March 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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PEARLS IN ALLERGY AND IMMUNOLOGY

March 2013 – content:


• BENEFITS OF EXERCISE IN ASTHMA (Craig TJ, Denenza MC. Ann Allergy Asthma Immunol 2013; 110: 133–140).


• ADVANCES IN BASIC AND CLINICAL IMMUNOLOGY IN 2012 (Chinen J, Notarangelo LD, Shearer WT. J Allergy Clin Immunol 2013; 131).

• CLINICAL PHENOTYPES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND ASTHMA: RECENT ADVANCES (Carolan BJ, Sutherland ER. J Allergy Clin Immunol 2013; 131: 627-634).

• CORTICOSTEROID RESISTANCE IN PATIENTS WITH ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (Barnes PJ. J Allergy Clin Immunol 2013; 131: 636-645).

• INTERFERON REGULATORY FACTOR 3 ACTIVATION MEDIATES VIRAL STIMULUS-INDUCED BRONCHIAL PRODUCTION OF THYMIC STROMAL LYMPHOPOIETIN (TSLP) (Uller L. J Allergy Clin Immunol 2013; 131: 926).


• THE EXOSOME IN LUNG DISEASES: MESSAGE IN A BOTTLE (Eissa NT. J Allergy Clin Immunol 2013; 131: 904-905).


• DEVELOPMENT OF NATURAL TOLERANCE AND INDUCED DESENSITIZATION IN COW’S MILK ALLERGY (Savilahti EM, Savilahti E. Pediatr Allergy Immunol 2013: 24: 114–121).


ALLERGY:

  - Authors suggest that AR may be a risk factor for ED, possibly in a severity-dependent manner.
  - **Hypothesis**: AR → systemic inflammation → atherosclerosis → ED.
  - **Study limitations**: (i) diagnosis of AR and ED relied on administrative data; (ii) some information, including BMI and smoking, was not available; (c) subjects were only of Chinese ethnicity.

  - Extracellular DNA traps: host defense mechanism against extracellular (bacteria, fungi) and intracellular (e.g. Toxoplasma, Leishmania) pathogens; contain DNA (nuclear or mitochondrial), histones and other antimicrobial proteins (e.g. cathelicidin, tryptase); produced by viable neutrophils, eosinophils, mast cells and monocytes 5 to 60 minutes after activation; may require NADPH oxidase activity; may contribute to immunopathology (endothelial and epithelial damage, cross-talk between immune cells).
  - PIDs with impaired formation of extracellular DNA traps: complete MPO deficiency, CGD.
  - Staphylococci and S. pneumoniae produce DNases → destroy NETs → severe infections, such as necrotizing fasciitis and pneumonia.
  - Extracellular DNA traps are observed in tissues affected by allergic diseases (asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity), autoimmune diseases (bullous pemphigoid, psoriasis, SLE), vasculitis and thrombosis → target for therapies.
  - **Research questions**: How do cells release DNA? Is the DNA mitochondrial, nuclear or both? Does cell death play a role in extracellular DNA traps? Do these traps play a role in cancer?

  - Authors show that the epitope galactose-α-1,3-galactose (α-Gal) is present within the gastrointestinal tract of the tick Ixodes ricinus.
  - Tick bite → production of specific IgE to α-Gal → severe allergic reactions after ingestion of red meat (beef, pork or lamb), which contain α-Gal; severe allergic reactions to Cetuximab (a chimeric mouse-human mAb that targets EGF; contains the α-Gal epitope on the Fab portion).
  - **Northern Europe**: expanding deer and rodent populations (major tick vectors), climate changes → increased exposure to ticks → more people will be at risk of developing red meat allergy.

- **INTRODUCTION OF COMPLEMENTARY FOODS IN INFANCY AND ATOPIC SENSITIZATION AT THE AGE OF 5 YEARS: TIMING AND FOOD DIVERSITY IN A FINNISH BIRTH COHORT** (Nwaru

- In a Finnish cohort of 3674 children, authors analyzed (i) timing of infant feeding up to the age of 2 years, and (ii) serum specific IgE to 4 food allergens (egg, cow’s milk, fish and wheat) and 4 inhalant allergens (HDM, cat, timothy grass and birch) measured at the age of 5 years →
- Early introduction of foods (cereals, fish and egg) may protect against atopic sensitization in childhood, particularly among high-risk children.
- Less food diversity as already at 3 months of age may increase the risk of atopic sensitization.


- Mast cells: tissue cells that mediate allergic and inflammatory reactions; can be activated by different ways (IgE receptor, complement receptors, opioid receptors, etc.).
- Mast cells can activate in acute/episodic states (e.g. allergic reactions) or in a chronic state (e.g. mastocytosis). Severity of symptoms depends on: (i) number of activated mast cells; (ii) local or systemic activation of mast cells; (iii) clonal state of mast cells due to genetic mutations; (iv) amount of specific IgE and allergen; (v) cytokine environment.
- How to diagnose mast cell activation (MCA)? (i) Symptoms: wheals, pruritus, flushing, bronchospasm, hypotension, abdominal cramping, diarrhea (symptoms of chronic MCA are less specific, including headache, fatigue, nausea and insomnia); (ii) good response to ant mediator drugs (not only antihistamines); (iii) ↑ levels of mast cell mediators in biological fluids (e.g. ↑ serum tryptase ≥20% above baseline + additional 2 ng/ml histamine or metabolites; PGD2); (iv) MCA assays (limitation: mast cells are not accessible unless a tissue biopsy is performed).
- 3 criteria to diagnose MCA syndrome (MCAS): (i) clinical signs of severe recurrent or chronic systemic MCA; (ii) positive biochemical measurements (preferably ↑ tryptase following the 20% + 2 formula); (iii) good response to mast cell-stabilizing agents or antimediator drugs.
- Classification of MCAS: (i) Primary MCAS: caused by KIT-mutated monoclonal mast cells, usually CD25+; most patients have systemic or cutaneous mastocytosis. (ii) Secondary MCAS: caused by an underlying inflammatory disease, often an IgE-dependent allergy. (iii) Idiopathic MCAS: neither underlying inflammatory disease, nor KIT-mutated mast cells.
- A primary mast cell disease and an IgE-dependent allergy may coexist in the same patient → dangerous situation (e.g. hymenoptera venom or food allergy in patients with mastocytosis).
- Considerations: (i) lack of response to antimediator drugs does not exclude MCAS (e.g. mastocytosis + anaphylactic shock refractory to antihistamines); (ii) ↑ tryptase level alone is not indicative of MCA; (iii) less severe or local forms of MCA represent clinical challenges.


- Obesity has shown to: ↑ asthma incidence, ↑ asthma severity, ↓ sensitivity to corticosteroids.
• **Obesity**: ↑ serum leptin, ↓ serum adiponectin, ↓ respiratory system compliance → ↑ allergic airway inflammation, ↓ lung function.

• Authors performed a **systematic review of 31 studies** to assess the impact of weight changes on asthma → obesity ↑ the odds for incident asthma by 1.82 in adults and 1.98 in children; one RCT showed benefits of losing weight on asthma control and lung function; several observational studies provided limited evidence of these beneficial effects.

• It is recommended to **target obesity as part of asthma treatment.**
Annals of Asthma, Allergy & Immunology:

  - **STAT3 mutation** → autosomal dominant (AD) hyper-IgE syndrome (HIES): markedly ↑ serum IgE; recurrent infections (S. aureus abscesses, pneumonias, candidiasis), eczema, coarse facial features, pneumatoceles, delayed shedding of primary teeth, joint hyperextensibility, scoliosis, osteopenia; NIH STAT3 score >40.
  - Authors report a 36-year-old man with AD HIES (pneumonias, empyema, knee abscess, right arm abscess, candidiasis, pneumatocele, characteristic facies, hyperextensibility; IgE: 2,728 Ku/L; NIH STAT3 score: 53; mutation in exon 12 of STAT3) complicated by right peroneous brevis/longus myositis: leg pain and swelling; no history of trauma, except for scratching in nearby areas; no local warmth or erythema; no fever or systemic symptoms; no leukocytosis; negative blood cultures; MRI: inflammation of the peroneus brevis and longus muscle bellies; elevated CPK; rapid response to IV vancomycin and cefepime.

• **Always look for bacterial infection** in patients with AD HIES, despite absence of inflammation.

  - **HAE**: low C1-INH levels (type 1 HAE) or function (type 2 HAE) → ↓ inhibition of kallikrein → ↑ bradykinin production → recurrent attacks of angioedema (skin and mucosa) without urticaria; can be life-threatening. **Drugs to treat attacks**: C1-INH concentrate, kallikrein inhibitor (ecallantide), bradykinin receptor blocker (icatibant).
  - Authors analyzed 732 HAE attacks treated with ecallantide → a single dose (30 mg) was effective for most attacks (88%); a 2nd dose was required in 12% of attacks; peripheral attacks were more likely to require a 2nd dose after 4 hours.

• **Benefits of Exercise in Asthma** (Craig TJ, Dispenza MC. Ann Allergy Asthma Immunol 2013; 110: 133–140):
  - Exercise-induced bronchospasm (EIB): bronchospasm symptoms within or after physical exertion; tend to resolve within 1 hour; diagnosis: ↓ FEV1 (10–15%) with exercise; risk factors: atopy, exercising in dry air, exhaustive exercise (e.g. elite athletes), sports with high minute ventilation (basketball, cycling, soccer), cold weather sports (cross-country skiing, hockey, skating), respiratory irritants.
  - EIB may occur in individuals with or without asthma → patients with uncontrolled asthma must be careful with exercise.
  - **Benefits of exercise** (low-evidence data): ↓ inflammatory mediators, ↑ Treg responses, ↑ cardiopulmonary fitness, ↑ quality of life → patients with controlled asthma should do exercise; it is not well defined the type and intensity; definitive data is lacking.

  - Antimicrobial peptides (AMPs): small molecules with activity against bacteria, fungi and enveloped viruses.
  - Human β-defensins (HBDs): family of AMPs expressed by epithelial cells on mucosal surfaces; wide range of antimicrobial activities (gram-positive and gram-negative bacteria, fungi, viruses). HBD-2 is strongly expressed in tonsil tissue, compared with nasal sinus mucosa and adenoids.
  - Authors analyzed tonsils and adenoids from 30 patients with no history of recurrent tonsillitis or asthma → patients with allergic rhinitis had ↓ levels of HBD-2.
  - Hypothesis: allergic rhinitis → ↓ expression of HBD-2 in tonsils → ↓ innate immunity → ↑ predisposition to respiratory infections.


  - Sesame seed: “emerging” food allergen; used in some perfumes, cosmetics and lubricants; may cause IgE- and non-IgE-mediated allergic reactions, ranging from contact dermatitis to severe anaphylaxis; diagnosis: slgE detection by skin or in vitro tests, oral provocation tests.
  - Tahini: 100% sesame creamy sauce; produced in India; commercialized in Italy by Alimenta Srl.
  - Authors report a 55-yr-old man with suspected anaphylaxis to sesame → conventional SPT and ISAC testing did not detect specific IgE to sesame → SPT with “Tahini” was positive → diagnosis of sesame allergy was confirmed by a positive BAT to commercial sesame extracts → electrophoretic analysis detected an allergenic protein in “Tahini” source that was not present in conventional sesame extracts → hypothesis: roasting increases the allergenicity of sesame proteins contained in “Tahini”.
  - Skin tests with “Tahini” should be considered in patients with high suspicion of sesame allergy and negative slgE detection by conventional tests.

• **INTRACTABLE SHELLFISH ANAPHYLAXIS: SENSITIZATION BY CROSS-REACTIVE SUBSTANCES IN A COMPLEMENTARY “IMMUNE STIMULANT” AND ACRYLIC NAILS** (Rolland JM, Varese N, Zubrinich CM, O’Hehir RE. Ann Allergy Asthma Immunol 2013; 110:211–212):

  - Authors report a 46-yr-old woman with shellfish anaphylaxis → despite shellfish avoidance she presented 20 new episodes of severe anaphylaxis over 30 months; no identified trigger; normal random serum tryptase; patient used acrylic fingernails and daily “immune stimulant” powder → positive slgE and BAT to shrimp extracts, chitin powder and the “immune stimulant” powder → final diagnosis: anaphylaxis to chitin → avoidance of shellfish, acrylic nails and the “immune stimulant” prevented new episodes of anaphylaxis.
  - The “immune stimulant” contained arabinogalactan, aloe vera gel extract, gum tragacanth, glucosamine hydrochloride (from shrimp), lecithin powder, calcium carbonate, dibasic calcium phosphate, gelatin, brown rice flour, cellulose, silicon dioxide, magnesium stearate and wakame.
• Patients with shellfish allergy must be careful with chitin-associated products.
• Keep in mind that allergy to complementary products is increasing.

• PERCEPTION AND PRACTICE OF SUBLINGUAL IMMUNOTHERAPY (SLIT) AMONG PRACTICING ALLERGISTS IN THE UNITED STATES: A FOLLOW-UP SURVEY (Sikora JM, Tankersley MS, Ann Allergy Asthma Immunol 2013; 110: 194–197):

  • SLIT represents 45% of specific immunotherapy practice in Europe.
  • Authors surveyed >520 allergists to assess SLIT practice in the US → 11.4% of allergists reported experience using SLIT (compared to 5.9% in 2007); 66.7% of allergists believed that SLIT was safer than SCIT (compared to 73.4% in 2007).
  • Main barrier to use SLIT: lack of FDA approval → it is anticipated that once an FDA-approved product is available, there will be widespread use of SLIT in the US.


  • SJS: severe immune reaction that affects skin and mucosas; may be fatal; drugs are the causal agent in most cases; diagnosis: mainly clinical, histology may help; treatment: removal of the causal agent, immunosuppressive agents, supportive care.
  • Authors describe 14 cases of SJS → average age: 51 yrs (range: 27 to 82 yr); 13 cases were drug-induced; average time from initiation of the culprit agent to onset of eruption: 15 days (range: 1 to 34 days), excluding one case (many years taking allopurinol); 3 cases had some features of DRESS (eosinophilia and mild liver dysfunction); 3 patients received IVIG and corticoids, 3 only IVIG, 4 only corticoids, 4 only supportive therapy; 1 patient died.

• TERMINOLOGY, CLOSE-CALLS, AND BRACKETOLOGY FOR ALLERGY, ASTHMA, AND IMMUNOLOGY (Greenberger PA. Ann Allergy Asthma Immunol 2013; 110: 141–145):

  • Authors present an interesting list of 64 allergy/immunology terms linked in pairs, so that it would be easier to remember them. For example:
  • α-Gal vs tick bites: some tick bites induce synthesis of IgE against α-gal (galactose-α1,3-galactose) → α-gal can be present on beef, pork and lamb → patients who eat these foods may have nonimmediate (3-6 hrs later) urticaria or anaphylaxis. α-gal is present in cetuximab.
  • Lebrikizumab vs periositin: lebrikizumab (anti-IL-13) ↑ FEV1 in patients with asthma not controlled by ICS. A target of lebrikizumab is periositin, a matrix protein involved in airway remodeling. Patients with higher levels of periositin had better response to lebrikizumab.
• ADVANCES IN BASIC AND CLINICAL IMMUNOLOGY IN 2012 (Chinen J, Notarangelo LD, Shearer WT. J Allergy Clin Immunol 2013; 131):
  
  • Atopic children → lower expression of thymic TSLP → slower thymic Treg differentiation.
  
  • Spleen tyrosine kinase (SYK) has an essential role in activation of human memory B cells → target for B-cell-mediated diseases (e.g. autoimmune diseases).
  
  • PIDs with ↑ susceptibility to HPV infection: 1) warts as a major clinical finding: EVER 1 and 2 deficiency, WHIM syndrome, GATA2 deficiency, DOCK8 deficiency, idiopathic T-cell lymphopenia, Netherton syndrome, STK4 deficiency; 2) warts as a common occurrence: SCID, WAS, A-T, NEMO deficiency, CVID, CD40L deficiency, LAD-I.
  
  • Screening methods for SCID: a) absolute lymphocyte counts: high availability, risk of false-negative results (maternal lymphocytes, oligoclonal cells, elevated B cells), unclear cost/benefit ratio; b) TREC measurement: currently the best method.
  
  • ADA deficiency → dermatofibrosarcoma, pulmonary alveolar proteinosis.
  
  • Dyskeratosis congenita → defects in telomere length or function.
  
  • SP110 deficiency → venoocclusive disease and immunodeficiency (VODI) syndrome: ↓ B cell activation; ↓ IL-10 secretion by B cells; association with Crohn disease.
  
  • Lymphocyte-specific protein tyrosine kinase (LCK) deficiency: recurrent infections, panniculitis, autoimmunity; low CD4 and CD8 expression; the 1st reported patient inherited 2 maternal copies of the entire chromosome 1 that carried the mutant allele.
  
  • Panhypogammaglobulinemia → antibiotics might be required to complement IVIG replacement.
  
  • X-linked agammaglobulinemia → ↑ production of inflammatory cytokines by monocyte-derived cells after TLR activation → Bruton tyrosine kinase may have a role in controlling inflammation.
  
  • Screening method for agammaglobulinemia: k-deleting recombination excision circles (KRECs).
  
  • CD40L deficiency → ↓ expression of activation markers against fungal antigens in monocytes.
  
  • 848 CVID patients → 4 phenotypes: (1) no complications other than infections; (2) autoimmune cytopenias; (3) polyclonal lymphoproliferation; (4) unexplained persistent enteropathy. 69% increase in lymphoproliferation risk for every 100 mg/dL increase in serum IgA; 14% increase in cytopenias risk for every 100 mg/dL increase in serum IgG. Survival expectancy was least in the enteropathic group, followed by the lymphoproliferation group and the autoimmune group.
  
  • Consider CMV infection in patients with CVID and inflammatory complications.
  
  • LPS-responsive beige-like anchor (LRBA) deficiency: autosomal recessive syndrome that resembles severe CVID; hypogammaglobulinemia, autoimmune cytopenias, IBD.
  
  • CD21 deficiency: recurrent infections, moderate hypogammaglobulinemia, impaired responses to polysaccharides, reduction of memory B cells.
• **CD27 deficiency**: humoral and cellular dysfunction, severe EBV infection, lack of CD27 expression in T and B lymphocytes.

• Child with **selective polysaccharide antibody deficiency** → impaired production of antibodies to polysaccharides by the CD20+CD43+CD27+CD70- B cell subset (analog to murine B-1 cells).

• 11 patients with **CGD** were treated with **HSCT** from matched related or matched unrelated donors → **100% survival** with minimal graft-versus-host disease.

• Gene defects associated with **CMC**: CARD9, IL17F, IL17R, STAT3, STAT1, AIRE.

• **β-glucan** from Candida → recognition by *dectin 1* → intracellular signalling that involves AIRE → TNF-β production by PBMCs. This may explain why patients with AIRE defect have CMC (apart from autoantibody production to IL-17 and IL-22).

• **STAT3-deficiency** → ↓ IgG+ and IgA+ memory B cells → IgG substitution may be important.

• TGF-β regulates TH17 response; IL-6, IL-23, IL-1β induce a more inflammatory TH17 response.

• **Blau syndrome** associated with NOD2 mutations → **TH17 and TH1 environment** in the granulomas; systemic inflammatory manifestations.

• **Crohn disease** associated with NOD2 mutations → **TH1 environment** in the granulomas; manifestations limited to the gastrointestinal tract.

• **Tocilizumab** (anti–IL-6 mAb) was successful for 3 patients with **Schnitzler syndrome** who were resistant to conventional treatment, including IL-1 inhibitors.

• Patients with **HIV** infection → increased **asthma** prevalence.

• **CLINICAL PHENOTYPES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASTHMA: RECENT ADVANCES** (Carolan BJ, Sutherland ER. J Allergy Clin Immunol 2013; 131: 627-634):

• **COPD**: adult patients with dyspnea, chronic cough and sputum production; history of significant tobacco exposure; expiratory airflow limitation (post bronchodilator FEV1/FVC <0.70).

• **Asthma and COPD**: the 2 most prevalent chronic lung diseases; high clinical, molecular and radiographic heterogeneity; significant clinical overlap between them.

• It is important to classify **specific asthma and COPD phenotypes** → personalized management.

• **CORTICOSTEROID RESISTANCE IN PATIENTS WITH ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE** (Barnes PJ. J Allergy Clin Immunol 2013; 131: 636-645):

• **Asthma**: 10% of patients require maximal ICS dose; 1% need regular OCS (corticosteroid-dependent asthma); some patients are refractory to high doses of OCS (corticosteroid-resistant asthma). Genetic factors may contribute to corticosteroid resistance.

• **COPD** patients are less sensitive to corticosteroids. Steroid resistance may also occur in rheumatoid arthritis, IBD and SLE.

• **Mechanism of action of corticosteroids**: diffusion across the cell membrane → binding to the glucocorticoid receptor α (GRα) in the cytoplasm → GRα liberates from chaperone proteins
(HSP90) → GRα enters the nucleus through nuclear import proteins (importin α) → GRα homodimerizes and binds to promoter region of many genes → GR complex switches off many activated inflammatory genes (cytokines, chemokines, adhesion molecules, etc.).

- **Mechanisms of corticosteroid resistance:** 1) phosphorylation of the GRα by kinases (p38MAPK, JNK1), ↓ activity of phosphatases (MKP-1, PP2A) → ↓ nuclear translocation; 2) ↑ expression of GRβ, which competes with activated GRα; 3) ↑ proinflammatory transcription factors (AP-1, JNK); 4) oxidative stress → activation of PI3Kδ → ↓ expression of histone deacetylase 2 (HDAC2), which normally switches off activated inflammatory genes.

- **Strategies for managing steroid resistance:** 1) anti-inflammatory drugs: phosphodiesterase 4 inhibitors (e.g. oral roflumilast for COPD), p38MAPK inhibitors, NFκB inhibitors, macrolides; 2) drugs that ↑ HDAC2 expression: theophylline, nortriptyline, PI3Kδ inhibitors; 3) LABA: ↑ PP2A, ↓ GRα phosphorylation, ↑ GRα translocation to the nucleus; 4) antioxidants: Nrf2 activators.


- Authors report 8 cases of pork-cat syndrome. Diagnosis was done by clinical history, skin tests and in vitro IgE detection. Oral challenges were not performed.

- **Pork-cat syndrome:** specific IgE to cat serum albumin (SA) → cross-reaction with porcine SA → severe allergic reactions after eating pork; most patients are >8 yr of age; patients may tolerate well-cooked pork; reactions are immediate (30-45 min), to differentiate from delayed anaphylaxis caused by IgE to α-gal; some patients have no clinical allergy to cat; some patients do not tolerate beef.

- **Protein homology** between porcine and cat SA = 82%.

- Suspicion of allergy to a mammalian meat → request sIgE to pork, beef, cat SA and α-gal.

**INTERFERON REGULATORY FACTOR 3 ACTIVATION MEDIATES VIRAL STIMULUS-INDUCED BRONCHIAL PRODUCTION OF THYMIC STROMAL LYMPHOPOIETIN (TSLP)** (Uller L. J Allergy Clin Immunol 2013; 131: 926):

- **Hypothesis:** respiratory syncytial virus infection in asthma or COPD patients → stimulation of NF-κB and IRF3 in bronchial epithelial cells → overproduction of TSLP and type I IFN → respiratory exacerbation.

- Simvastatin inhibited this pathway by interfering with IRF3 phosphorylation.


- **SJS and TEN:** severe immune cytotoxic reaction against keratinocytes → massive apoptosis; mostly induced by drugs.

- Authors report 7 patients with SJS/TEN and 7 patients with erythema multiforme major (EMM) → SJS/NET patients had increased circulating IL-17–producing CD4+ T cells compared to...
patients with EMM and healthy subjects; these cells were also present in the blister fluid and decreased significantly after SJS/TEN improvement.

- **Skin-homing TH17 cells** might be involved in the pathogenesis of SJS/TEN.

- **THE EXOSOME IN LUNG DISEASES: MESSAGE IN A BOTTLE** (Eissa NT. J Allergy Clin Immunol 2013; 131: 904-905):
  - **Exosomes**: secreted membranous nanovesicles (30-100 nm) that arise from endosomal compartments; might participate in intercellular communication; might be involved in physiologic and pathologic processes, including cancer; have been detected in saliva, breast milk, bronchoalveolar lavage fluid (BALF), blood and urine; contain miRNAs (regulators of intracellular signalling); potential diagnostic biomarkers and therapeutic targets.

- Exosomes from BALF of patients with asthma promoted leukotriene and IL-8 release from bronchial epithelial cells.

- 16 miRNAs contained in the BALF exosomes differentiated asthmatics from healthy subjects.

- Less invasive methods of sampling exosomal miRNA are needed (induced sputum, exhaled breath condensates, blood, urine).

- **TOLERANCE TO WHEAT IN WHOLE-GRAIN CEREAL BISCUIT IN WHEAT-ALLERGIC CHILDREN** (Turner PJ, Wong M, Varese N, Rolland JM, O’Hehir RE, Campbell DE. J Allergy Clin Immunol 2013; 131: 920-923):
  - **IgE-mediated wheat allergy**: typically starts in infancy and resolves by 3-5 yrs of age; culprit proteins are not well defined; cross-reactivity with other grains is possible; diagnosis: clinical history, IgE detection, oral food challenge (OFC). OFCs are frequently performed with whole-grain wheat cereal biscuits (WWCBs).

- Authors report 2 children with confirmed wheat allergy who tolerated an OFC with WWCBs but continued reacting to other wheat-containing products. Possible explanation: pressure cooking degraded allergenic wheat proteins in WWCBs.

- Some wheat-allergic children are able to tolerate WWCBs → a negative OFC to WWCBs does not rule out allergy to other wheat products.


- **HAE**: autosomal-dominant disease resulting from mutation of the C1-INH gene; **type I HAE**: reduced C1-INH protein; **type II HAE**: dysfunctional protein; **clinical history**: recurrent attacks of angioedema in the skin and mucosas due to excessive bradykinin production; **drugs to treat attacks**: plasma-derived (pd) or recombinant human C1-INH, ecallantide (kallikrein inhibitor), icatibant (bradykinin B2 receptor antagonist).

- **pdC1-INH** (Berinert, CSL Behring) is the only approved drug for pediatric use; half-life in children: 33 h.
• Authors analyzed the efficacy and safety of pdC1-INH for HAE attacks in 27 pediatric patients (<18 yr old) → onset of symptom relief: 15-60 min; maximal time for resolution: 48 h; subcutaneous edema usually responded slower; upper airway edema responded quicker; attacks did not progress or recur during the next 48 h; no adverse events potentially related to treatment; no antibodies to pdC1-INH concentrate were generated; repeated dosing was infrequent.

• pdC1-INH concentrate was effective and safe for the treatment of HAE attacks in children.
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.

**PEDIATRIC ALLERGY AND IMMUNOLOGY:**

- **DEVELOPMENT OF NATURAL TOLERANCE AND INDUCED DESENSITIZATION IN COW’S MILK ALLERGY** (Savilahti EM, Savilahti E. Pediatr Allergy Immunol 2013: 24: 114–121):
  - Normal gut immune system: a) eliminates pathogens; b) tolerates harmless environmental antigens (e.g. food proteins, drugs); c) tolerates commensal bacterial flora.
  - Risk factors in infants for impaired oral tolerance: (i) immature gut barrier → more antigenic access; (ii) lower secretion of gastric acid and proteolytic enzymes → less antigenic degrading; (iii) lower gut IgA levels; (iv) Th2 deviation in pregnancy; (v) atopy; (vi) disturbed gut microbiota.
  - Physiological response to CM: Treg response; predominant IgG1 and IgG4 production (peaks 3-4 months after CM initiation); low IgE production.
  - Optimal timing and dosage of CM exposure to avoid sensitization is unknown.
  - Cow’s milk allergy (CMA): abnormal immunologic reaction to CM (about 20 allergenic proteins); 2-3% of infants; can be IgE-mediated, non-IgE-mediated or both; Teff responses predominate over Treg responses; most children outgrow CMA spontaneously.
  - IgE-mediated CMA: immediate symptoms after exposure (urticaria, angioedema, bronchospasm, anaphylaxis); diagnosis: SPT, sIgE detection, BAT, oral challenge.
  - Non-IgE-mediated CMA: delayed reactions (hours or days) after exposure; probably T cell mediated; diagnosis is more difficult; typically resolves earlier than IgE-mediated allergy.
  - Early exposure to small amounts of CM appears to ↑ risk of IgE-mediated CMA.
  - Early exposure to large amounts of CM appears to ↑ risk of non-IgE-mediated CMA.
  - Exposure to CM may occur through skin or breast milk → CMA can occur in exclusively breastfed infants; CMA may be sustained by cross-reactivity to proteins in human breast milk.
  - Specific IgE to bovine serum albumin (BSA) is associated with allergy to both CM and beef.
  - Risk factors for CMA persistence: severe reactions, small eliciting doses, allergy to heated CM, high (or increasing) positivity of sIgE or SPT to CM, low levels of CM-specific IgG4, allergy to other foods, asthma, allergic rhinitis.
  - Subjects who outgrow CMA: ↓ Th2 response to CM, ↑ Th1 and Treg response; ↓ specific IgE production; ↑ specific IgG4 and IgA production.
  - IL-4: ↑ IgG4 and ↑ IgE production; IL-10: ↑ IgG4 and ↓ IgE production.
  - CM-specific IgE levels ↓ as tolerance develops, but may remain at increased levels even in tolerant individuals.
  - High intestinal IgA in infancy may ↓ risk of IgE-mediated allergies. IgA production is induced rather by innate immunity signals than T helper cells.
  - Probiotics (e.g. Lactobacillus rhamnosus) may accelerate development of tolerance to CM.
• Oral CM immunotherapy (OIT) induces desensitization in most cases where spontaneous recovery has not yet occurred. Evidence for long-time tolerance is limited. Problem: risk of adverse reactions during OIT.

  - Hypersensitivity reactions to NSAIDs: 0.3% of the general population. (i) Pharmacological mechanisms: COX inhibition; patients are generally cross-intolerant (CI) to other NSAIDs. (ii) Immunologic mechanisms: IgE or T cell production; patients are usually selective reactors (SR).
  - Facial angioedema is the main symptom reported by children with NSAID hypersensitivity, especially in CI patients; this symptom ↑ in frequency with age till 21 yr of age.
  - Reactions to paracetamol in CI patients are estimated at between 4 and 25%.
  - Authors performed 119 DPT in 63 children with a history of NSAID hypersensitivity → 68.2% of the children were confirmed as having hypersensitivity (58.1% classified as CI and 41.9% as SR); angioedema occurred in 86.3% of cases; all CI patients tolerated paracetamol; atopy was more frequent in CI patients, compared with SR patients and non-allergic controls.

  - Peach allergy: main cause of vegetable food allergy in the Mediterranean area; Pru p 3 (a nonspecific lipid transfer protein) is the major allergen (mainly found in the peel).
  - Authors studied 57 children with allergic reactions after peach ingestion or contact → 88% of children had positive SPT with peach peel, 35% with peach pulp; 100% of children had ↑ sIgE to peach, 96% had ↑ sIgE to rPru p 3; OFC with peeled peach was negative in 93% of children.

  - Antinflammatory molecules in human plasma: IL-10, TGF-β, antagonists of cytokine receptors, IgG, IgA, galectins, adenosine, lipids, vit A, vit D, adiponectin, etc.
  - Immunomodulatory role of plasma is especially important in neonates to: (i) maintain fetomaternal tolerance; (ii) tolerate microbial colonization after birth.
  - Plasma is a potential immunoregulatory therapy for autoimmune, allergic, and inflammatory disease. Advantages: easily accessible, affordable, widely available.
  - Research questions: What are the immune suppressive factors in plasma? Where are they produced? By which mechanism do they mediate their effect?

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.

- Previous studies show that only 5% of patients with suspected drug allergy have a real allergy.
- Authors evaluated 10,096 children → 7.87% had parent-reported immediate drug allergy → diagnostic work-up confirmed allergy in only 0.11% of children.
- A positive clinical history is not enough to diagnose drug allergy; a careful diagnostic work-up is essential to confirm diagnosis.

**TESTING CHILDREN FOR ALLERGIES: WHY, HOW, WHO AND WHEN**


- Authors provide a 15-page document with practical recommendations for diagnostic testing in children with suspected or confirmed food, drug and respiratory allergies.
- The information is outstanding all over the document. I strongly suggest reading it all. Some summarized recommendations are:
  - Skin prick and specific IgE testing should be directed by the clinical history.
  - Allergy test results should always be interpreted in correlation with clinical relevance.
  - If performed by experienced allergists, allergen challenges are usually safe and confirm/exclude diagnosis, reducing unnecessary avoidance of medications or foods.
  - Food challenges might be necessary to assess the clinical relevance of a positive IgE test before introducing exclusion diets.
  - Infants with early onset severe eczema are at high risk for developing food allergies.
  - Food allergies must be considered in children <3 yr old with moderate-severe atopic eczema.
  - An allergic cause for acute urticaria/angioedema is likely when: (i) symptoms occur within 2 h of a potential allergic trigger; (ii) symptoms last for <24 h.
  - Some aeroallergens (pollens, cat, dog, HDM) may give rise to urticaria ± angioedema.
  - Chronic urticaria is primarily caused by excessive sensitivity of the skin leading to spontaneous mast cell degranulation.
  - Allergy testing in chronic urticaria is very rarely diagnostic and has high risk of false-positive results.
  - Allergy work-up for anaphylaxis during anaesthesia (immediate or non-immediate) must include neuromuscular blocking agents, latex, hypnotics, antibiotics, opioids and other agents.
  - Seasonal rhinitis/conjunctivitis should be tested for allergy in treatment-resistant cases; perennial rhinitis/conjunctivitis should be tested in all cases.
  - All children with asthma should be tested for allergies.
  - Allergy testing for rhinitis/conjunctivitis and asthma should be guided by the clinical history and include the most relevant local allergens.
In a child with **cough**, other causes should be considered prior to allergy testing.

**Chronic vomiting and diarrhoea** as primary symptoms of allergy are uncommon; other causes must be excluded. Celiac or eosinophilic GI diseases should be considered in the differential diagnosis. Testing may include non-IgE tests, food exclusion/challenges and endoscopy.

**Colic**: 5-19% of infants; defined as excessive crying >3 h/day, >3 days/wk and lasting >3 wks. Colic may occur in 30–46% of infants with cow’s milk allergy.

**Natural course of crying in infancy**: (i) little crying between 0 and 2 wks; (ii) 2–3 h crying per day between 2–6 wks; (iii) <1 h crying per day at 12 wks.

Infants with **extreme crying** and signs of atopic diseases should be investigated for food allergy.

Diagnosis of **food allergy in infants with colic** should be confirmed by elimination/challenge procedures.

Suspicion of **food allergy in exclusively breast-fed infants** → supervised elimination of maternal intake of relevant food protein for at least 1 wk followed by controlled challenge.

Allergy diagnosis should be considered in young atopic children with **failure-to-thrive** and other GI symptoms after excluding other causes and optimizing nutritional input. Diagnosis will mostly be based on exclusion/reintroduction of suspected foods.

**Anaphylaxis** occurring in an otherwise healthy child should be investigated with allergy tests.

Only children with a history of systemic reaction after an **insect sting** will need an allergy work-up. Allergy diagnosis will provide guidance for immunotherapy and preventive measures.

**Siblings of food allergic children** might be considered for allergy testing to foods, especially if they have moderate-severe eczema.