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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.

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October 2013 – content:


- **INCREASED MORTALITY IN ALLERGIC RHINITIS PATIENTS?** (Mösges R, Hellmich M. Allergy 2013; 68: 1209–1210).


- **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).


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• **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).

• **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).

• **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).


• **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).


"But knowledge puffs up while love builds up” 1 Corinthians 8:1
**ALLERGY:**

**ABOUT THE ROLE AND UNDERLYING MECHANISMS OF COFACTORs IN ANAPHYLAXIS**


- **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).


- **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.

  - **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’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.


  - 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)

  “But knowledge puffs up while love builds up” 1 Corinthians 8:1
**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).


- **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.


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.

“‘But knowledge puffs up while love builds up’” 1 Corinthians 8:1
• 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:


  • 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°C-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).
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• **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 threat**: stings (imported species are aggressive, can sting multiple times in a radial pattern); (v) **natural reaction to a 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**:


“**But knowledge puffs up while love builds up**” 1 Corinthians 8:1
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.


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.


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: immnosuppressive 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.


• 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.

• RAG 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.


“But knowledge puffs up while love builds up” 1 Corinthians 8:1
• **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).


  • 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.
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.

• **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, Phil 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).


  • 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.


  • **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).

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• 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).


  • 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 TREC, 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, Szeffler 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.

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**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 pseudoephedrine-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):

  “But knowledge puffs up while love builds up” 1 Corinthians 8:1
• 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.


  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
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:

“*But knowledge puffs up while love builds up*” 1 Corinthians 8:1
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 (Cy2), 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 slgE 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
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.

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 (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).

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