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- TREATMENT OF THE BRONCHIAL TREE FROM BEGINNING TO END: TARGETING SMALL AIRWAY INFLAMMATION IN ASTHMA (van den Berge M, ten Hacken NHT, van der Wiel E, Postma DS. Allergy 2013; 68: 16–26).


• **THE LONG-ACTING B-ADRENERGIC AGONIST CONTROVERSY IN ASTHMA: TROUBLEsome TIMES!** (Szefler SJ, Busse WW. J Allergy Clin Immunol 2012; 130: 1256-1259).


ALLERGY:

• **DO MAST CELLS LINK OBESITY AND ASTHMA?** *(Sismanopoulos N, Delivanis D-A, Mavrommati D, Hatzigelaki E, Conti P, Theoharides TC. Allergy 2013; 68: 8–15):*
  - **Obesity** → asthma worsening; increased need of inhaled steroids.
  - **Obesity:** adipocytes release cytokines (IL-6, RANTES) → chronic inflammation.
  - **Advanced glycation end products** and **oxidized lipoproteins** activate mast cells.
  - **Westernized diet** (low antioxidant intake, high saturated fat intake) → activation of innate immune response → inflammation in asthma.
  - **Mast cells:** source and target of adipocytokines, proallergic cytokines (IL-9, IL-33) and stress molecules (CRH, neurotensin (NT)); counteract Treg cell suppression; promote T17 cells involved in autoimmune diseases; often found within white adipose tissue; involved in asthma and obesity.
  - **Asthma** → mast cells are present in the airway lamina propria (adjacent to blood vessels), epithelium and smooth muscle.
  - **IL-33** → mast cell activation → IL-13, IL-33 and VEGF production.
  - **Stress** → CRH and NT secretion from the hypothalamus and mast cells → HPA axis activation, mast cell activation, increased vascular permeability.
  - **Mast cell inhibitors** may be useful for asthma and obesity (quercetin/luteolin flavonoids: ↓ inflammation, inhibit mast cells, ↑ sensitivity to insulin).
  - **Omalizumab** is used for severe asthma; 33% of patients do not respond.
  - New approach: aggregation of the FcεRI with the inhibitory IgG receptor FcγRIIB by a novel bispHERic fusion protein → more effective basophil inhibition than omalizumab.

  - **Chronic autoimmune urticaria:** 50% of CU patients; autoantibodies against IgE or FcεRIα, complement activation; positive basophil histamine release assay, positive autologous serum skin test; mast cell activation by complement fractions; basophil activation by complement fractions, IgG1 and IgG3; association with other autoimmune diseases; association with HLA-DR4 haplotype; good response to immunotherapies.
  - **C5a receptors** are expressed mainly by skin mast cells → patients with urticaria due to complement activation mainly present cutaneous symptoms.
• We need a new ‘gold standard’ for the diagnosis of ACU.


  • Atopic dermatitis: skin barrier defect, with abundant mast cells and histamine.

  • Histamine addition to human keratinocyte cultures → ↓ differentiation-associated proteins (keratin 1/10, filaggrin and loricrin) by 80–95%; ↓ tight junction proteins (zona occludens-1, occludin, claudin-1 and claudin-4); ↓ desmosomal junction proteins (corneodesmosin and desmoglein-1) → thinning of the epidermis and stratum corneum by 50%; loss of the granular layer.

  • **2-pyridylethylamine** (H1R agonist) had the same effects as histamine. Cetirizine (H1R antagonist), virtually abrogated the effect of histamine.


  • 25 patients with a history of HAE attacks ≥ every 2 wks → 50 U/kg IV rhC1INH weekly for 8 wks, follow-up for 6 wks more → HAE attack frequency ↓ from 0.9 (over the past 2 years) to 0.4 (during the treatment period) attacks/wk.

  • Weekly administrations of 50 U/kg rhC1INH were safe and well tolerated. Adverse effects: dry mouth, dizziness and anxiety in one patient; hypotension in another. No allergic reactions, no neutralizing antibodies.

  • 84% of patients had at least one breakthrough attack despite prophylaxis.

  • Why it is hypothesized that pdC1INH is better than rhC1INH for HAE-attack prophylaxis? Because of half lives (1.6 h for rhC1INH; >30 h for pdC1INH).

  • Which HAE patients should be considered for long-term prophylaxis? Frequent attacks despite optimized on-demand treatment; frequency is controversial (i.e. >12 moderate-to-severe attacks per year; 24 days per year with even mild angioedema symptoms; >1 severe attack per year); controversy also exists comparing LTP with on-demand treatment of early symptoms (LTP ↓ attack frequency and severity, and ↑ quality of life; however, breakthrough attacks still occur and total usage of pdC1INH is often increased).

• **TREATMENT OF THE BRONCHIAL TREE FROM BEGINNING TO END: TARGETING SMALL AIRWAY INFLAMMATION IN ASTHMA** (van den Berge M, ten Hacken NHT, van der Wiel E, Postma DS. Allergy 2013; 68: 16–26):

  • Small airways: internal diameter <2 mm; generation number generally >8; 98.8% (4500 ml) of lung volume (compared to 50 ml in large airways); overall
resistance is very low because of high cumulative cross-sectional area (despite lower airway diameter); contain little or no cartilage → easily collapsible.

- **Small airways** may have an important role in asthma symptoms and severity. All layers are inflamed with a Th2 inflammation similar to larger airways.

- **Unknown issues:** 1) Is small airway disease present in all patients or is it a specific phenotype of asthma? 2) Is small airway disease a risk factor for poorer therapeutic outcomes and prognosis? 3) How to measure more accurately small airway inflammation and remodeling in asthma? 4) What is the optimal treatment for patient with high level of small airway disease? 5) What is the optimal particle size of ICS and β2-agonists?

- **Conventional spirometry (FEV1)** and peak flow mainly reflects large airway function. There is no golden standard test with accepted cutoff values to assess and monitor small airway involvement.

- **Small-particle adenosine 5’-monophosphate (AMP) provocation:** promising test to detect small airway disease; may predict response to small particle aerosols.

- **Small-particle aerosols** (HFA-ciclesonide, HFA-beclomethasone dipropionate) enable higher drug deposition into the small airways (half of the dose is deposited in the large and intermediate airways; half is deposited in the small airways) → additional clinical benefits compared to large-particle treatment (corticosteroid and β2-receptors are present in the small and large airways).

- Inhaled salbutamol with mass median aerodynamic diameter (MMAD) of 2.8 μm improved FEV1 more effectively than salbutamol with MMAD of 1.5 μm.

- **Small-particle HFA-BDP** is as effective as 2-3 times the dose of CFC-BDP for improving FEV1.

- **Cross-sectional area** of small airways ↑ exponentially after the 8th generation → higher dose of small-particle aerosol might be needed for an optimal effect → higher risk of systemic side-effects (unlikely because of pharmacokinetics properties of new drugs: original compounds are pro-drugs, metabolism to active drugs occur mainly in the airways, high binding to plasma proteins).

- **Montreal Protocol (1987):** no more ozone-depleting chlorofluorocarbons (CFCs) → reformulation of CFC-based to HFA (hydrofluoroalkane-134a)-based inhalers → new formulations are solutions instead of suspensions.

• **Rhinitis**: symptomatic inflammation of the nasal mucosa → ≥2 nasal symptoms for >1 hour per day.

• State-of-the-art documents: **ARIA** for AR; **EPOS** for CRS.

• In real life, 20% with AR and CRS continue with symptoms despite adequate treatment → **severe chronic upper airway disease (SCUAD)**.

• The concept of **disease control** has recently been introduced for AR and CRS: no more symptoms or not-bothersome symptoms.

• A VAS score is proposed to assess AR control (**VAS ≥5** → uncontrolled disease).

• **Poor control** despite guideline-directed pharmacotherapy → we should consider: a) disease-related factors; b) treatment-related issues; c) diagnosis-related factors; d) patient-related factors.

• **Disease-related issues in AR and CRS**: presence of SCUAD, nasal hyperreactivity (challenge with cold dry air), hormonal factors (female sex hormones, pregnancy), neuroinflammatory factors.

• **Treatment-related issues in AR and CRS**: inadequate pharmacologic treatment, inadequate avoidance of triggers (allergens, cigarette smoke, pollutants, occupational factors), inappropriate/incomplete surgery, inadequate use of IT.

• **Diagnosis-related issues in AR and CRS**: anatomic nasal deformities, nasal polyps, immunodeficiencies, cystic fibrosis, ciliary dysfunction, adenoid hypertrophy, choanal atresia, aspirin intolerance, CSF leakage (measure β2 transferrin in nasal secretions), granulomatous diseases (Wegener, sarcoidosis).

• **Patient-related issues in AR and CRS**: lack of adherence (prejudices about treatment, fear of adverse events, economic reasons), incorrect use of medication (i.e. inappropriate use of intranasal spray: inadequate blowing of the nose prior to spray application, bad positioning of the nasal spray, nasal expiration at the time of nebulization).

• **First step AR therapy**: pharmacotherapy. Consider immunotherapy if medical treatment fails and surgical therapy (surgery of inferior turbinates or septal deviation) when nasal obstruction persists.

• **First step CRS therapy**: anti-inflammatory medication + saline douching. **Consider surgery** if prolonged medical treatment fails.
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

  
  52 y-o man → anaphylaxis (urticaria, facial angioedema, wheezing, laryngeal edema) after ingestion of food containing cilantro → SPT with fresh cilantro leaf (-); ImmunoCAP FEIA for IgE anti-cilantro seed: 0.99 Ku/L (reference<0.35).

• Cilantro: ‘spice of happiness’ (aphrodisiac); flavoring agent (tobacco, meat sauce, alcoholic drinks, candies, perfumes); may help in rheumatoid arthritis.

• Adverse reactions to spices: a) non-IgE mediated: irritant; b) IgE-mediated: spectrum of anaphylaxis.

• Bet v1 (pathogenesis-related protein) and Bet v2 (profilins) are often responsible for allergic reactions to spices.

• Cross-reactive IgE to vegetables (including spices) and aeroallergens (pollen) may happen.

  
  ICS + rapid-onset LABA as maintenance and reliever therapy → synergistic benefit; ↓ risk of severe exacerbations in patients not controlled by an ICS alone; total doses of ICS are lower compared to ICS plus SABA; most benefit may be due to the additional ICS delivered during the exacerbation.

• Approved LABAs for asthma: A) Formoterol: full β2-receptor agonist, earlier onset of action (5 min, same as SABAs); provides increasing bronchodilation with increasing doses. B) Salmeterol: partial β2-receptor agonist.

  
  Reservoirs for S aureus: anterior nares, subungual spaces.

  How do children self-contaminate or recolonize with S aureus? From anterior nares to skin through their own fingers.

  S aureus does not colonize the skin at birth → it must be transmitted from the surrounding environment after birth.

  Patients with AD must keep the nails short and clean.
  
  - **PGD2**: prostanoid produced by mast cells, TH2 cells, DCs, keratinocytes, brain → allergic inflammation (vasodilation; recruitment of eosinophils, basophils and TH2 cells; TH2 cytokine synthesis, bronchoconstriction), sleep regulation, pain perception.
  
  - **CRTH2** (chemoattractant receptor homologous molecule expressed on TH2 cells): receptor of PGD2; member of the prostanoid receptor family.
  
  - **PGD2** promotes IL-4, IL-5 and IL-13 production by TH2 cells without costimulation. **CRTH2** plays a key role in paracrine activation of TH2 cells.
  
  - **CRTH2 cells** are increased in allergic skin, nasal mucosa and bronchial mucosa.
  
  - The **CRTH2** antagonist **OC000459** is a novel oral treatment for asthma. **Indole-3-acetic acid derivatives** are potent and selective CRTH2 antagonists.
  
  - **Ramatroban** (CRTH2 antagonist) is marketed in Japan with a trade name of Baynas for the treatment of perennial allergic rhinitis.
  
  - **Indomethacin** has selective binding for CRTH2 and is a potent CRTH2 agonist.

• **FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME TRIGGERED BY ORANGE JUICE** *(Federly TJ, Ryan P, Dinakar Ch. Ann Allergy Asthma Immunol 2012; 109: 472–473):*

  - **FPIES**: non-IgE-mediated; most common foods: cow’s milk, soy and rice.
  
  - Reports of **fruit-induced FPIES**: mixed fruit (apple, pear and banana), banana.
  
  - **Case report**: 2-year-old boy; 5 episodes of emesis, dehydration and lethargy 1 to 2 hours after ingestion of orange juice; negative SPT to orange extract and fresh orange juice; specific IgE to orange <0.1 kU/L.
  
  - **OFC**: 10 mL of orange juice every 15-20 min (total of 30 mL). 90 min after last dose → emesis, tachycardia, lethargy, neutrophilia. Successful rehydration. Treatment: strict avoidance of orange juice and other citrus products. Follow-up: 1 mild episode of emesis after ingesting pineapple.


  - AAAAI, ACAAI, EAACI, WAO → International Collaboration in Asthma, Allergy and Immunology (iCAALL) → **ICON documents**. This document focuses on **angioedema without hives**, especially on C1INH deficiency syndromes.
Angioedema: vasodilation and ↑ permeability of blood vessels of the deeper layers of skin and mucosal tissues → asymmetric, nonpitting, nonpruritic swelling that resolves without scarring or discoloration.

Main mediators: histamine and bradykinin (BK), both act through G protein-coupled receptors expressed on cell membranes.

BK → phosphorylation of vascular endothelial cell cadherin; intracellular Ca\(^{2+}\) increase → plasma flow from vascular to interstitial compartment → edema.

Hereditary angioedema (HAE): C1INH defect → no inhibition of FXII and kallikrein → excess of BK.

HAE type 1: low C1INH levels; HAE type 2: dysfunctional C1INH; HAE with normal C1INH: mutations in FXII gene or unknown cause.

Acquired bradykinin-mediated angioedema: 1) Acquired C1INH deficiency (ACID): lymphoproliferative or autoimmune disorders → antibodies to C1INH → C1INH consumption; 2) Caused by angiotensin-converting enzyme inhibitors (ACEI), which interfere with BK degradation.

HAE-1/2: AD mutations of SERPING1 (20-25% are de novo); 1:50000 individuals (85% HAE-1, 15% HAE-2); variable severity, even with same mutation; mean age of attacks onset: 8-12 years (75% of patients have the 1\(^{st}\) attack <15 years old); site of attacks: extremities, bowel, face, pharynx, larynx, genitourinary tract (>50% of patients have ≥1 attack with risk for asphyxiation); duration of attacks: 72-96 hours; 50% of patients have prodromal symptoms hours before an attack (fatigue, irritability, nausea, erythema marginatum); triggers: stress, trauma, estrogens, ACEIs, menses, alcohol, vigorous exercise, infections.

Diagnosis of C1INH deficiency: C4, C1INH antigenic and C1INH functional levels.

↓ C4 level in nearly 100% of attacks; C4 may be normal between attacks.

HAE with normal C1INH: most patients female; triggers: estrogen (pregnancy, exogenous administration); key differences to HAE-1/2: older age of symptom onset, fewer attacks, more cutaneous and facial attacks, less abdominal and multisite attacks, no erythema marginatum preceding attacks.

When to suspect HAE with normal C1INH? Normal C4, C1INH antigenic and C1INH functional levels; strong family history of angioedema without hives, refractory to antihistamines → search for the FXII mutation (lack of FXII mutation does not rule out this diagnosis).

ACID: similar presentation to HAE-1/2; lack of family history; generally develops >40 years old; low C1q level (which is generally normal in HAE).

Angioedema related to ACEIs: 0.1-0.7% of treated patients; risk factors: genetic variants affecting function of BK-degrading enzymes, immunosuppressive
therapy for organ transplantation affecting dipeptidyl peptidase IV function, smokers, African Americans, women; predilection for face, lips and tongue; attacks usually start in the 1st month of treatment (25% of patients may have the 1st attack ≥6 months after starting therapy); deaths have been reported; attacks may continue months after ACEI removal; all ACEIs should be avoided; 10% risk of angioedema in patients who switch to angiotensin receptor blockers or aliskiren, a renin inhibitor (consider risk-benefit).

- Treatment of HAE: 1) on-demand treatment for attacks; 2) short and long term prophylaxis; 3) avoid triggers. All patients should have a therapeutic plan.

- Therapeutic problems: drug availability, adherence to medication.

- Fresh frozen plasma (FFP): used to treat HAE attacks when no other treatment is available; generally effective; risks: worsening symptoms, viral transmission.

- ACID patients may be less responsive to attenuated androgens but more responsive to antifibrinolytic agents.

- If effective short-term treatment is not available, therapy focuses on long-term prophylaxis (e.g. >50% of Brazilian HAE patients are treated with danazol).

- Idiopathic angioedema: exclusion of all other causes, including C1INH def.

- World Health Report: “more people would benefit from efforts to improve medication adherence than from development of new treatments”. Developed countries → adherence to medication for chronic conditions: 50-60%.


  - TIV administration is safe even in children with histories of severe egg allergy. 2-step split dosing appears unnecessary.

  - 1.5% of children have egg allergy; 1/3 of food allergic children have asthma → many children who should receive TIV vaccine do not get it due to egg allergy.

- **RAG1**: DNA binding and cleavage; **RAG2**: essential cofactor for RAG1 function.

- Complete RAG mutations → SCID. Hypomorphic RAG mutations → Omenn syndrome. RAG mutations may present as immunodeficiency with γδ T-cell expansion and granulomas.

- Authors report a novel homozygous mutation in RAG2 resulting in 2 different phenotypes: Omenn syndrome and hyper-IgM syndrome. Why there is phenotypic heterogeneity? Diverse genetic setting, epigenetics, environment.

- **Patient 1**: 1st-degree consanguineous parents; from 4 months old: P aeruginosa pneumonia, erythroderma, autoimmune hemolytic anemia, onichomycosis; markedly low T and B cells, normal NK cells; T cells were mainly CR45RO+ memory cells; HLA typing: no maternal cell engraftment; markedly decreased lymphocyte proliferation to PHA and anti-CD3 mAb; low IgG, IgA and IgM; homozygous missense mutation in RAG2 (c.1375A>C), causing a methionine to leucine change at position 459 (M459L); successful matched sibling HSCT.

- **Patient 2**: 1st-degree consanguineous parents; from 4 months old: pneumonias, skin abscesses, P aeruginosa sepsis, colitis, coagulopathy, CMV viremia, oral candidiasis, hepatosplenomegaly, autoimmune hemolytic anemia, low T and B cells, normal NK cells; very low IgG, low IgA, normal IgM; 5 years old: IgM ↑ to 1048 mg/dL; T cells were mainly CR45RO+ memory cells; low lymphocyte proliferation to PHA and anti-CD3 mAb; same mutation as patient 1.

- **Family history** → the great-grandparents of patients 1 and 2 were cousins.

- **Hyper IgM and progressive lymphopenia** → consider RAG mutations.


  - **DRESS syndrome**: generalized skin rash, eosinophilia and multiple organ failure induced by drug-specific T cells (type IV allergic hypersensitivity); drugs most frequently implicated: allopurinol, anticonvulsants, antibiotics.

  - **Allergy to aminoglycosides** can rarely present as severe Lyell syndrome.

  - Authors report a case of amikacin-induced DRESS syndrome confirmed by allergologic workup (patch tests and ELISPOT assay) 6 months after resolution.
• A 2nd series of patch tests (gentamicin, netilmicin, tobramycin, neomycin, mupirocin, spectinomycin) was done 3 months later to assess cross-reactivity → results + only to amikacin → gentamicin was given, no adverse reactions.

• ELISPOT assay may help to detect drug-specific T cells, identify the culprit drug, and select a non–cross-reactive aminoglycoside in cases of DRESS syndrome.

  
  - Control of HIV depends on virus-specific CD8+ T-cell response. Acute infection → CD8 responses decrease viremia. Chronic infection → CD8 exhaustion.
  - HIV controllers: patients who control HIV without antiretroviral therapy; potent CD8 response; strong capacity to eliminate infected CD4+ T cells.
  - IgG-opsonized HIV → decreased stimulatory capacity of DCs → decreased HIV-specific CD8+ T-cell response.
  - Complement-opsonized HIV → increased stimulatory capacity of DCs → enhanced HIV-specific CD8+ T-cell response.

  
  - Authors report 3 siblings with heterozygous mutation (c.1145G>A, p.R382Q) in exon 13 of STAT3; parents had wild-type STAT3 (peripheral blood samples).
  - It seemed rare that all 3 siblings had independent sporadic identical mutations → gDNA from the semen and oral mucosa of the father was analyzed → the mutation was present only in the semen gDNA (paternal germline mosaicism, mutation may have occurred in a stem cell that gave rise to gonadal tissue).
  - Usual rule: autosomal dominant diseases in children with healthy parents → spontaneous in utero mutations → minimal risk of ensuing affected offspring.
  - Mosaicism: one individual has 2 or more cell lines with a different genotype that developed from a single fertilized homogeneous zygote.
  - Other PIDs where germline mosaicism have been observed: Wiskott-Aldrich syndrome, X-linked SCID, DiGeorge syndrome, severe congenital neutropenia.
  - We advise to inform the family of patients with STAT3-HIES about possible mosaicism → genetic testing of every subsequent newborn is suggested.
• **EPIGENETIC MECHANISMS AND THE DEVELOPMENT OF ASTHMA (Yang IV, Schwartz DA. J Allergy Clin Immunol 2012; 130: 1243-1255):**

  • **Epigenetics:** study of heritable changes in gene expression not caused by alteration of DNA sequence. Epigenome changes in response to environment, diet and aging.

  • **Common characteristics of asthma and epigenetics:** heritable, influenced by the environment, modified by in utero exposures and aging.

  • Epigenetic mechanisms regulate the expression of transcription factors that are involved in T-cell differentiation (TH1, TH2, Treg cells).

  • **Epigenetic marks** (DNA methylation, modifications of histone tails, and noncoding RNAs) control gene expression. **Technology** to measure epigenetic marks is improving. **Air pollution** and **tobacco smoke** alter epigenetic marks.

  • **Asthma:** 36-79% heritability; polymorphisms in >100 genes, not always replicable; parent-of-origin transmission (e.g. FCERIB locus, Spink5 gene): affected mother more likely to transmit the disease than an affected father.

  • **Risk factors for asthma:** prenatal exposure to maternal and grand-maternal cigarette smoke and air pollution. **Protective factors:** higher maternal fruit and vegetable intake, oily fish (omega-3 fatty acids) intake during gestation (trout, salmon, mackerel, sardines, pilchards, herring, kipper, whitebait, fresh tuna).

  • **Noncoding RNAs:** microRNAs (miRNAs), PIWI-interacting RNAs, small nucleolar RNAs, transcribed ultraconserved regions, large intergenic noncoding RNAs. Almost 2000 mature miRNAs have been identified in the human genome (http://www.mirbase.org/)

  • Animal study: prenatal administration of *Acinetobacter Iwoffii F78A* → more acetylation at IFN-γ promoter, less acetylation at IL-4 promoter → more IFN-γ expression in CD4+ T cells → reduction of asthmatic phenotype in progeny.

• **EVALUATION OF A SKIN TEST DEVICE DESIGNED TO BE LESS PAINFUL (Nelson HS, Lopez P, Curran-Everett D. J Allergy Clin Immunol 2012; 130: 1422-1423):**

  • Melzack and Wall (1965) → “gate control theory of pain”: pain signals can be suppressed in the spinal cord by central influences (attention, emotions) and peripheral stimuli inducing A-beta nerve fibers (vibration, scratching, pressure) → theoretic basis of massage, heat and cold use, acupuncture, TENS, pressure before IM injections, leg massage to ↓ pain of a heel stick in babies.

  • **MultiTest PC (pain control):** skin test device that applies light pressure before puncturing → larger wheal compared to the ComforTen device; no greater discomfort → preceding touching of the skin may diminish pain perception.

- Maternal acetaminophen during 3rd trimester was not associated with asthma.
- Acetaminophen in infancy was associated with early childhood asthma, but not with asthma at 7 years old.


- Case report: 4 years old girl; generalized lymphadenopathy, splenomegaly, neutropenia, thrombocytopenia, hemolytic anemia, chronic diarrhea; antineutrophil antibodies positive; lymph node biopsy: reactive changes; bone marrow aspirate: normal; autoimmune enteropathy: duodenal villous atrophy and large bowel lymphocytic infiltration; psoas abscess associated with chronic neutropenia; erythema nodosum, transient arthritis of both feet.
- Initial workup: ↑ IgG (22.6 g/L); ↓ NK cells; normal: IgA, IgM, T and B cell numbers, DN T cells, T-cell proliferation, tetanus vaccine responses, NBT.
- Diagnosis: autoimmunity → immunosuppression, including multiple courses of rituximab → recurrent infections (S pneumoniae facial cellulitis, S pneumoniae sepsis, H influenzae empyema) after stopping immunoglobulin therapy → normal B cell numbers and IgG; absent vaccine responses; lung biopsy: florid diffuse lymphoid interstitial infiltrate.
- Family history: consanguineous parents (1st cousins) → homozygous mutation? → exome sequencing: large homozygous deletion that removed exons 1 to 30 of the 58-exon LPS-responsive vesicle trafficking, beach, and anchor containing (LRBA) gene.
- No LRBA product after stimulation of EBV-transformed B cells. Western blot: no detection of LRBA using anti-LRBA. Immunofluorescence: no expression of LRBA protein the cytoplasm of patient’s cells.
- LRBA gene encodes a broadly expressed protein of unknown function that is involved in intracellular vesicle trafficking. Recently 5 patients were reported with LRBA mutation → idiopathic thrombocytopenic purpura, lymphoid interstitial pneumonia, autoimmune enteropathy, hypogammaglobulinemia.
- Database of Genomic Variants (http://projects.tcag.ca/variation/).
• Mutations in LRBA gene may present as **autoimmune syndrome without CVID**. 
  Think of LRBA defects in patients with **immunodeficiency and autoimmunity**.

  
  - This 15-page paper standardizes DBPCFC. Why is it important? A) Increasing number of immunotherapeutic trials for food allergy; B) DBPCFC play a pivotal role in interpreting the outcomes of these trials.

• **THE LONG-ACTING B-ADRENERGIC AGONIST CONTROVERSY IN ASTHMA: TROUBLESOME TIMES!** (Szefler SJ, Busse WW. J Allergy Clin Immunol 2012; 130: 1256-1259):
  
  - Inhaled SABAs and ICS/LABA combinations are generally safe.
  
  - **Safety concerns** from early LABA studies were based on LABA monotherapy.
  
  - If a patient achieves asthma control using ICS/LABA, **which drug (ICS or LABA) should be stepped down, and when?** Controversial (FDA suggest that LABAs should be stopped as soon as control is achieved; recent evidence shows adverse consequences of LABA step-down in patients with controlled asthma).
  
  - No comparative study has addressed **discontinuing a LABA versus decreasing the ICS dose**.
  
  - FDA requested studies of LABA safety → **a large RCT of ICSs and ICS/LABA combinations is ongoing (~50,000 participants, including 6,200 children aged 5 to 11 years). Results will not be available until 2016.**
  
  - **Suggestions of the authors**: 1) consider asthma as a fluctuant disease; 2) in patients who are receiving high-dose ICS/LABA the decision might be to ↓ ICS dose; 3) in patients who are receiving low-dose ICS/LABA the decision would be to discontinue LABA.
  
  - At certain times of the year asthmatic patients are prone to exacerbations (e.g. “September epidemic” → avoid reduction in maintenance controller therapy.
  
  - Educate patients about signs and symptoms of asthma worsening before stepping down therapy.
  
  - **Alternative therapeutic strategies**: Omalizumab, allergen immunotherapy, tiotropium combined with an ICS, biomarker-directed therapy.
  
  - **How to monitor asthma control and airway inflammation?** Peak flow, spirometry, FENO, induced sputum eosinophil numbers.
**PEDIATRIC ALLERGY AND IMMUNOLOGY:**

  - **Probiotics:** viable microorganisms administered in appropriate amounts to alter the host’s microflora to produce beneficial health effects; mainly members of the genera Lactobacillus and Bifidobacterium; ↓ intestinal inflammation, promote adequate gut barrier and microecology, may control gut immune responses; used as prevention and treatment of atopic diseases.
  - A probiotic (**Acidophilus Ultra**) caused anaphylaxis in a 6-yr-old girl with cow’s milk and egg allergy → authors assessed the safety of probiotic compounds available in Spain → 11 probiotics were studied (no label advertised about egg content, 8 labels warned about lactose, lactic acid or cow’s milk, 1 label claimed to be milk-free, and 2 gave no information) → 91% of the analyzed probiotics contained cow’s milk, 27% contained hen’s egg proteins.
  - Probiotic compounds may contain hidden food allergens and may not be safe for subjects with allergy to cow’s milk or hen’s egg.
  - We should always read the label of ingredients; however, we must consider that labeling is often deficient or incomplete.

  - A recent study showed that 3-weeks of supplementary clarithromycin added clinical benefit in patients who were admitted with acute asthma attacks → ant inflammatory and immunomodulatory effect of macrolides.
  - Problem: high risk of increasing antibiotic resistance (M pneumoniae, H pylori and S pyogenes have very high levels of resistance to macrolides).
  - Rational antibiotic use → macrolides should be used for cystic fibrosis, bronchiectasis, COPD and asthma associated to atypical bacterial infections.

  - Multiple drug hypersensitivity (MDH): hypersensitivity to ≥2 chemically different drugs. 2 types of MDH: a) when sensitizations develop to drugs administered simultaneously; b) when sensitizations develop sequentially. MDH include both immediate and non-immediate reactions.
• Prospective study to evaluate 279 children with clinical history of MDH (most frequent reactions were maculopapular and urticarial eruptions) → skin tests, patch tests, sIgE assays, DPT → MDH was confirmed in 7 children (2.5%). Responsible drugs: β-lactams (penicillins and cephalosporins) in 5 episodes; ibuprofen and anticonvulsants in 3; erythromycin, fentanyl, cotrimoxazole and methylprednisolone in 1.

• Positive late reaction to intradermal tests: infiltrated erythema >5 mm at 48 and 72 hours.

• Non-immediate reactions to anticonvulsants → patch tests with lamotrigine, carbamazepine or phenobarbital (5% in petrolatum). Reagents were prepared by the pharmacy department using the commercially available pure powder.

• MDH can occur in children → some individuals with a previous hypersensitivity drug reaction may be at higher risk of further reactions to other drugs.

• It is crucial to evaluate children with clinical history of MDH using both in vivo and in vitro allergologic tests, including challenges → rule out MDH (avoid falsely labeling: “allergic to multiple drugs”) or confirm it.

• **FOOD ALLERGY AND ANAPHYLAXIS IN PEDIATRICS: UPDATE 2010-2012 (Santos AF, Lack G. Pediatr Allergy Immunol 2012: 23: 698–706):**

  • Food allergy is the main cause of anaphylaxis in children, particularly allergy to peanut and tree nuts.

  • Food allergy can be viewed as a dysregulation of oral tolerance.

  • Parental allergic diseases, especially maternal allergy → increased risk of food allergy in the offspring up to 4 yr old.

  • The incidence of food allergy has increased more rapidly than changes in the genome → environmental factors may have a more important role.

  • Certain probiotics → prevention against eczema; not clear for food allergy.

  • Microbial stimulation of the gut → secretion of mucosal IgA → antigen neutralization before they can reach GALT → oral tolerance.

  • OFC is essential in some situations (e.g. suspicion of non-IgE mediated allergy).

  • OFCs are often not performed → overdiagnosis of FA → unnecessary allergen avoidance. Why? Because OFCs have risk and require trained personnel and considerable time.

  • Overall FA is an uncommon cause of acute urticaria in children.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- **Allergy test panels** should include suspected foods identified in the clinical history and common food allergens considering patient’s age, allergic condition and geographical location.

- Theoretically any food can cause allergic reactions; **most common allergens:** cow milk, egg, wheat, soya, peanut, sesame, tree nuts, fish and shellfish.

- **SPT and serum sIgE:** high NPV, low PPV → more useful to exclude FA than to confirm the diagnosis.

- Allergen-specific **oral tolerance induction (SOTI)** is an area of active research in food allergy. For now there have been no fatal events.

- Whether SOTI induces **long-term tolerance** (continued effect beyond food discontinuation) or only **transient desensitization** remains to be seen.

- Few months of **oral IT** → clinical improvement, ↓ effector T-cells, ↑ Treg cells, ↑ non-reactive CD4+ T cells.

- **Polysensitization** to food and aeroallergens is common and may be a marker of a more severe atopic phenotype rather than antibody cross-reactivity.

- Choosing the **most appropriate CM formula** may be difficult; always consider costs. Additives may modulate gut immune response (e.g. lactose added to an extensively hydrolyzed formula ↑ the fecal counts of Lactobacillus and Bifidobacteria and ↓ the populations of Bacteroides and Clostridia).

- **MMR vaccination** can be safely administered to egg-allergic children at the primary care level. **Influenza** and **yellow fever** vaccines may justify a two-dose administration in hospital.