to produce protective antibodies, other causes must be excluded; recurrent infections; clinical diversity is a problem, so phenotyping is useful.

  • Authors of this article used data of 334 CVID patients to define 4 clinical phenotypes with very little overlap (83% of the patients had only 1 clinical phenotype). Phenotypes were correlated with prognostic indicators.

  • Phenotyping criteria: a) no other disease-related complications (‘infections only’); b) cytopenias (thrombocytopenia/anemia/neutropenia); c) polyclonal lymphoproliferation (granuloma/lymphoid interstitial pneumonitis/persistent unexplained lymphadenopathy); d) unexplained persistent enteropathy.

• DO ALL ASTHMATICS WITH ATOPY HAVE ATOPIC ASTHMA? (Arbes SJ. J Allergy Clin Immunol 2012; 130: 1202-1204):

  • Atopic asthma: extrinsic or allergic; nonatopic asthma: intrinsic or nonallergic.

  • 7245 persons aged ≥6 years old → 57% of asthma cases among atopics could be attributable to atopy; in 43% atopy was incidental.

• EARLY PROBIOTIC SUPPLEMENTATION FOR ALLERGY PREVENTION: LONG-TERM OUTCOMES (Jensen MP, Meldrum S, Taylor AL, Dunstan JA, Prescott SL. J Allergy Clin Immunol 2012; 130: 1209-1211):

  • Regular dosing with Lactobacillus acidophilus (LAFTI L10/LAVRI-A1) from 0 to 6 months of age had no long-term benefits (at 5 years old) on allergy prevention.

  • Factors that may affect the effect of probiotics: probiotic strain, timing of administration, type of delivery (cesarean vs vaginal).

  • Previous studies showed beneficial effects of probiotics administered pre- (4 weeks) and postnatally (6 months). Lactobacillus rhamnosus GG → reduction of eczema during the first 7 years of life. Probiotic mixture (2 lactobacilli, 1 Bifidobacterium, and 1 Propionibacterium) for cesarean-delivered children → reduction of IgE-associated allergic diseases (sensitization and eczema).


  • Egg allergy: 1-2% of young children. Most patients outgrow allergy.
• **Influenza vaccine** contains residual egg protein → theoretical concerns about anaphylaxis in egg allergic patients.

• 4172 patients with egg allergy (513 patients with a history of severe reactions) received influenza vaccine (4729 doses in total) → no anaphylaxis.

• The published number of egg-allergic patients safely vaccinated against influenza is nearly 4 times as large as the number that ended the precautions regarding measles, mumps and rubella (MMR) vaccine (4172 vs 1227).

• Egg-allergic patients, even those with severe allergy, can be safely vaccinated against influenza like all other individuals.

• **FOOD PROTEIN–INDUCED ENTEROCOLITIS SYNDROME CAN OCCUR IN ADULTS** (Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. J Allergy Clin Immunol 2012; 130: 1199-1200):

  • **Food protein–induced enterocolitis syndrome (FPIES):** rare non-IgE–mediated food allergy; potentially severe; typically presents during infancy, most cases resolve by age 3 years; most common causes are cow’s milk and soya milk; solid foods have also been reported, notably rice.

  • Authors report a 53-year-old man with FPIES to scallops (Mollusca: Bivalvia: Pectinidae): diarrhea and vomiting 2-4 hours after eating scallops; no specific IgE (in vitro and skin tests); open food challenge: 95 min after last dose (34 g) → vomiting, diarrhea, hypotension, leukocytosis, neutrophilia, normal tryptase, no eosinophilia.

  • **Differential diagnosis** of gastrointestinal symptoms following seafood ingestion: gastroenteritis, scombroid poisoning, allergy to Anisakis simplex.


  • Epithelial herpes virus entry mediator (HVEM) might induce STAT3 activation → mucosal immunity against Candida and Staphylococcus species.

  • **Chronic mucocutaneous candidiasis (CMC)** can result from mutations in STAT3, AIRE, IL12RB1, IL12B, TYK2, IL17RA, IL17F and STAT1. Defective IL-17 and/or IL-22 immunity are the pathogenic basis of CMC.

  • **STAT3 mutation** → defect in IL-6 signalling → defect in Th17 differentiation → susceptibility to Candida and Staphylococcus.

  • **AIRE mutation** → defective thymic Treg differentiation → antibodies to IL-17, among others → susceptibility to Candida and autoimmunity.

  • **IL-12Rβ1 or IL-12p40 mutation** → defect in IL-12 and IL-23 signalling → defect in Th17 and Th1 differentiation → susceptibility to Candida, MSMD.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **IL-17RA or IL-17F mutation** → defect in Th17 immunity → susceptibility to Candida.

- **STAT1 gain-of-function mutations** → excessive signalling to IFNα/β, IFN-γ, IFN-λ and IL-27; defective signalling to IL-6, IL-21 and IL-23 → defect in Th17 immunity → susceptibility to Candida.

- **Phagocytes** are critical to defend against Candida and Staphylococcus species. Defects in neutrophil count (severe congenital neutropenia), phagocyte killing (CGD) or phagocyte chemotaxis predispose to infections by those microbes.

- **Antibodies to IL-6** may cause susceptibility to Staphylococcal infections without susceptibility to Candida species.

- It is not known in full detail why some PIDs predispose to Staphylococcus or Candida in varying degrees.


  - **Epinephrine**: 1st-line treatment for all forms of anaphylaxis. Autoinjectors are available in 2 fixed doses (0.15 and 0.30 mg); adults and children weighing >25 kg should be prescribed 0.30 mg regardless of their weight or body habitus.

  - 10-20% of patients with anaphylaxis receive a 2nd dose of epinephrine; risk factors remain poorly defined. Obesity is supposed to be a risk factor because: a) weight; b) thickness of tissues.

  - 321 ED patients (261 children and 60 adults) with anaphylaxis, 18% overweight, 22% obese → 83% received 1 dose of epinephrine, 17% receive ≥2 doses) → obesity was not associated with receipt of >1 dose.

  - A previous work showed that the more likely explanation for repeated administration of epinephrine was an inadequate treatment response.


  - **Dietary therapy**: therapeutic nonpharmacologic cornerstone for EoE.

  - Modalities: a) amino acid–based formula: the most effective in children, poor palatability, difficult to achieve; b) 6-food elimination diet (SFED) with reintroduction and endoscopic re-evaluation: high effectiveness in children and adults, lengthy, expensive; c) selective elimination diet based on skin testing: promising results in children (75% symptomatic and histologic improvement), with high PPV (>74%) and NPV (88-100%) for almost all foods.
• **Results of the study:** 4/15 adult patients achieved complete remission on a selective 6-week elimination diet; 1/15 patients achieved clinical remission with partial histologic response (14 eos/hpf); 10/15 patients did not respond.

• A selective elimination diet based on skin testing has suboptimal efficacy for adults with EoE. Sensitization to aeroallergens may affect response to diet.

• **warts and all: human papillomavirus in primary immunodeficiencies**
  
  (Leiding JW, Holland SM. J Allergy Clin Immunol 2012; 130: 1030-1048):

• This article reviews PIDs that confer susceptibility to severe and recurrent infections by HPV.

• **PIDs with warts as a major feature:** epidermodysplasia verruciformis, WHIM syndrome, DOCK8 deficiency, GATA2 deficiency, Netherton syndrome, STK4 deficiency, idiopathic CD4 lymphopenia, Ras homolog family member H deficiency (RHOH, an intracellular transducer from TCR and BCR).

• **PIDs with reports of warts:** NEMO deficiency, ataxia-telangiectasia, SCID, CVID, LAD type 1, Wiskott-Aldrich syndrome, CD40L deficiency.

• HPV induces poor immune responses in healthy subjects.

• **Mechanisms of evasion:** 1) HPV replication is confined to keratinocytes, with an exclusively intraepithelial lifecycle (HPV infects basal keratinocytes through epithelial microabrasions, leaving the basal lamina intact; encapsidation, viral assembly and maturation occurs in the most superficial epithelial cells) → little inflammatory signals; 2) HPVs are not lytic but live in terminally differentiated cells at a high level of viral replication; 3) dendritic cells, such as Langerhans’ cells, are not activated after uptake of HPV antigens; 4) HPV does not replicate in antigen-presenting cells; 5) there is no viremic state; 6) adaptive immunity in draining lymph nodes has poor access to HPV antigens; 6) HPV inhibits type 1 interferon synthesis and signalling in keratinocytes.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

**PEDIATRIC ALLERGY AND IMMUNOLOGY:**

  - L. plantarum (twice/day for 12 wk) versus placebo in children with atopic dermatitis aged 12 months to 13 yr → L. plantarum group: significant ↓ in SCORAD, lower eosinophil blood count, lower levels of IL-4 and IFN-γ.
  - Supplementation with L. plantarum may benefit therapy of pediatric AD.

  - Advantages of IT: modification of natural history of allergies, prevention of new sensitizations and progression to asthma.
  - SLIT has a better safety profile, ideal route to administer IT in children.
  - 46% of 150 children (<6 years old) with respiratory allergies discontinued SLIT. Economic aspect was not a confounding factor, because SLIT was fully reimbursed by the healthcare system.
  - Adverse events (18.6% of children): tiredness, headache, abdominal pain, oral/lip itching, rhinoconjunctivitis (2 patients), wheezing (1 patient).
  - Recommendations: start SLIT after 4 years old (more adherence, probably owing to more tolerance to unpleasant taste and local side effects); frequent control visits; monitoring of adherence.
  - Previous studies reported high compliance for SIT (60-90% in the long term). However, marketing data showed 90% of discontinuation after 3 yrs.

  - Risk factors for allergy: hygiene, infections, pollution, allergen exposure, breast-feeding practices, nutrition, obesity. Prevention focus is moving away from avoidance of allergen exposure and toward tolerance induction.
  - Some developed countries may have reached a plateau in asthma prevalence; in developing countries allergic diseases are still increasing.
  - Hygiene (viral and bacterial infections, microbial stimulation, farming environment, day care attendance, older siblings) is one of the most relevant factors associated with increasing asthma and allergies.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- The strongest risk factor for allergy may be a **positive family history**. Recent study: familial predisposition for an allergic disease is **gender-dependent** (maternal allergy ↑ risk in girls; paternal allergy ↑ risk in boys). Target organ of allergic diseases may also be affected by hereditary factors.

- **Bronchiolitis caused by HRV** is associated with a markedly higher risk of persistent wheezing at 6 yr of age compared to **RSV bronchiolitis**.

- Recent investigation: uniform positive association between **tuberculosis** and allergic disease outcomes → controversial with previous studies.

- How does **growing in a farm** protect from allergic diseases? Microbial diversity (including bacteria and helminths); infant diet; maternal diet (different cytokine sets in the milk of breast-feeding mothers).

- **Urban air pollution**, pre- and postnatal exposure to **tobacco smoke** (active and passive) → increased incidence of airway disease.

- Negative effect of **indoor allergens** (HDM, pets, fungi) in allergy development is debated → avoidance is not recommended as a primary prevention strategy.

- Systematic review and meta-analysis: protective effect for intake of **vit D** (OR 0.56) and **vit E** (OR 0.68) during pregnancy in the outcome of wheezing. Serum **vit A** was lower in children with asthma compared to controls (OR 0.25).

- **Vit C, vit D or Mg intake in asthma**: heterogeneous results on their benefit.

- Recent studies have not shown major associations between respiratory allergy symptoms and **dietary behavior/body mass index** of children and adolescents.

- Allergic sensitization in the pre-clinical phase is weaker and molecularly **simpler** → earlier component resolved immunotherapy could be more successful in treating or preventing respiratory allergies.

- **Probiotics** for prevention and treatment of allergies? Not enough evidence.

- Preventive effect of **breast-feeding** on allergies is controversial. Owing to many benefits, breast-feeding for minimum 6 months is strongly recommended.

- **Multifaceted interventions**: avoid risk factors and provide protective factors.


  - Belderbos et al.: breastfeeding down-modulates secretion of **TNF-α** and **IL-10** by white blood cells in term children during the first month of life.
• Recent report: preterm children who received breastfeeding had lower levels of IL-10 and RANTES secreted by the upper respiratory tract 1 year after birth.

• Immunomodulatory effect of breastfeeding: protection against infections (immunoglobulins and antimicrobial peptides in maternal milk); tolerance induction to environmental and dietary antigens (antigen transfer across mammary epithelium; tolerogenic molecules in maternal milk: immunoglobulins, oligosaccharides) → potential preventive effect against allergies.

  
  • 3 phyla of edible seafood: Mollusca, Arthropoda and Chordata. Invertebrate phyla (molluscs and crustaceans) are commonly known as ‘shellfish’.

  • Seafood: high nutritive value. Problem: allergies, especially in communities with high consumption (China, Japan, USA). Prevalence of fish allergy in children: ≤0.2%; shellfish allergy: ≤0.5%.

  • Problems with seafood allergy: potentially persistent through decades (80% of cases); difficulty to identify species because of its wide diversity; seafood allergenicity may be increased by heating.

  • Codfish allergy is the best studied. Gad c 1 (major allergen) is a parvalbumin.

  • Parvalbumin is a calcium-binding sarcoplasmic protein; molecular mass ~12 kDa; resistant to heat, chemical denaturation and proteolytic enzymes; becomes airborne with steam without denaturation; storage can increase capacity to bind IgE; high amounts in the white muscle of fish (cod, flounder or whiff have higher proportions of fast-twitching white muscle, important for continuous swimming); low amounts in dark muscle (tuna, skipjack or swordfish have more dark muscle → lower allergenicity).

  • Parvalbumins from different fish share 60-80% of aminoacid homologies → variable degrees of clinical cross-reactivity in patients with fish-allergy (50% of individuals allergic to fish are at risk for reacting to a second species).

  • Allergens in shellfish: the muscle protein tropomyosin (the major allergen); the 40-kDa arginine kinase (it might be a new class of invertebrate pan-allergens).

  • Tropomyosins from different shellfish have high similarity (crustaceans have homologies of up to 98%; shrimp has 57% and 61% homology with mussels and abalone, respectively → 75% of individuals allergic to shellfish are at risk for reacting to a second species → shellfish-allergic patients should avoid all shellfish in the absence of evidence of tolerance.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **Shellfish allergens do not cross-react with fish allergens.** However, recent data reports that 21–43% of fish-allergic individuals are also allergic to shellfish. This cross-reactivity may be explained by increased atopic predisposition.

- There is cross-reactivity between seafood allergy, mites and insects (high amino acid homology of invertebrate tropomyosin) → 'mite–crustacean–mollusc syndrome'. Recent observations show that during immunotherapy to HDM some patients develop clinical sensitization to shellfish tropomyosin.

- **Differential diagnosis of seafood allergy:** hypersensitivity to preservatives (eg. sulfites, which can be added to shellfish to stop them discoloring), allergy to Anisakis simplex, scombroid fish poisoning, ciguatera, paralytic shellfish.

- **Anisakis simplex:** worldwide-distributed nematode; life cycle involves fish or marine animals that may be eaten by humans; eight allergens, including tropomyosin, which cross-reacts with shellfish allergens; cooking for ≥20 min above 60ºC or storage in industrial freezers kill the parasite; clinical signs of anisakiasis depend on where in the digestive tract the larva is deposited, it may cause immediate allergic reactions, including anaphylaxis.

- **Diagnosis:** clinical history (mainstay), specific IgE against seafood (cutaneous or in vitro testing), oral food challenge.

- **Skin prick test** with cooked food, raw food and commercial extracts: high sensitivity and NPV; low specificity and PPV (<50%). In shrimp allergy, the NPV of 30% from commercial SPT is unacceptable because a significant number of sensitive patients will be missed.

- Patients with fish-allergy should be skin tested to cod fish, as a pan-allergen, (unless clinical reactivity to a specific fish has been shown) and to shellfish.

- For fish (cod) allergy, specific IgE >20 KUA/l can predict clinical reactivity.

- >20% of children allergic to salmon or tuna tolerated the fish in a canned form, accompanied with ↓ in SPT size. Canned fish eating may induce tolerance.

- **Double Blind Placebo Controlled Food Challenge (DBPCFC):** gold standard for diagnosing seafood allergy; method of choice in cases of atopic eczema (AE), subjective symptoms or isolated digestive late reactions. Patients with a clear history of anaphylaxis should not be challenged. Proposed starting dose for fish and shrimp: 5 mg (the actual starting dose must always be individualized).

- **Open food challenges** can replace DBPCFC in children <3 years old without AE.

- **Therapy for seafood allergy:** a) **strict avoidance** to all fish and shellfish species (unless clinical tolerance has been proven to a specific species by challenge); consider challenge to canned fish; be careful with unjustified restricted diets; b) **immunotherapy**, including mutated less allergenic recombinant proteins (eg. ‘Hypoallergenic’ parvalbumin).
• Seafood allergy is known as a persistent allergy. However, it can be outgrown in the adulthood, so a food challenge may be considered.

• Allergies to egg, milk, peanut and fish may serve as early markers for persistent asthma symptoms and morbidity, even as children outgrow the food allergies.

• Persistent vs transient allergy may be the result of different epitope specificity of IgE. IgE to linear epitopes of egg and milk tend to cause persistent allergy; IgE to conformational epitopes tend to cause transient allergy.

• Early fish oil supplementation (during pregnancy, lactation, infancy, and childhood) may protect against allergic diseases and asthma.


  • RAG1 and RAG2 genes: located in 11p13, separated by 15 kb.
  
  • RAG1 protein: 1.043 aminoacids, 119 kDa; RAG2: 527 residues, 59 kDa.
  
  • RAG defects → 3 different phenotypes: T-B-NK+ SCID; Omenn syndrome (OS); atypical SCID/Omenn or Omenn-like syndrome (intermediate phenotype).
  
  • RAG mutations (usually insertions, deletions and nonsense mutations) → no protein or no function → SCID.
  
  • Hypomorphic RAG mutations (usually missense mutations) → protein with partial function → OS.
  
  • The same RAG mutation can cause both T-B-NK+ SCID and OS → epigenetic and environmental factors must contribute in determining the phenotype.
  
  • Case report: RAG1 deficient patient (mutation c.631delT) → reduced-intensity conditioning HSCT → successful response → 2 years later presented with OS.
  
  • A myeloablative conditioning regimen that eliminates reminiscent T cells might have improved patient’s outcome and it should be considered in similar cases.


  • Neonatal jaundice →higher rate and severity of childhood asthma (OR: 1.64) up to 10 years old, including late onset asthma (onset after 3 yr of age).

  • Confounding factors were excluded: preterm/low birth weight, neonatal infection, other respiratory conditions, other birth conditions.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- Hypothesis to explain the association between neonatal jaundice and asthma: bilirubin >12.5 mg/dl is a strong prooxidant; bilirubin can inhibit Th1 response; increased heme is a potentially prooxidant; detrimental effect from secreted bile in the intestinal flora; detrimental effect of bilirubin on lung surfactant surface tension properties; decreased activity of antibody-dependent cellular cytotoxicity (ADCC).