PEARLS IN ALLERGY AND IMMUNOLOGY

October 2013

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- The content of this educational material does not intend to replace the clinical criteria of the physician.
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Juan Carlos Aldave Becerra, MD
Allergy and Clinical Immunology
Hospital Nacional Edgardo Rebagliati Martins, Lima-Peru
jucapul_84@hotmail.com

Juan Félix Aldave Pita, MD
Medical Director
Luke Society International, Trujillo-Peru

Juan Carlos Aldave Becerra, MD
Allergy and Clinical Immunology
Rebagliati Martins National Hospital, Lima-Peru

October 2013 – content:

- **ABOUT THE ROLE AND UNDERLYING MECHANISMS OF COFACTORS IN ANAPHYLAXIS** (Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T. Allergy 2013; 68: 1085–1092).
- **CAUSES OF SLIT DISCONTINUATION AND STRATEGIES TO IMPROVE THE ADHERENCE: A PRAGMATIC APPROACH** (Savi E, Peveri S, Senna G, Passalacqua G. Allergy 2013; 68: 1193–1195).
- **DIAGNOSIS OF IMMEDIATE HYPERSENSITIVITY REACTIONS TO RADIOCONTRAST MEDIA** (Salas M, Gomez F, Fernandez TD, Doña I, Aranda A, Ariza A, Blanca-López N, Mayorga C, Blanca M, Torres MJ. Allergy 2013; 68: 1203–1206).
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- **PAEDIATRIC RHINITIS: POSITION PAPER OF THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY** (Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, Papadopoulos NG, Rotiroti G, Scadding G, Timmermans F, Valovirta E. Allergy 2013; 68: 1102–1116).
- **THE HISTORY OF MAST CELL AND BASOPHIL RESEARCH – SOME LESSONS LEARNT FROM THE LAST CENTURY** (Blank U, Falcone FH, Nilsson G. Allergy 2013; 68: 1093–1101).
- **VITAMIN A SUPPLEMENTATION AND BCG VACCINATION AT BIRTH MAY AFFECT ATOPY IN CHILDHOOD: LONG-TERM FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL** (Kiraly N, Benn CS, Biering-Sørensen S, Rodrigues A, Jensen KJ, Ravn H, Allen KJ, Aaby P. Allergy 2013; 68: 1168–1176. Allergy 2013; 68: 1093–1101).
- **WHERE TO PRICK THE APPLE FOR SKIN TESTING?** (Vlieg-Boerstra BJ, van de Weg WE, van der Heide S, Dubois AEJ. Allergy 2013; 68: 1196–1198).
- **CONTEMPORARY APPROACHES TO THE DIAGNOSIS AND MANAGEMENT OF PHYSICAL URTICARIA** (Lang DM, Hsieh FH, Bernstein JA. Ann Allergy Asthma Immunol 2013; 111: 235-241).
- **IMPORTED FIRE ANT ALLERGY: CASE PRESENTATION AND REVIEW OF INCIDENCE, PREVALENCE, DIAGNOSIS, AND CURRENT TREATMENT** (Steigelman DA, Freeman TM. Ann Allergy Asthma Immunol 2013; 111: 242-245).
- **UPDATE ON INFLUENZA VACCINATION OF EGG ALLERGIC PATIENTS** (Kelso JM, Greenhawt MJ, Li JT. Ann Allergy Asthma Immunol 2013; 111: 301-302).
- **A GENERAL STRATEGY FOR THE GENERATION OF HYPOALLERGENIC MOLECULES FOR THE IMMUNOTHERAPY OF FISH ALLERGY** (Swoboda I, Balicc N, Klug Ch, Focke M, Weber M, Spitzauer S, Neubauer A, Quirce S, Douladiris N, Papadopoulos NG, Valenta R. J Allergy Clin Immunol 2013; 132: 979-981).
- **D-DIMER: A BIOMARKER FOR ANTIHISTAMINE-RESISTANT CHRONIC URTICARIA** (Asero R. J Allergy Clin Immunol 2013; 132: 983-986).
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- **IL-13/IL-22–COPRODUCING T CELLS, A NOVEL SUBSET, ARE INCREASED IN ATOPIC DERMATITIS** (Teraki Y, Sakurai A, Izaki S. J Allergy Clin Immunol 2013; 132: 971-974).
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- **ROLE OF THE BASOPHIL ACTIVATION TEST IN THE DIAGNOSIS OF LOCAL ALLERGIC RHINITIS** (Gómez E, Campo P, Rondón C, Barrionuevo E, Blanca-López E, Torres MJ, Herrera R, Galindo L, Mayorga C, Blanca M. J Allergy Clin Immunol 2013; 132: 975-976).
- **SERUM PROCALCITONIN AS A BIOMARKER DIFFERENTIATING DELAYED-TYPE DRUG HYPERSENSITIVITY FROM SYSTEMIC BACTERIAL INFECTION** (Yoon S-Y, Baek SH, Kim S, Lee YS, Lee T, Bae Y-J, Kwon H-S, Huh JW, Hong S-B, Cho YS, Chun S, Lim Ch-M, Koh Y, Moon H-B, Kim T-B. J Allergy Clin Immunol 2013; 132: 981-983).
- **SKELETAL ABNORMALITIES AND SUCCESSFUL HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH RETICULAR DYSGENESIS** (Al-Zahrani D, Al-Ghonaium A, Al-Mousa H, Al-Kassar A, Roifman CM. J Allergy Clin Immunol 2013; 132: 993-996).
- **STRESS, β-BLOCKERS, AND PUTTING** (Knight A. J Allergy Clin Immunol 2013; 132: 1014-1015).
- **THE EDITORS' CHOICE** (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2013; 132: 809-810).
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- **ANGIOEDEMA WITHOUT URTICARIA IN CHILDHOOD** (Ertoy Karagol HI, Yilmaz O, Bakirtas A, Topal E, Demirsoy MS, Turktas I. Pediatr Allergy Immunol 2013; 24: 685–690).
- **CLINICAL SIGNIFICANCE OF INCREASED PERIPHERAL BLOOD CD4+CD28− T CELLS OF ASTHMATIC CHILDREN** (Ertoy Karagol HI, Yilmaz O, Bakirtas A, Topal E, Demirsoy MS, Turktas I. Pediatr Allergy Immunol 2013; 24: 685–690).
- **HOW TO REINTRODUCE COW'S MILK?** (Dupont C. Pediatr Allergy Immunol 2013; 24: 627–632).
- **IMMUNOTHERAPY – RISK/BENEFIT IN FOOD ALLERGY** (Kostadinova AI, Willemsen LEM, Knippels LMJ, Garssen J. Pediatr Allergy Immunol 2013; 24: 633–644).
- **PEDIATRIC ALLERGY AND IMMUNOLOGY IN JAPAN** (Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatr Allergy Immunol 2013; 24: 704–714).
- **PERSISTENT ALLERGY TO COW'S MILK: OF GREATER A CLINICAL CONCERN THAN OTHER FOOD ALLERGIES** (Turner PJ. Pediatr Allergy Immunol 2013; 24: 624–626).
- **STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS IN CHILDREN** (Atanaskovic-Markovic M, Medjo B, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Nikoli D, Nestorovic B. Pediatr Allergy Immunol 2013; 24: 645–649).

Juan Carlos Aldave Becerra, MD
Allergy and Clinical Immunology
Rebagliati Martins National Hospital, Lima-Peru

ALLERGY:

- **ABOUT THE ROLE AND UNDERLYING MECHANISMS OF COFACTORS IN ANAPHYLAXIS** (Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T. Allergy 2013; 68: 1085–1092)**:**

  - Anaphylaxis: severe allergic reaction, potentially fatal; lifetime prevalence: 0.05-2%; incidence: 1/10,000 patient-yr; most common mechanism: IgE-mediated reactions; most common culprits: foods, drugs, hymenoptera venoms; factors that influence severity: allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors.

  - Augmentation factors (cofactors) for anaphylaxis (↓ anaphylaxis threshold; appear in 30% of anaphylactic episodes; >1 cofactor may be needed to elicit anaphylaxis): **(i) physical exercise:** most frequent cofactor (e.g. 'food-dependent exercise-induced anaphylaxis', which only occur in the presence of exercise; described for wheat, shrimps, meat, pistachio, spinach, etc.; most frequent with hard exercise and high degree of food sensitization; may also occur with minimal exercise [e.g. ironing]); differential diagnosis: cholinergic urticaria, exercise-induced asthma, physical urticaria; **(ii) alcohol:** relevant factor in up to 15% of anaphylactic episodes; **(iii) infections (mild or severe):** relevant factor in up to 11% of reactions; may complicate venom or pollen immunotherapy (SIT must be paused or ↓ during infections); **(iv) NSAIDs:** relevant factor in up to 9% of reactions; **(v) other drugs:** mast cell-activating drugs (iodinated RCM [most frequently iomeprol and iopromide], muscle relaxants [most frequently suxamethonium], quinolones, opioids), drugs that suppress gastric acid (proton pump inhibitors, H2-receptor blockers [↑ risk of anaphylaxis in patients with oral allergy syndrome to acid-sensitive allergens]), drugs that block counteracting mechanisms during anaphylaxis (β-adrenergic antagonists, ACE inhibitors, angiotensin receptor blockers); **(vi) menstruation**; **(vii) stress**.

  - Mechanisms underlying cofactor-induced anaphylaxis: **(i)** ↑ gut permeability (exercise-induced, NSAID-induced, alcohol-induced) → ↑ allergen bioavailability; **(ii)** ↓ activation threshold of mast cells and basophils (exercise-induced, NSAID-induced, infection-induced); **(iii)** ↑ synthesis of leukotrienes (NSAID-induced); **(iv)** ↓ gastric acid (drug-induced) → ↑ allergen bioavailability; **(v)** immune system stimulation (infection-induced): formation of IgG and IgM immune complexes, release of complement anaphylotoxins (C5a is more potent than C3a for mast cell degranulation; mucosal mast cells do not express anaphylotoxin receptors), cell activation through innate immune receptors (e.g. peptidoglycan can induce mast cell degranulation).

  - Diagnosis of cofactor-induced anaphylaxis: clinical history; *in vitro* and *in vivo* specific IgE detection; provocation tests (with and without cofactors).

- **CAUSES OF SLIT DISCONTINUATION AND STRATEGIES TO IMPROVE THE ADHERENCE: A PRAGMATIC APPROACH** (Savi E, Peveri S, Senna G, Passalacqua G. Allergy 2013; 68: 1193–1195)**:**

  - Sublingual immunotherapy (SLIT): (i) advantages: self-administration, convenience, safety; (ii) disadvantages: very low adherence (56% of patients discontinue SLIT during the 1st year; only 15% of patients complete 3 years of SLIT); (iii) reasons for SLIT discontinuation: side-effects, no perception of efficacy, cost.

  - Proposed methods to ↑ adherence to SLIT: adequate education, strict follow-up.

- **DIAGNOSIS OF IMMEDIATE HYPERSENSITIVITY REACTIONS (IHR) TO RADIOCONTRAST MEDIA (RCM)** (Salas M, Gomez F, Fernandez TD, Doña I, Aranda A, Ariza A, Blanca-López N, Mayorga C, Blanca M, Torres MJ. Allergy 2013; 68: 1203–1206)**:**
  - IHR to RCM (within 1 hour): (i) IgE-mediated reactions; (ii) non-IgE-mediated reactions: changes in blood osmolarity and ion concentration, direct activation of mast cells and basophils, activation of complement system, activation of bradykinin-induced contact system.
  - Mild IHR: (i) ionic RCM: 10% of procedures; (ii) nonionic RCM: 1% of procedures.
  - Severe IHR: (i) ionic RCM: 0.2% of procedures; (ii) nonionic RCM: 0.02% of procedures.
  - Authors evaluated 90 patients with a history of IHR to RCM → (i) hypersensitivity to RCM was confirmed in only 8 patients: 5 by skin tests (3 patients had positive prick test [undiluted], 5 had positive intradermal test [1/10 dilution]) and 3 by drug challenge (intravenous administration at 45-min intervals using 5 cc, 15 cc, 30 cc and 50 cc [cumulative dose = 100 cc]); (ii) BAT was performed in the 8 hypersensitive patients, being positive in 5; (iii) 2 of the 5 patients with positive skin tests had a positive drug challenge to an alternative RCM.
  - Author's recommendations: (i) subjects with a history of reaction (especially severe) to a RCM should be skin tested; (ii) positive skin tests may indicate an immunologic mechanism and should not be ignored even in patients with a history of mild immediate reaction; selection of an alternative RCM (by negative skin tests) would be better than only premedication use; (iii) drug challenge and BAT can be useful to diagnose hypersensitivity to RCM.
- **INCREASED MORTALITY IN ALLERGIC RHINITIS (AR) PATIENTS?** (Mösges R, Hellmich M. Allergy 2013; 68: 1209–1210)**:**
  - Su et al (Allergy 2013; 68: 440–445): AR is a predisposing factor for erectile dysfunction.
  - Su's paper (case-control study) showed that mortality was increased in AR patients (RR=2.97) → possible explanations: ↑ accidents due to AR effect on sleep and mental status; ↑ accidents due to sedative antiallergic drugs; adverse effects of drugs for erectile dysfunction.
  - Larger studies are needed to evaluate the association between AR and increased mortality.
- **PAEDIATRIC RHINITIS: POSITION PAPER OF THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY** (Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, Papadopoulos NG, Rotiroti G, Scadding G, Timmermans F, Valovirta E. Allergy 2013; 68: 1102–1116)**:**
  - Allergic rhinitis in children (<18 yrs of age): IgE-mediated inflammation of the nasal mucosa; **(i) prevalence:** up to 15% of children; **(ii) impact:** ↓ physical, social, mental and psychological well-being; **(iii) clinical manifestations:** rhinorrhea, nasal blockage, sneezing, itching, mouth breathing, snoring, nasal voice, cough, 'allergic shiners' (darkened lower eyelids due to chronic congestion), minor epistaxis; **(iv) comorbidities/complications:** conjunctivitis, sinusitis, hyposmia, Eustachian tube dysfunction, middle ear effusion, otitis, ↓ hearing, lymphoid hypertrophy (adenoids, tonsils), pharyngitis, obstructive sleep apnea, asthma, dental malocclusion, dizziness, impaired school or work performance, atopic eczema, pollen-food syndrome; **(v) diagnosis:** clinical history, anterior rhinoscopy, allergy tests (25% of AR cases are 'local' [entopy], which means that specific IgE is not detected by skin or serum tests); **(vi)**

differential diagnosis (may coexist with allergic rhinitis): nonallergic rhinitis (infectious, irritant-induced, hormonal, drug-induced, vasomotor, idiopathic), nasal polyps, septal deviation, choanal atresia, stenosis of the piriform aperture, cleft lip, adenoidal hypertrophy, malignancy, leakage of cerebrospinal fluid, GERD, foreign body; **(vii) treatment:** (depends on severity): education about the disease, allergen avoidance, antihistamines (oral, intranasal), intranasal corticosteroids, antileukotrienes, decongestants, intranasal anticholinergics, saline douches, allergen immunotherapy, omalizumab (if concomitant uncontrolled severe asthma).

- Frequency of viral upper respiratory tract infections [2% can lead to clinically important bacterial sinusitis]: (i) up to 11/yr in infancy; (ii) up to 8/yr at preschool age; (iii) up to 4/yr at school age.
- Rhinitis → postnasal drip → stimulation of cough receptors in nasal cavity, pharynx and larynx.
- Rhinitis + cough may be incorrectly diagnosed as asthma.
- Nasal polyps in children are rare → look for cystic fibrosis, primary ciliary dyskinesia or encephalocoele (if unilateral polyp).
- Kallmann syndrome: anosmia due to hypoplasia of the olfactory bulb.
- Excessive epistaxis → exclude neoplasms (e.g. nasopharyngeal angiofibroma) and coagulopathies.
- Although scarce evidence, pet allergen avoidance is suggested for children with allergic rhinitis.
- Intranasal corticosteroids: (i) 1st-line treatment for moderate-severe allergic rhinitis; (ii) approved in children ≥2 yrs of age; (iii) therapeutic effect may be observed within the 1st day of use; (iv) may improve concomitant asthma and conjunctivitis; (v) good safety profile (be careful with epistaxis and nasal perforation); (vi) adherence may be suboptimal due to discomfort.
- H1-antihistamines: (i) oral and intranasal drugs have similar efficacy; (ii) oral drugs are usually better tolerated; (iii) intranasal drugs act quicker; (iv) 2nd-generation drugs may cause sedation in some children (fexofenadine might be the exception).
- Oral corticosteroids and oral/intranasal decongestants should be avoided. If needed, give only short courses (e.g. 3 to 7 days of prednisone).

- **THE HISTORY OF MAST CELL AND BASOPHIL RESEARCH – SOME LESSONS LEARNT FROM THE LAST CENTURY** (Blank U, Falcone FH, Nilsson G. Allergy 2013; 68: 1093–1101)**:**
  - 1863 → Friedrich von Recklinghausen described mast cells as 'granulated cells in connective tissues'.
  - 1878 → Paul Ehrlich coined the term 'mast cells' (due to their appearance of 'having ingested large amounts of nutrients').
  - 1879 → Paul Ehrlich described basophils.
  - 1902 → Paul Portier and Charles Richet described the phenomenon of anaphylaxis (from the Greek ana = against and phylaxis = protection).
  - 1903 → Maurice Arthus described the Arthus phenomenon (repeated subcutaneous injections of the same horse antiserum caused local inflammation and necrosis due to hypersensitivity).

- 1906 → Clemens von Pirquet described the term 'allergy' (from the Greek allos = other and ergon = work, reaction).
- 1921 → Carl Prausnitz and Heinz Küstner described the Prausnitz–Küstner (PK) reaction: 'allergy can be transferred by transferring serum from the allergic subject to a healthy person' (this discovery ended the belief that an anaphylactic/allergic reaction was caused by poisons).
- 1968 → IgE was considered as the 5th type of immunoglobulin.
- Mast cells and basophils: (i) originate from HSCs; (ii) can *de novo* synthesize and secrete >30 cytokines; (iii) can also preform and store cytokines (e.g. TNF, IL-4); (iv) mast cells, but not basophils, can synthesize PGD2; (v) cytokine spectrum appears to be more TH2-restricted for basophils; (vi) in humans, IL-3 gives rise to basophils and not mast cells (in contrast to mouse); (vii) 2 subtypes of mast cells in humans: mast cells that contain only tryptase (MCT) [correspond in part to the mucosal type of mouse mast cells] and mast cells that contain both tryptase and chymase (MCTC) [correspond to the connective tissue type of mouse mast cells]; (viii) mast cells can either be pro-inflammatory, anti-inflammatory or immunosuppressive.
- Functions of mast cells and basophils (some are better established than others): (i) defense against ticks (e.g. histamine promotes scratching and tick removal); (ii) defense against helminths (helminths are the most potent inducers of IgE responses); (iii) contribution to defense against some fungi, bacteria and virus; (iv) inflammation (e.g. activation by pathogen or danger signals through PRRs); (v) tissue remodeling and repair; (vi) protection against foreign agents (e.g. mast cell-derived proteases degrade exogenous toxins [venoms] or endogenous molecules [endothelin-1 and VIP]); (vii) angiogenesis; (viii) tumor immunity.

- **VITAMIN A SUPPLEMENTATION AND BCG VACCINATION AT BIRTH MAY AFFECT ATOPY IN CHILDHOOD: LONG-TERM FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL** (Kiraly N, Benn CS, Biering-Sørensen S, Rodrigues A, Jensen KJ, Ravn H, Allen KJ, Aaby P. Allergy 2013; 68: 1168–1176. Allergy 2013; 68: 1093–1101)**:**
  - Authors evaluated the effect of BCG vaccination and oral vit A supplementation (25000 IU) in low-birthweight newborns on the prevalence of atopy (SPT ≥3 mm) at childhood (follow up at age 3–9 yrs) → (i) ↓ atopy in children who responded to BCG with a scar (OR=0.42); (ii) no difference in atopy between early and delayed BCG administration; (iii) ↑ atopy in children who received vit A (OR=2.88); (iv) ↑ wheeze in children who received vit A (OR=2.45).
  - Author's commentaries: (i) BCG vaccination may ↓ risk of atopic diseases; (ii) neonatal vit A supplementation may ↑ risk of atopic diseases.
- **WHERE TO PRICK THE APPLE FOR SKIN TESTING?** (Vlieg-Boerstra BJ, van de Weg WE, van der Heide S, Dubois AEJ. Allergy 2013; 68: 1196–1198)**:**
  - Apple allergy: (i) clinical manifestations include oral allergy syndrome [OAS] in patients with birch allergy (oropharyngeal symptoms after ingesting fresh apple due to cross-reactivity between Bet v 1 [from birch pollen] and Mal d1 [from apple]); (ii) diagnosis: clinical history, prick testing with commercial extracts, prick-to-prick [PTP] testing with fresh apple, serum specific IgE detection, food challenge.

- Authors performed PTP testing with fresh apples in 32 adults (18-73 yrs of age) with OAS → PTP testing with material obtained from 2 cm near the apple's stalk yielded significantly greater skin responses than when taken from the middle region.

- Author's commentaries: (i) Mal d 1 is unequally distributed over the apple; (ii) when performing PTP testing, the apple should be pricked near the stalk rather than in the middle.

ANNALS OF ASTHMA, ALLERGY & IMMUNOLOGY:

- **CONTEMPORARY APPROACHES TO THE DIAGNOSIS AND MANAGEMENT OF PHYSICAL URTICARIA** (Lang DM, Hsieh FH, Bernstein JA. Ann Allergy Asthma Immunol 2013; 111: 235-241)**:**

  - Chronic urticaria (>6 wks): (i) spontaneous: no clear triggers; (ii) physical: triggered by physical stimuli (cold, heat, touch, pressure, vibration, sunlight, water, exercise); (iii) both spontaneous and physical urticaria can occur in the same patient; (iv) concomitant angioedema may occur; (v) pseudoallergens (food additives, vasoactive substances, fruits, vegetables, spices) and NSAIDs may cause flares.

  - Physical urticaria: (i) pathogenesis: unclear; (ii) diagnosis: clinical history (wheal and flare after physical stimuli; >1 stimuli may be relevant in the same patient), skin provocation testing (in most cases tests are not standardized); (iii) treatment (depends on severity and type of trigger; should be individualized): avoidance of physical stimuli (e.g. increasing room temperature and prewarming fluids during surgery in patients with cold urticaria; sunscreen in patients with solar urticaria), antihistamines (H1R and H2R blockers), mast cell-stabilizing drugs (e.g. ketotifen), antileukotrienes, corticosteroids (topical and systemic), biologic therapy (e.g. omalizumab, anti-TNF-α, IVIG), epinephrine, desensitization, moisturizers, UV phototherapy, cyclosporin A, sulfasalazine, chloroquine, dapsone, pseudoallergen-free diet, anticholinergic agents, androgens (e.g. stanozolol), selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis; (iv) prognosis: worse than spontaneous urticaria (CU without physical component: 45% of remission in 3 yrs; CU with physical component: 15% remission in 3 yrs).

  - Aquagenic urticaria: triggered by contact with water (regardless of water temperature); different from aquagenic pruritus (only itch, no wheal); provocation tests: water compress at 35°C for 30 min on the skin, water immersion of a hand or distal upper extremity.

  - Cholinergic urticaria: triggered by ↑ corporal temperature; provocation tests: intradermal injection of methacholine (poor NPV), exercise challenge, immersion in hot water (42°C), skin test with autologous diluted sweat.

  - Cold urticaria: triggered by cold, provocation test: ice-cube (0°-4°C) for 5-10 min on the forearm (false-negative results may occur).

  - Delayed pressure urticaria and angioedema (DPUA): triggered by pressure (0.5 to 12 hrs later, peak at 4 to 6.5 hrs); provocation tests: pressure challenge (15 lb across the shoulder for 15 min), use of a calibrated dermographometer.

  - Exercise-induced urticaria: triggered by exercise; anaphylaxis may occur (exercise-induced anaphylaxis); food may act as a cofactor (food-dependent exercise-induced anaphylaxis); provocation test: exercise challenge (with or without food; be prepared for anaphylaxis).

  - Simple dermatographism: most frequent form of physical urticaria (5% of the population); triggered by contact with the skin; provocation test: stroking the skin with a firm object.

  - Solar urticaria: triggered by sun exposure (mainly UVA or visible wavelengths); provocation test: phototesting on skin.

  - Vibratory urticaria and angioedema: triggered by vibration; provocation test: contact with a vortex mixer for 1-5 min.

- **IMPORTED FIRE ANT ALLERGY: CASE PRESENTATION AND REVIEW OF INCIDENCE, PREVALENCE, DIAGNOSIS, AND CURRENT TREATMENT** (Steigelman DA, Freeman TM. Ann Allergy Asthma Immunol 2013; 111: 242-245)**:**

  - Fire ants: (i) taxonomy: order Hymenoptera, superfamily Vespidae, family Formicidae, subfamily Myrmicinae, tribe Solenopsidini, genus Solenopsis; (ii) native US species: Solenopsis xyloni, Solenopsis geminata, Solenopsis aurea; (iii) imported species (from Asia, Australia, North and South America): Solenopsis richteri (native to Uruguay), Solenopsis invicta (native to Argentina, dominant species); (iv) potential threaten: stings (imported species are aggressive, can sting multiple times in a radial pattern); (v) natural reaction to an sting: sterile pseudopustule (1-2 mm) secondary to piperidine alkaloids (insecticidal, bactericidal and fungicidal activity).

  - Imported fire ant (IFA) allergy: IgE-mediated hypersensitivity reactions to venom components; increasing prevalence in endemic regions; risk factors: children, farm workers (reactions can also occur indoors, especially in immobilized individuals); clinical manifestations: large local reactions (17-56% of subjects who are stung), generalized skin reactions, anaphylaxis (2% of stung subjects); diagnosis: skin prick test with IFA whole body extract (WBE), intradermal tests with IFA WBE (more sensitive), serum specific IgE detection; treatment (depends on severity of prior reactions and patient's risk factors): avoidance, autoinjectable epinephrine, immunotherapy with IFA-WBE (efficacy >95%).

- **UPDATE ON INFLUENZA VACCINATION OF EGG ALLERGIC PATIENTS** (Kelso JM, Greenhawt MJ, Li JT. Ann Allergy Asthma Immunol 2013; 111: 301-302)**:**

  - How to approach a patient with IgE-mediated egg allergy who needs influenza vaccine? (i) administer an entire dose of inactivated influenza vaccine (IIV) without prior skin testing, even in patients with anaphylaxis to egg; (ii) use approved vaccine brands in age-appropriate doses; (iii) observe 30 min after vaccination; (iv) be prepared to manage anaphylaxis; (v) injectable IIV is preferred over nasal live attenuated vaccine because its safety in egg-allergic patients has been studied more extensively; (vi) 2 egg-free influenza vaccines are approved for patients ≥18 yrs of age: Flucelvax [Optaflu] (prepared from virus propagated in cell culture), Flublok (recombinant hemagglutinin proteins produced in an insect cell line).

  - All patients with egg allergy, including anaphylaxis, should receive IIV annually.

JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:

- **A GENERAL STRATEGY FOR THE GENERATION OF HYPOALLERGENIC MOLECULES FOR THE IMMUNOTHERAPY OF FISH ALLERGY** (Swoboda I, Balicc N, Klug Ch, Focke M, Weber M, Spitzauer S, Neubauer A, Quirce S, Douladiris N, Papadopoulos NG, Valenta R. J Allergy Clin Immunol 2013; 132: 979-981)**:**

- Fish allergy: (i) prevalence: up to 0.5% of the population; (ii) impact: significant morbidity and mortality, ↓ QoL; (iii) major allergen: parvalbumin (calcium-binding protein; very resistant to heat and digestion; patient's sIgE may react either to cross-reactive parvalbumin [present in different fish] or to fish-specific parvalbumins); (iv) diagnosis: SPT, serum sIgE detection, food challenge; (v) conventional treatment: avoidance (does not prevent accidental exposure), autoinjectable epinephrine; (vi) optimal treatment: restore tolerance to allergens (immunotherapy).

- Limitations of food immunotherapy: (i) potential lack of efficacy; (ii) frequent allergic reactions during therapy (approach to ↓ allergic reactions: use of hypoallergenic molecules).

- Authors show that the exchange of 4 calcium-coordinating aspartic acids (which are highly conserved in fish parvalbumins) to alanines represents a generally applicable strategy to generate hypoallergenic molecules from different fish species.

- **D-DIMER: A BIOMARKER FOR ANTIHISTAMINE-RESISTANT CHRONIC URTICARIA** (Asero R. J Allergy Clin Immunol 2013; 132: 983-986)**:**

  - Chronic urticaria (CU): (i) lifetime prevalence: ~1% of the general population; (ii) impact: significant morbidity, ↓ QoL; (iii) 1st-line treatment: antihistamines at usual dosing (50% of patients may not respond); (iv) 2nd-line treatment: up to quadruple dose of antihistamines (50% of patients may not respond → antihistamine-resistant CU).

  - Authors studied 91 patients (male/female 22/69; mean age: 46.9 yrs; range: 11-85 yrs) with spontaneous CU → (i) D-dimer levels were ↑ in cetirizine-resistant CU; (ii) ↑ D-dimer levels correlated with ↑ CRP and ↑ ESR.

  - Author's commentaries: (i) D-dimer may be used as a biomarker for antihistamine-resistant CU (hypothesis: eosinophil infiltration → secretion of tissue factor and VEGF → activation of coagulation cascade → ↑ D-dimer plasma levels); (ii) patients with severe antihistamine-resistant CU may benefit from anticoagulant therapy; (iii) mediators other than histamine may be involved in CU (e.g. thrombin can activate mast cells through protease-activated receptor-1); (iv) D-dimer levels can also be ↑ in C1-inh-deficient angioedema and in nonallergic asthma.

- **EFFICACY AND SAFETY OF THALIDOMIDE IN PATIENTS WITH INFLAMMATORY MANIFESTATIONS OF CHRONIC GRANULOMATOUS DISEASE: A RETROSPECTIVE CASE SERIES** (Noel N, Mahlaoui N, Blanche S, Suarez F, Coignard-Biehler H, Durieu I, Godeberge P, Sokol G, Catherinot E, Poiree S, Chapdelaine H, Dunogue B, Bodemer Ch, Lecuit M, Fischer A, Lortholary O, Hermine O. J Allergy Clin Immunol 2013; 132: 997-1000)**:**

  - Chronic granulomatous disease (CGD): genetic defects of the phagocyte NADPH oxidase → phagocyte dysfunction → susceptibility to bacteria and fungi, granuloma formation, inflammatory manifestations (e.g. colitis [mimicking Crohn disease], interstitial pneumonitis, nodular pneumonia, neutrophilic dermatosis, granulomatous hepatitis, cystitis).

  - Treatment of CGD: (i) curative treatment: HSCT, gene therapy; (ii) supportive treatment for infections: antimicrobials, IFN-γ; (iii) supportive treatment for granulomas and inflammatory manifestations: immunosuppressive agents (corticosteroids, azathioprine, anti-TNF-α; significant side effects; ↑ infection risk).

  - Thalidomide: immunomodulatory drug with anti-TNF-α properties; major side effects: infections, asthenia, constipation, peripheral neuropathy, deep venous thrombosis

- Authors followed 119 patients with CGD → (i) 70 patients (58.8%) had ≥1 inflammatory manifestations; (ii) 8 patients (7 CYBB mutations, 1 NCF1 mutation) received thalidomide for inflammatory manifestations (colitis, interstitial lung disease or nodular pneumonia, neutrophilic dermatosis, granulomatous hepatitis) [7 of these patients had received at least 1 previous immunosuppressive drug, with no response]; (iii) thalidomide was effective and relatively safe in most patients (marked efficacy in nodular pneumonia, neutrophilic dermatosis and granulomatous hepatitis; moderate efficacy in colitis; no efficacy in interstitial/fibrotic lung disease); (iv) median time to clinical efficacy = 6 months.

- Author's commentaries: (i) thalidomide can be effective and relatively safe for the management of inflammatory manifestations in patients with CGD; (ii) early use of thalidomide may ↓ iatrogenic morbidity and gastrointestinal surgery requirement.

- **EXPANDING THE SPECTRUM OF RECOMBINATION-ACTIVATING GENE 1 DEFICIENCY: A FAMILY WITH EARLY-ONSET AUTOIMMUNITY** (Henderson LA, Frugoni F, Hopkins G, de Boer H, Pai S-Y, Lee YN, Walter JE, Hazen MM, Notarangelo LD. J Allergy Clin Immunol 2013; 132: 969-971)**:**

  - Lymphocyte receptor diversity: (i) generated by recombining VDJ gene segments of the BCR and TCR loci; (ii) V(D)J recombination requires DNA breakage, a process mediated by recombination-activating gene (*RAG*) 1 and 2.

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

  - *RAG* mutations may present with different phenotypes (partially explained by residual RAG activity): (i) T-B- SCID (null mutations); (ii) Omenn syndrome (hypomorphic mutations); (iii) CMV infection with γδ T-cell expansion; (iv) combined immunodeficiency with granuloma; (v) hyper-IgM syndrome; (vi) isolated CD4+ lymphopenia.

  - Authors report an apparent healthy female patient (B) with undetectable TRECs at newborn screening → patient's sister (A) died at 2 yrs of age with early-onset severe autoimmunity, infections, severe T-cell lymphopenia and partially preserved B-cell counts → laboratory studies in patient B: severe T-cell lymphopenia, poor lymphocyte proliferation to mitogens, normal NK cell counts, partially preserved B-cell counts, normal immunoglobulin levels → due to patient's A death, patient B received aggressive therapy: prophylactic SMX/TMP, IVIG, 10/10 HLA-matched unrelated HSCT (at 3 months of age) → excellent clinical condition and full immune reconstitution at 14-month follow up → further genetic analysis: compound heterozygous missense mutations in *RAG1* (c.2522 G>A, p.R841Q; c.2920 T>C, p.F974L) in both patient B (alive) and patient A (frozen genomic DNA); father and mother were carriers (paternal allele: p.R841Q; maternal allele: p.F974L).

  - Author's commentaries: (i) RAG deficiency may present as early-onset autoimmunity with preserved B cell counts; (ii) potential mechanisms: abnormal BCR editing, autoreactive B-cell survival promoted by ↑ BAFF levels, chronic innate immune system activation.

- **HEREDITARY ANGIOEDEMACAUSED BY THE P.THR309-LYS MUTATION IN THE *F12* GENE: A MULTIFACTORIAL DISEASE** (Gómez-Traseira C, López-Lera A, Drouet Ch, López-Trascasa M, Pérez-Fernández E, Favier B, Prior N, Caballero T. J Allergy Clin Immunol 2013; 132: 986-989)**:**

- Hereditary angioedema (HAE): (i) type I: ↓ C1-INH levels; (ii) type II: normal C1-INH levels, ↓ C1-INH function; (iii) type III: normal C1-INH levels and function, positive family history, associated to high estrogen levels, FXII mutations may contribute to pathogenesis.

- Metabolism of bradykinin (BK): FXII converts prekallikrein intro kallikrein → kininogenases (kallikrein, FXII, plasmin) convert high-molecular-weight-kininogen into BK → BK acts through type 1 and type 2 BK receptors → BK is catabolized mainly by kininases (angiotensin-converting enzyme [ACE], aminopeptidase P [APP], carboxypeptidase N [CPN]).

- BK → ↑ endothelial permeability → ↑ vascular leakage → angioedema.

- Authors show that HAE type III could be a multifactorial disease: (i) *FXII* mutations may be a condition for the expression of symptoms; (ii) other genetic factors (e.g. low level of kininase activity) may ↑ or ↓ disease expression; (iii) environmental factors (e.g. estrogen) may ↑ disease expression; (iv) further studies are needed to evaluate influencing factors.

- **IL-13/IL-22–COPRODUCING T CELLS, A NOVEL SUBSET, ARE INCREASED IN ATOPIC DERMATITIS** (Teraki Y, Sakurai A, Izaki S. J Allergy Clin Immunol 2013; 132: 971-974)**:**

  - Atopic dermatitis (AD): chronic, relapsing, inflammatory skin disease; pathogenic factors: skin barrier defect, innate immune dysregulation, adaptive immune dysregulation (↑ TH2 responses, ↑ TH22 responses), microbial skin colonization.

  - TH2 responses: (i) driven by TH2 lymphocytes; (ii) important cytokines: IL-3, IL-4, IL-5, IL-9, IL-13; (iii) pathogenic mechanisms: IgE production, mast cell, basophil and eosinophil activation.

  - TH22 responses: (i) driven by TH22 lymphocytes; (ii) important cytokine: IL-22; (iii) pathogenic mechanisms: keratinocyte proliferation, diffuse epidermal hyperplasia (acanthosis).

  - Authors studied 13 patients (mean age: 32 yrs) with severe chronic AD → AD patients had in the circulation: (i) ↑ IL-4/IL-13–producing CD4+ T cells; (ii) ↓ IFN-γ–producing CD4+ and CD8+ T cells; (iii) ↑ IL-22–producing CD4+ and CD8+ T cells (~50% of these cells coproduced IL-13); (iv) most IL-13/IL-22–coproducing CD4+ and CD8+ T cells were CLA+CCR4+ (suggestive of skin-homing capability).

  - Author's commentaries: (i) IL-13/IL-22–coproducing T cells seem to play a key role in AD pathogenesis; (ii) TH22 cells may shift to TH22/TH2 or TH22/TH1 cells in the skin microenvironment; (iii) IL-22-producing cells may be heterogeneous and vary in their cytokine production in different inflammatory skin diseases (e.g. AD, psoriasis).

- **PROPHYLACTIC USE OF SUBLINGUAL ALLERGEN IMMUNOTHERAPY IN HIGH-RISK CHILDREN: A PILOT STUDY** (Holt PG, Sly PD, Sampson HA, Robinson P, Loh R, Lowenstein H, Calatroni A, Sayre P. J Allergy Clin Immunol 2013; 132: 991-993)**:**

  - Exposure to allergens via the nasopharyngeal mucosa in genetically susceptible subjects → specific TH2 responses to allergens → IgE-mediated allergic respiratory diseases.

  - Early interventions to induce immunologic tolerance (e.g. administration of potential allergens by a tolerogenic route [such as sublingual]) → ↓ TH2 immune responses (e.g. induction of allergen-specific Treg cells) → ↓ IgE-mediated allergies.

- Allergen immunotherapy: only treatment that can change the natural history of IgE-mediated allergies; sublingual route is safe and potentially effective (antigen presentation by tolerogenic mucosal dendritic cells; it is important to keep the allergen 2 to 3 minutes under the tongue).
- Authors show that sublingual administration of allergens (mixture of Der p1, Der p2, Fel d1, Phl p5 given daily for 12 months) prior to IgE-sensitization in high-risk children (12 to 30 months of age; family history of atopy; personal history of atopic dermatitis; sensitization to ≥1 food allergens) did not prevent development of IgE-sensitization and asthma (at 3 yrs posttreatment).
- Limitations of the study: small sample size, limited sublingual exposure (infants could not hold the allergen drops for 2-3 min).

- **ROLE OF THE BASOPHIL ACTIVATION TEST IN THE DIAGNOSIS OF LOCAL ALLERGIC RHINITIS** (Gómez E, Campo P, Rondón C, Barrionuevo E, Blanca-López E, Torres MJ, Herrera R, Galindo L, Mayorga C, Blanca M. J Allergy Clin Immunol 2013; 132: 975-976)**:**
  - Local allergic rhinitis (LAR, 'entopy'): local production of allergen-specific IgE (sIgE), negative detection of sIgE by skin and serum tests (absence of systemic atopy); prevalence: 25% of all rhinitis cases (usually misdiagnosed as nonallergic rhinitis); diagnosis: nasal provocation tests (advantages: high sensitivity and specificity, very reproducible; limitations: requires well-trained personnel, time consuming), measurement of sIgE in nasal secretion (advantages: noninvasive, very specific; limitation: low sensitivity).
  - Basophil activation test (BAT): validated technique for *in vitro* diagnosis of sensitization to aeroallergens, food allergens, Hymenoptera venom and several drugs.
  - Authors show in this pilot study that BAT might be a useful test to diagnose LAR caused by Dermatophagoides pteronyssinus.
  - Important points: (i) BAT could diagnose at least 50% of patients with LAR to D pteronyssinus; (ii) BAT could detect sIgE on blood basophils from LAR patients; (iii) after local production of sIgE, basophils might be the first or only target cells before the detection of sIgE in serum and skin; (iv) advantages of BAT: higher sensitivity than nasal sIgE detection, less time-consuming than nasal provocation test.
- **SERUM PROCALCITONIN AS A BIOMARKER DIFFERENTIATING DELAYED-TYPE DRUG HYPERSENSITIVITY FROM SYSTEMIC BACTERIAL INFECTION** (Yoon S-Y, Baek SH, Kim S, Lee YS, Lee T, Bae Y-J, Kwon H-S, Huh JW, Hong S-B, Cho YS, Chun S, Lim Ch-M, Koh Y, Moon H-B, Kim T-B. J Allergy Clin Immunol 2013; 132: 981-983)**:**
  - Drug hypersensitivity: (i) varied clinical presentation (especially in delayed allergic reactions); (ii) often confused with infection (especially in drug reactions that involve systemic symptoms such as fever).
  - Fever and skin rash while using several drugs → drug allergic reaction or infection?
  - It is essential to find biomarkers that can differentiate between drug hypersensitivity and systemic bacterial infection because: (i) treatment is different (e.g. corticosteroids for allergic reactions; antibiotics for infections); (ii) wrong treatment may aggravate the disease (e.g. corticosteroids for bacterial infections).

- Procalcitonin (precursor of calcitonin) serum levels: (i) are usually increased in patients with systemic bacterial infection; (ii) correlate with severity and outcomes of sepsis; (iii) are not lowered by corticosteroids (unlike CRP and IL-6 levels); (iv) may differentiate bacterial infection from autoimmune disease flares.

- Authors show that serum procalcitonin levels (best cutoff value = 1.67 ng/mL) can differentiate between delayed-type drug hypersensitivity reactions (maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, fixed drug eruption, vasculitis, purpura, acute generalized exanthematous pustulosis) and systemic bacterial infection with a greater sensitivity and specificity than the serum CRP level (best cutoff value = 6.67 mg/dL).

- **SKELETAL ABNORMALITIES AND SUCCESSFUL HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH RETICULAR DYSGENESIS** (Al-Zahrani D, Al-Ghonaium A, Al-Mousa H, Al-Kassar A, Roifman CM. J Allergy Clin Immunol 2013; 132: 993-996)**:**

  - Adenylate kinase (AK): (i) protein that regulates intracellular levels of ADP and maintains mitochondrial membrane potential; (ii) 2 types: AK1 (cytoplasmic), AK2 (mitochondrial); (iii) most tissues express AK1 and AK2; (iv) neutrophils, T cells and cells of the stria vascularis in the inner ear only express AK2.

  - Reticular dysgenesis (RD): AK2 deficiency (AR inheritance) → T-B- SCID, severe congenital neutropenia (arrest at promyelocytes), sensorineural deafness → life-threatening infections.

  - Authors report the case of a male patient with RD → (i) clinical manifestations: prematurity, recurrent sepsis, sensorineural deafness; (ii) laboratory: severe neutropenia refractory to G-CSF, undetectable TRECs, profound lymphopenia, presence of blast cells in bone marrow (due to G-CSF therapy?); (iii) imaging: abnormal chest X-rays (squaring of the scapular tips; cupping and fraying of the rib costochondral junctions anteriorly); (iv) genetic analysis: homozygous mutation (c.524 G>C, p.R175P) in the AK2 gene; (v) successful treatment: sibling-donor HLA-identical HSCT (full myeloablative conditioning) at 6 months of age (current follow up: 4.4 yrs).

  - Author's commentaries: (i) RD patients may have skeletal abnormalities; (ii) HSCT may be a successful therapy for RD patients (previous reports described high failure rate); (iii) G-CSF should be avoided in patients with RD due to inefficacy and possibility of malignant conversion.

- **STRESS, β-BLOCKERS, AND PUTTING** (Knight A. J Allergy Clin Immunol 2013; 132: 1014-1015)**:**

  - Nosbaum et al (J Allergy Clin Immunol 2011; 128: 1113): β-blockers may improve "idiopathic aquagenic pruritus".

  - Author's commentaries: (i) stress (activation of autonomic nervous system) seems to be an important trigger of chronic urticaria; (ii) β-blockers may improve chronic urticaria by interfering with stress pathways.

- **THE EDITORS' CHOICE** (Leung DYM, Szefler SJ. J Allergy Clin Immunol 2013; 132: 809-810)**:**

  - Recombination-activating gene (RAG) deficiency may present as early-onset systemic autoimmunity with preserved B-cell counts.

  - RAG re-expression during lymphoid development is important in modifying antigen receptor specificity and reducing the pool of self-reactive lymphocytes.

- Chronic cough → ↓ QoL → effective treatments are necessary.
- Capsaicin (chili pepper extract) inhalation challenge: (i) procedure to evaluate new antitussive therapies; (ii) limitation: abnormal results are not well defined (e.g. concentrations of capsaicin evoking 2 and 5 coughs poorly discriminate healthy from ill subjects).
- Hilton et al (current issue of JACI) → the maximum number of coughs evoked by capsaicin can better discriminate healthy from ill subjects.
- Children with hemophagocytic lymphohistiocytosis → (i) increased long-term cognitive and psychosocial impairment, even after successful HSCT; (ii) cognitive impairment can occur even without obvious neurologic defect at diagnosis.
- Fraction of exhaled nitric oxide (FENO) and blood eosinophil count (B-Eos) provided independent information to: (i) diagnose asthma and wheeze, (ii) predict asthma exacerbations.
- FENO may primarily reflect IL-4/IL-13 inflammation; B-Eos may mostly reflect IL-5 inflammation.
- TH2 cells from asthmatic subjects: ↑ expression of Socs3 → ↓ expression of STAT1 → ↑ resistance to IL-27 inhibition, ↑ susceptibility to viral infections.
- TH22 and TH17 cells are considered to be major T-cell subsets that produce IL-22 in patients with AD and psoriasis, respectively.
- IL-13/IL-22–coproducing T cells might play a key role in AD pathogenesis.
- TH22 cells may shift to TH22/TH2 or TH22/TH1 cells in the skin microenvironment.
- IL-22-producing cells might be heterogeneous and vary in their cytokine production in different inflammatory skin diseases.

PEDIATRIC ALLERGY AND IMMUNOLOGY:

- **AN UNUSUAL CASE OF NON-PIGMENTING FIXED DRUG ERUPTIONS IN A CHILD** (Ponvert C, Rufin P, de Blic J. Pediatr Allergy Immunol 2013; 24: 715–716)**:**
  - Fixed drug eruption (FDE) may leave or not leave residual pigmentation.
  - Non-pigmenting FDE (NPFDE) has been reported to pseudoepinephrine-containing drugs, diflunisal and furazolidone in adults; never reported in children.
  - Authors report the case of a 12-yr-old girl with 2 episodes of NPFDE (burning bullous desquamative eruptions in palms and soles 24 hrs after initiation of rifamycin [2009] and amoxicillin [2012]) → treatment: local antiseptics, oral antihistamines (resolution within 12 days) → allergy tests with several beta-lactams (8 months after the reaction to amoxicillin): negative prick tests, negative intradermal tests (reading at 15–20 min [immediate], 6-8 h [semi-late], 2-3 days [late] and 6-7 days [hyper-late]), negative patch tests (late and hyper-late reading; performed in the patient's back; not performed in the site of lesions [palms and soles] for patient's comfort) → positive challenge tests with amoxicillin and rifamycin; negative challenge tests with penicillin V and cefpodoxime.
- **ANGIOEDEMA WITHOUT URTICARIA IN CHILDHOOD** (Ertoy Karagol HI, Yilmaz O, Bakirtas A, Topal E, Demirsoy MS, Turktas I. Pediatr Allergy Immunol 2013; 24: 685–690)**:**

- Authors evaluated 95 children referred for angioedema and no urticaria (Aw/oU) → (i) frequency of Aw/oU = 1.6%; (ii) etiology was found in only 45 patients (49%); (iii) causes of Aw/oU: infection (21%; mainly common cold), allergy (14%; mainly allergic conjunctivitis and stinging insect bite), thyroid autoimmunity-related (8%), NSAID hypersensitivity (6%); (iv) antihistamines were effective in most cases; (v) prognosis was good in the short-term follow-up.

- Limitations of the study: cross-sectional design, single-center experience, small size, no patients with HAE were detected, FXII mutations were not investigated, short follow up.

- **CLINICAL SIGNIFICANCE OF INCREASED PERIPHERAL BLOOD CD4+CD28− T CELLS OF ASTHMATIC CHILDREN** (Ertoy Karagol HI, Yilmaz O, Bakirtas A, Topal E, Demirsoy MS, Turktas I. Pediatr Allergy Immunol 2013; 24: 685–690)**:**

  - CD4+CD28- T-cell population can be increased in patients with immune-mediated disorders (e.g. multiple sclerosis, Wei Geshi granuloma, rheumatoid arthritis, unstable angina).

  - Authors evaluated 57 asthmatic children (mean age: 8±2.1 yrs) → compared to healthy controls, asthmatic patients had in peripheral blood: (i) ↑ % of CD3+CD4+ T cells; (ii) ↑ CD4+/CD8+ ratio; (iii) ↑ % of CD4+CD28- T cells (which correlated with ↑ asthma severity, ↑ IgE, ↑ IL-4, ↑ IL-5, ↓ IFN-γ); (iv) ↑ levels of IgE, IL-4 and IL-5; (v) ↓ levels of IFN-γ.

  - Author's commentaries: (i) CD4+CD28- T-cell population might play an important role in the initiation and development of asthma in children; (ii) CD4+CD28- T-cell subset has strong pathogenic potential.

- **HOW TO REINTRODUCE COW'S MILK?** (Dupont C. Pediatr Allergy Immunol 2013; 24: 627–632)**:**

  - Cow's milk (CM) allergy: (i) IgE-mediated: urticaria/angioedema, bronchospasm, anaphylaxis; (ii) non-IgE-mediated: proctocolitis, enterocolitis, enteropathy; (iii) mixed IgE- and non-IgE-mediated: atopic dermatitis, EoE; (iv) other conditions that might not be allergic ('allergic dysmotility'): GERD, diarrhea, constipation.

  - Important points about IgE-mediated CM allergy: (i) 50-80% of children outgrow CM allergy spontaneously by 8 yrs of age; (ii) skin testing, serum sIgE detection and BAT may help to predict resolution of CM allergy; (iii) up to 75% of children with CM allergy tolerate baked CM products (in this children consumption of baked CM accelerates tolerance to raw CM); (iv) some children recover tolerance to CM 'incompletely' (e.g. some children tolerate minimal quantities of CM but react to 'normal' intake; others react to CM only when cofactors are present [e.g. infections, exercise]); (v) CM immunotherapy can restore tolerance to CM in a subset of patients.

  - Reintroduction of CM in a child who received elimination diet for IgE-mediated CM allergy: (i) importance: confirms resolution of allergy, provides nutritional benefit, ↑ QoL; (ii) duration of elimination diet should be individualized; (iii) reintroduction should be done gradually at home after a negative complete oral food challenge performed in the hospital (usually up to 200 ml of CM; wait minimum 1 day before giving CM at home); (iv) reintroduction can be performed with raw and/or baked products, according to patient's age, clinical presentation and past allergy tests; (v) tolerance to milk in a one day oral challenge does not always mean that daily iterative ingestions will be tolerated; (vi) be careful with those children with 'incomplete recovery' of CM tolerance (food allergy is no longer a matter of 'yes' or 'no' but a matter of 'how much is

tolerated'); (vii) it is unknown if recovered tolerance to CM will last permanently; (viii) education, cooperation and communication between physician and patient's family is essential.

- Vegetable juices (often labeled 'milks'): (i) derived from soy, rice, almond, coconut, chestnut; (ii) mostly sold in organic outlets; (iii) do not meet the nutritional needs of an infant.

- Food neophobia: (i) refusal by children to eat new food; (ii) may be normal between 2 and 10 yrs of age; (iii) seems to be more common in children with elimination diets due to food allergy.

- **IMMUNOTHERAPY – RISK/BENEFIT IN FOOD ALLERGY** (Kostadinova AI, Willemsen LEM, Knippels LMJ, Garssen J. Pediatr Allergy Immunol 2013; 24: 633–644)**:**

  - Immune tolerance: nonresponsiveness of the adaptive immune system or active Treg cell response to antigens; mechanisms: anergy or deletion of reactive lymphocytes, generation of Treg cells.

  - Immune tolerance is essential to prevent: (i) self-destruction; (ii) inflammatory response to beneficial or harmless exogenous molecules (e.g. food, commensal bacteria, allergens).

  - Loss of immune tolerance ⟶ allergic or autoimmune disorders.

  - IgE-mediated food allergy: (i) increasing prevalence worldwide (6% of children and 4% of adults in the westernized world); (ii) impact: significant morbidity, ↓ QoL, mortality risk; (iii) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soybeans, seafood; (iv) conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling; (v) optimal treatment: restore tolerance by exposing patients to gradually increasing doses of allergen (immunotherapy).

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

  - Tolerance: no reactivity to a food even after a large period of discontinuation (months or years); mediated by reprogramming immune response (development of Tregs, allergen-specific anergy and/or clonal deletion, ↓ specific IgE, ↑ specific IgG4).

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

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

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

  - Main limitations of food oral immunotherapy (OIT): (i) lack of evidence of long-lasting efficacy (RCT with cow's milk, egg and peanut OIT have reported desensitization in 33–90% of subjects; however, ability for OIT to induce long-lasting tolerance remains uncertain); (ii) frequent allergic reactions during OIT, including reactions to previously tolerated doses (common cofactors:

infection, physical activity within 2 h of a dose, taking a dose on an empty stomach, poorly controlled asthma, pollen season, menses, stress).

- Immunotherapy for food allergy is still not ready for the clinic → what is needed? (i) to improve long-lasting efficacy; (ii) to improve safety; (iii) to define the best protocol (initiation phase, maintenance phase, dosing).

- How to increase efficacy and safety of OIT? (i) adding omalizumab (anti-IgE mAb); (ii) using modified allergens (baked food, recombinant allergens, tolerogenic peptides), (iii) adding immune response modifiers (monophosphoryl lipid A [TLR-4 agonist], CPG containing DNA [TLR-9 agonist], probiotics); (iv) using other administration routes (sublingual, epicutaneous, etc); (v) personalizing OIT schemes.

- Immunotherapy with peptides: (i) objective: to reduce allergen's IgE-binding capacity (allergenicity) while preserving T-cell-stimulating capability (tolerogenicity); (ii) immunologic basis 1: the distance between two FcεRI molecules ranges from 8 to 24 nm → peptides <30 aminoacids should not cross-link IgE on effector cells; (iii) immunologic basis 2: tolerance induction by one T-cell epitope can confer tolerance to other T-cell epitopes of the same protein ('linked epitope suppression', 'infectious tolerance'); (iii) clinical basis: allergy-protective effects of milk hypoallergenic formulas (protein lysates by enzymatic hydrolysis, heat treatment and ultrafiltration [not the same as recombinant peptides]).

- **PEDIATRIC ALLERGY AND IMMUNOLOGY IN JAPAN** (Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatr Allergy Immunol 2013; 24: 704–714)**:**

  - Authors describe in this encouraging paper: (i) the history and current activities of the Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI); (ii) current epidemiology, diagnosis and treatment of allergic diseases and primary immunodeficiencies (PID) in Japan; (iii) past and ongoing research in allergy and immunology in Japan.

  - Some important advances in PID work in Japan: (i) measurement of T-cell receptor excision circles (TREC) and immunoglobulin k-deleting recombination excision circles (KREC) as a screening method for combined and antibody deficiencies; (ii) measurement of cytokine production from mitogen-stimulated blood cells to help diagnosis of PIDs (e.g. HIES, AD-CMC, IRAK4/MyD88 deficiency, EDA-ID); (iii) detection of LPS-induced monocyte cell death for rapid diagnosis of CAPS; (iv) use of intracellular staining to rapidly diagnose FHL and CGD; (v) establishment of a genetic analysis center for PID (http://pidj.rcai.riken.jp/); (vi) identification of pathogenic genes in PID: IgG2 selective deficiency (Cγ2), HIES (STAT3 and Tyk2), AD-CMC (STAT1), autoinflammatory disorder with lipodystrophy (PSMB8).

- **PERSISTENT ALLERGY TO COW'S MILK: OF GREATER A CLINICAL CONCERN THAN OTHER FOOD ALLERGIES** (Turner PJ. Pediatr Allergy Immunol 2013; 24: 624–626)**:**

  - Important points about IgE-mediated CM allergy: (i) affects 2% of children; (ii) conventional therapy: avoidance (↓ QoL, does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling; (iii) optimal treatment: restore tolerance to CM (immunotherapy); (iv) 50-80% of children outgrow CM allergy spontaneously by 8 yrs of age; (v) subjects with severe persistent CM allergy are at constant risk of death; (vi) skin testing, serum sIgE detection and BAT may help to predict resolution of CM allergy; (vii) up to 75% of children with CM allergy tolerate baked CM products (in this children consumption of baked CM accelerates tolerance to

raw CM); (viii) some children recover tolerance to CM 'incompletely' (e.g. some children tolerate minimal quantities of CM but react to 'normal' intake; others react to CM only when cofactors are present [e.g. infections, exercise]); (ix) contamination of pre-packed foods with CM protein is common (e.g. contamination of chocolate with residual CM protein from milk chocolate produced on the same machinery); (x) when complete tolerance cannot be achieved, partial tolerance may be useful in preventing allergic reactions after inadvertent low exposure to CM protein; (xi) ≥0.1 mg of CM protein might be a reference point for food allergen labeling (limitation: this level of allergen may not be detected by commercially-available assays used to test for contamination); (xii) most children with CM allergy do not tolerate other mammalian milks.

- **STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS IN CHILDREN** (Atanaskovic-Markovic M, Medjo B, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Nikoli D, Nestorovic B. Pediatr Allergy Immunol 2013; 24: 645–649)**:**

  - Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): (i) most severe forms of hypersensitivity reactions affecting the skin; (ii) incidence: 0.05–3 cases per million individuals per year; (iii) SJS = epidermal necrolysis <10% of the body surface area; TEN ≥30%; SJS/TEN = between 10 and 30%; (iv) mortality rate: 7.5%; (v) clinical manifestations: polymorphic skin lesions (erythematous macules, papules, plaque, vesicles, bullae, positive Nikolsky's sign), mucosal erosion (oral, conjunctival, genital), fever, malaise, internal organ involvement; (vi) most common culprits: drugs (anti-epileptics, NSAIDs, acetaminophen, nevirapin, allopurinol, sulfonamides, aminopenicillins, cephalosporins, quinolones, tetracyclines, imidazole antifungals), infections (Mycoplasma pneumoniae, HIV, herpes virus, hepatitis A virus); (vii) diagnosis (there is no reliable laboratory test to determine the offending drug): clinical history, skin biopsy, allergy skin tests (patch tests have low sensitivity; delayed-reading intradermal tests have less specificity; NPV of drug skin tests = ~90%), *in vitro* lymphocyte transformation tests, detection of infectious agents; (viii) treatment: drug cessation, corticosteroids, immunosuppressants, IVIG, fluid replacement, analgesics, sedation, topical therapy; (ix) complications: infections, dehydration, electrolyte disbalance, hypoalbuminemia, anemia, ocular sequelae; (x) prognosis: can be calculated by SCORTEN (7 independent factors: age, skin detachment, subjacent malignant diseases, tachycardia, serum urea, serum glucose, serum bicarbonate).