November 2013

General considerations:

- The purpose of this educational material is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- The content of this educational material does not intend to replace the clinical criteria of the physician.

- If there is any correction or suggestion to improve the quality of this educational material, it should be done directly to the author by e-mail.

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November 2013 – content:


- **DIVERSITY OF ALLERGENS CONTAINED IN DOG SALIVA** (Codina R. Allergy 2013; 68: 1484–1485).


- **DELAYED ANAPHYLAXIS SECONDARY TO ALLERGY SKIN TESTING** (Ricketti PA, Unkle DW, Cleri DJ, Ricketti AJ. Ann Allergy Asthma Immunol 2013; 111: 420-421).


- **THE BURDEN OF ILLNESS IN PATIENTS WITH HEREDITARY ANGIOEDEMA** (Banerji A. Ann Allergy Asthma Immunol 2013; 111: 329-336).


• **OUTCOMES OF THE CHILDHOOD ASTHMA PREVENTION STUDY AT 11.5 YEARS** (Toelle BG, Garden FL, Ng KKW, Belousova EG, Almqvist C, Cowell CT, Tovey ER, Webb KL, Leeder SR, Marks GB. J Allergy Clin Immunol 2013; 132: 1220-1222).


• **RHINOVIRUS SPECIFIC IGE CAN BE DETECTED IN HUMAN SERA** (Tam JS, Jackson WT, Hunter D, Proud D, Grayson MH. J Allergy Clin Immunol 2013; 132: 1241-1243).


• **THE LONG ROAD TO OPTIMAL MANAGEMENT FOR CHRONIC GRANULOMATOUS DISEASE** (Notarangelo LD. J Allergy Clin Immunol 2013; 132: 1164-1165).

ALLERGY:


- **Airway dysfunction**: frequent problem in elite athletes (both summer and winter high-intensity sports); **impact**: affects their performance and health.

- **Exercise-induced bronchoconstriction**: (i) **definition**: transient, reversible bronchoconstriction after exercise; (ii) **prevalence**: occurs in 90% of asthmatics, 50% of elite athletes and 15% of the general population; (iii) **diagnosis**: clinical history, exercise challenge (↓ 10-15% of FEV1 within 30 min after exercise; exercise at suboptimal intensity/duration or with warm/humid inspired air may cause false-negative results), mannitol challenge.

- **Mechanisms of EIB**: (i) heating and humidifying large volumes of air in a short period → loss of water from the lower airways → hyperosmolar environment → activation and release of mediators (cysLTs, PGD2, ECP, adenosine, neurokinins, MUC5AC) from mast cells, eosinophils, epithelial cells and nerves → bronchoconstriction; (ii) very intense exercise in athletes → dehydration injury to the airway epithelium → microvascular leak and plasma exudation → bronchoconstriction; (iii) hyperpnoea → exposure to greater quantities of aeroallergens and pollutants.

- A 20-min warm-up at submaximal intensity or 30-sec repeated sprints cause refractoriness to following vigorous exercise (hypothesis: ↓ mast cell mediator stores, ↑ protective prostaglandins, desensitization of airway smooth muscle receptors to mediators).

- **Risk factors for EIB**: dry air, cold air, high load of aeroallergens and pollutants, high ventilation, mouth breathing.

- **Strategies to ↓ airway dysfunction in athletes**: (i) early proper diagnosis; (ii) sport environments with less concentration of aeroallergens and pollutants; (iii) warming up before exercise; (iv) use of β2-agonists before exercise (risk of adverse effects and tachyphylaxis); (v) use of daily inhaled corticosteroids; (vi) dietary modification (e.g. fish oil supplementation).

- **Elite athletes** should receive the same considerations for their airway health as others with relevant occupational exposures.


- **NSAID hypersensitivity**: (i) **intolerance**: pharmacologic mechanism (COX inhibition); cross-reactivity; urticaria/angioedema is the most frequent reaction; (ii) **allergy**: IgE or T-cell mediated; selective reactivity; less frequent.

- **Traditional management of intolerance to NSAIDs**: (i) avoidance of COX-1 inhibitors; (ii) use of selective COX-2 inhibitors as alternative drugs (usually well tolerated); (iii) desensitization to aspirin (effective but requires continuous therapy; tolerance disappears within 2 to 5 days after NSAID interruption).
• AERD (Samter’s triad): (i) clinical manifestations: intolerance to NSAIDs, nasal polyposis, chronic eosinophilic sinusitis, severe asthma; (ii) prevalence: 0.5% of the general population, 15% of asthmatics, 35% of asthmatics with nasal polyposis; (iii) treatment option for severe cases: aspirin desensitization (optimal maintenance dose is controversial; some authors recommend ≥325 mg bid, however, even doses of 325 mg/day are associated with a considerable risk of GI bleeding).

• Authors performed aspirin desensitization in 40 patients with AERD (maintenance dose = 300 mg/day) → (i) 29 patients continued treatment for ≥1 year, 18 patients for ≥3 yrs; (ii) beneficial effects of desensitization (up to 3 yrs of follow up): ↓ systemic corticosteroid use, ↓ episodes of sinusitis, ↓ surgery requirement.

• Author’s commentary: treatment with aspirin 300 mg/day was beneficial in patients with AERD.

• DIVERSITY OF ALLERGENS CONTAINED IN DOG SALIVA (Codina R. Allergy 2013; 68: 1484–1485):

• Pet allergy: (i) pet allergens are found in a variety of sources (e.g. dander, hair, epithelium, saliva, urine); (ii) most cat-allergic individuals react to Fel d 1 (standardized cat extracts are based on Fel d 1 concentrations); (iii) a distinctive major dog allergen has not been identified (different allergens are relevant in different patients); (iv) dander is the most common material used for the preparation of dog allergenic extracts; (v) there are patients with dog allergy who have negative tests to dog dander extracts; (vi) dog dander extracts might be contaminated with mite allergens (could lead to false positive SPT results).

• Polovic et al (Allergy 2013; 68: 585–592) → (i) dog saliva has a greater number and diversity of allergenic proteins compared to dog dander (e.g. BPIFA2, Mucin-5B, ANGPTL5, IgA heavy chain constant region); (ii) allergenic proteins in dog saliva vary among dog breeds; (iii) dog saliva extracts may improve diagnostics of dog allergy.

• It might be difficult to standardize allergenic extracts from dog saliva.


• IgE-mediated peanut allergy: (i) impact: significant morbidity and mortality, ↓ QoL; (ii) diagnosis: SPT, serum specific IgE detection, food challenge; (iii) conventional treatment: avoidance (does not prevent accidental exposure), autoinjectable epinephrine, nutritional counseling; (iv) optimal treatment: restore tolerance to allergens (immunotherapy).

• Proposed risk factor to develop peanut allergy: consumption of peanut by the infant’s family → high levels of peanut protein in the house (including areas where peanut is usually not consumed [e.g. bed], indicating a spreading of allergens) → IgE-sensitization through the infant’s skin, especially in patients with defective skin barrier (e.g. atopic dermatitis).

Immune tolerance: nonresponsiveness of the adaptive immune system or active Treg 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.

Factors that promote tolerance: (i) ↑ tolerogenic microbiota (Lactobacillus, Bifidobacterium); (ii) ↑ tolerogenic dendritic cells; (iii) ↑ tolerogenic molecules (retinoic acid, TGF-β, TSLP, indoleamine-2,3-dioxynoxygenase, IL-10, IgG4, IgA); (iv) ↑ T regulatory responses (CD4+CD25+ Tregs, Tr1 cells, CD8+ Tregs, regulatory B cells); (v) balanced TH1 responses.

Early interventions to induce immunologic tolerance and ↓ allergic diseases (efficacy is controversial or not fully established): (i) use of probiotics; (ii) use of prebiotics; (iii) ↑ tolerogenic dendritic cells; (iv) ↑ tolerogenic molecules (retinoic acid, TGF-β, TSLP, indoleamine-2,3-dioxynoxygenase, IL-10, IgG4, IgA); (v) ↑ T regulatory responses (CD4+CD25+ Tregs, Tr1 cells, CD8+ Tregs, regulatory B cells); (vi) balanced TH1 responses.

Authors gave n-3 LCPUFA supplementation (900 mg/day) to pregnant women from 21 weeks gestation until birth → their infants were evaluated at 1 and 3 yrs of age → there was a nonsignificant reduction (up to 22%) in IgE-mediated allergic diseases compared to controls (the study was powered to detect a 33% relative reduction).

Author’s commentaries: (i) n-3 LCPUFA supplementation during pregnancy did not significantly reduce IgE-mediated allergies in the first 3 yrs of life; (ii) the nonsignificant risk reduction of up to 22% may still be of public health significance (the burden of allergic disease is high while fish oil intervention is safe and relatively cheap).


Drug desensitization: (i) essential procedure to manage drug-allergic patients who need the culprit drug obligatorily; (ii) frequently necessary in patients with allergy to chemotherapy drugs and monoclonal antibodies.

Madrigal-Burgaleta et al (Allergy 2013; 68: 853–861) reported the outcomes of 189 desensitization procedures to antineoplastic agents (oxaliplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide, rituximab) in 23 patients (mean age=56 yrs) → (i) the novel desensitization protocol lasted ~4 hrs, with a high starting dose compared to other protocols; (ii) desensitization candidates were carefully elected by anamnesis, skin testing, risk assessment and graded challenge; (iii) 188 desensitizations were successful (1 patient revoked consent after a breakthrough reaction); (iv) 177 (94%) desensitizations had no breakthrough reactions; 8 desensitizations had mild reactions; 4 desensitizations had moderate/severe reactions; no deaths; (v) 11 patients had a reaction during their 1st desensitization (premedication [montelukast + acetylsalicylic acid] was useful to complete 2nd desensitizations, except for one oxaliplatin-reactive patient who needed additional steps); (vi) oxaliplatin skin testing had poor negative predictive value; (vii) specific IgE to oxaliplatin (ImmunoCAP) had 54% sensitivity (cutoff point=0.10 UI/l) and 100% specificity in 10 oxaliplatin-reactive patients; (viii) 2 patients had positive skin tests to paclitaxel.
• **Author’s commentary:** the desensitization protocol reported by Madrigal-Burgaleta et al might be risky because of the high starting dose.

• **EAACI Drug Allergy Interest Group** → needs for improving drug desensitization protocols: (i) multicenter clinical trials with standardized and well-characterized patients; (ii) comparison of different protocols in one well-characterized patient group; (iii) comparison of one protocol in various, well-characterized patient groups.


  • **Anaphylaxis:** (i) acute severe multisystemic allergic reaction; (ii) potentially fatal; (iii) caused by the release of chemical mediators from mast cells and basophils.

  • Authors present a systematic review (49 selected studies) describing the epidemiology of anaphylaxis in Europe (frequency, risk factors, outcomes).

  • **Important points about anaphylaxis:** (i) incidence seems to be increasing; (ii) incidence rate: ~1 per 20,000 person-yrs (0-4 yr-old children have higher incidence rates); (iii) lifetime prevalence: 0.3% of the population; (iv) case fatality ratio: <0.0001%; (v) most common triggers: foods, drugs, stinging insects, latex; (vi) important comorbidities: atopic dermatitis, asthma, allergic rhinitis, food allergy.
PEARLS IN ALLERGY AND IMMUNOLOGY:

- **DELAYED ANAPHYLAXIS SECONDARY TO ALLERGY SKIN TESTING** (Ricketti PA, Unkle DW, Cleri DJ, Ricketti AJ. Ann Allergy Asthma Immunol 2013; 111: 420-421):
  
  Authors report the case of a 59-yr-old man with asthma (medication: daily beclomethasone, as needed albuterol), seasonal allergic rhinitis (medication: as needed antihistamines) and hypertension (medication: valsartan, aspirin) → skin prick tests (SPT) with commercial extracts were highly positive to grass pollens, tree pollens and dust mites → 2 hrs after SPT the patient had signs of symptoms of anaphylaxis at home (burning and itching of the palms, nasal congestion, itchy eyes, facial angioedema and erythema, diffuse urticaria, wheezing, throat-closing sensation, tachypnea, tachycardia); no food or drug intake during this 2-hr interval; serum tryptase was not measured → successful treatment in the emergency department: diphenhydramine, intravenous corticosteroids, famotidine (epinephrine was not administered).

  Author’s commentaries: (i) SPT are usually safe; (ii) SPT have a minimal potential risk to cause anaphylaxis (overall risk <0.02%); (iii) risk factors for systemic reactions after SPT: uncontrolled asthma, concomitant use of certain drugs (e.g. ACE inhibitors), testing with foods, drugs or Hymenoptera venoms, (iv) deaths after intradermal testing have been reported; (v) after SPT, patients should be educated on signs and symptoms of anaphylaxis.

  
  July 31, 2013 → the FDA’s Nonprescription Drugs Advisory Committee approved the switch of Nasacort AQ (triamcinolone acetonide nasal spray) to OTC status for the same indications and ages as it is used as a prescription product → FDA has approved the petition on October 11.

  Arguments in favor of OTC use: (i) triamcinolone acetonide nasal spray is already approved for OTC use in 11 countries, including Australia, New Zealand, Finland, Norway, Sweden, Switzerland, Denmark, Uruguay, Malaysia and Malta; (ii) every country in the European Union has different intranasal corticosteroid (INS) brands available for OTC use; (iii) FDA has already approved 1st- and 2nd-generation antihistamines, oral and topical decongestants, and intranasal cromolyn sodium for OTC use; (iv) patients in many parts of the world have been using INSs without medical supervision for almost 20 yrs; (v) since launch, 50 million bottles of triamcinolone acetonide nasal spray have been distributed in the US, with an excellent safety profile (most common adverse effects: nasal dryness, nasal irritation, mild epistaxis, changes in taste and smell); (vi) serious local adverse effects of INS (e.g. nasal septal perforation) are extremely rare; (vii) systemic adverse effects of INS (e.g. adrenal suppression, growth retardation) are usually non significant; (viii) patients with allergic rhinitis would have easier access to INS (1st-line therapy); (ix) costs for the patient could be reduced (more competition between INS-producing companies, no payment for medical consultation, no time loss for medical consultation); (x) most patients are able to use INS appropriately; (xi) patients and guardians could be advertised in the labeling about possible adverse effects of INS; (xii) patients could request medical advice when INS use fails; (xiii) currently, some patients do not receive the INS brand indicated by the physician due to insurance issues.

• July 31, 2013 → the FDA’s Nonprescription Drugs Advisory Committee approved the switch of Nasacort AQ (triamcinolone acetonide nasal spray) to OTC status for the same indications and ages as it is used as a prescription product → FDA has approved the petition on October 11.

• Arguments against OTC use: (i) use of INS for wrong diagnosis, delaying treatment of other conditions; (ii) use of INS devices in a wrong manner; (iii) lack of medical supervision of INS serious adverse effects (nasal perforation, severe epistaxis, Candida infection, ↑ intraocular pressure, cataracts, adrenal suppression, ↓ growth velocity, ↑ bone resorption, adverse metabolic effects); (iv) although serious adverse effects of INS are rare, there are sensitive subjects who would be at high risk for OTC use; (v) systemic adverse effects of OTC INS could be potentiated by concomitant use of inhaled or skin-applied corticosteroids; (vi) very-long-term safety of INS is not fully established; (vii) unawareness of drug-drug interactions (e.g. ritonavir or itraconazole may ↑ triamcinolone levels; triamcinolone may ↓ efficacy of tretinoin; fluoroquinolones + INS may ↑ risk of tendon rupture); (viii) patients may expect immediate relief after using OTC INS (confusion with OTC topical decongestants), which might lead to INS overuse; (ix) patients or guardians may not read or comprehend INS package labeling.


  • Omalizumab: (i) anti-IgE mAb → binds to free IgE → ↓ IgE binding to its receptors, ↓ expression of IgE receptors → ↓ IgE-mediated inflammation; (ii) approved for [uncontrolled asthma + serum IgE levels between 30 and 700 IU/mL + sensitization to perennial allergens]; (iii) dose is calculated in a chart, based on pretreatment IgE levels (between 30 and 700 IU/mL) and body weight; (iv) alternative formula when the chart is not suitable: ≥0.016 mg/kg per IgE unit every 4-wk period; (v) suggested maximum dose: 750 mg every 4 wks; (vi) efficacy has also been documented in patients with chronic urticaria, mastocytosis, idiopathic anaphylaxis, exercise-induced anaphylaxis, eosinophilic chronic rhinosinusitis.

  • Authors report the case of a girl with cutaneous mastocytosis from birth (skin biopsy: severe mast cell infiltration) → 7 yrs of age: daily pruritus and diarrhea, recurrent severe asthma attacks, serum tryptase=15.4 ng/mL; good response to antihistamines, cromoglycate and ICS → 12 yrs of age: severe idiopathic urticaria/angioedema, recurrent anaphylaxis, serum basal tryptase=8.57 ng/mL, total IgE= 508 kU/L, sIgE to D pteronyssinus= 56.9 kU/L, skin biopsy: mastocytosis (less MC infiltration compared to biopsy at birth), parents refused bone marrow study → incomplete response to conventional treatment (antihistamines, cromoglycate, high-dose ICS/LABA, prednisone 1 mg/kg/day) → successful treatment (patient’s weight=76 kg): omalizumab 450 mg every 4 wks for 3 doses (complete response 48 hrs after the 1st injection, total discontinuation of other therapies in 2 months, no symptoms up to 12 months of follow-up).

  • Author’s commentaries: (i) cutaneous mastocytosis might be successfully treated with short-term courses of omalizumab; (ii) larger studies are needed to confirm this beneficial effect.

• THE BURDEN OF ILLNESS IN PATIENTS WITH HEREDITARY ANGIOEDEMA (Banerji A. Ann Allergy Asthma Immunol 2013; 111: 329-336):

  • 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]).

- **C1-inhibitor (C1-INH) deficiency or dysfunction** (autosomal dominant mutations in the *SERPING1* gene; *de novo* mutations occur in ~25% of cases) → ↑ activity of FXII and kallikrein → ↑ production of BK → ↑ endothelial permeability → ↑ vascular leakage → **hereditary angioedema (HAE)**: recurrent angioedema without urticaria, painful, unpredictable, potentially fatal (markedly affects patient’s QoL).

- **Hereditary angioedema (HAE):** (i) type I (85% of cases): ↓ C1-INH levels; (ii) type II (15% of cases): normal C1-INH levels, ↓ C1-INH function; (iii) type III (very rare): normal C1-INH levels and function, positive family history, more frequent in women, associated to high estrogen levels, FXII mutations may contribute to pathogenesis (20-30% of cases).

- **Epidemiology of HAE:** (i) prevalence: 1/50,000 subjects; (ii) age of onset: 50% of cases by 10 yrs of age, nearly all cases by 20 yrs of age; (iv) diagnosis delay: 8 yrs in average; (v) >50% of patients may experience a **life-threatening attack**; (vi) many patients receive ineffective treatment and unnecessary medical procedures before diagnosis.

- **HAE attacks:** (i) clinical manifestations (severity is variable): nonpruritic painful angioedema without urticaria, abdominal pain, vomiting, nausea, constipation, diarrhea, throat tightness, circulatory collapse, loss of consciousness; (ii) most common sites: skin, GI tract (~50% of patients may experience ≥1 laryngeal attack); (iii) prodromal symptoms: erythema marginatum; (iv) frequency average (if untreated): 1 attack every 10 days; (v) duration average: 2-5 days; (vi) peak of symptoms: 12-36 hrs; (vii) possible triggers (do not always occur): physical trauma, medical procedures (e.g. surgery), infection, emotional stress, drugs (e.g. ACE inhibitors, estrogens); (viii) pregnancy might aggravate or reduce attacks.

- **Drugs to treat HAE attacks:** (i) plasma-derived or recombinant human C1-INH; (ii) ecallantide (inhibitor of kallikrein); (iii) icatibant (bradykinin receptor antagonist). For the 3 agents, many patients improve in <30 min, 75% of patients improve in <4 hrs, complete alleviation is often achieved in 8-12 hrs (none of the therapies completely control symptoms in every patient). Good safety profile for the 3 agents (3% risk of anaphylaxis with ecallantide).

- **Drugs to prevent HAE attacks:** (i) attenuated androgens: low price; considerable dose-dependent side effects; usually contraindicated in children, pregnancy and breastfeeding; (ii) plasma-derived C1-INH replacement therapy: good safety profile; very expensive (highest annual cost of any drug in the US); reduce 50% of attacks; (iii) tranexamic acid: agent of choice in children, rarely contraindicated (e.g. thrombophilia).

- Atopic dermatitis (AD): common chronic skin disease (3% of adults, 20% of children); impact: ↓ QoL, ↑ predisposition to skin infections (bacterial, viral) and other allergies (asthma, allergic rhinitis); pathogenic factors are multiple (genetic, epigenetic, environmental) and may result in varied clinical phenotypes.

- Pathogenic factors for AD: (i) skin barrier defects: scratching, ↓ synthesis of epidermal proteins (e.g. filaggrin, loricrin, involucrin, corneodesmosin, S100 proteins, proteases, antiproteases [e.g. LEKTI], tight junction proteins [e.g. claudin-1]) due to genetic mutations or TH2-cytokine influence → increased entry of allergens through skin.

- (ii) innate immune dysregulation: ↑ inflammatory dendritic cells, altered TLR signalling, ↓ production of antimicrobial peptides (e.g. cathelicidin, defensins), ↑ keratinocyte production of cytokines that promote TH2 environment (e.g. TSLP, IL-25, IL-33), ↑ production of neuropeptides (AD is usually associated with stress).

- (iii) adaptive immune dysregulation (determined by genetic factors [e.g. polymorphisms in IL4RA] and environmental factors [e.g. Staphylococcal superantigens, allergens, low vit D]): ↑ TH2 inflammation (IL-4, IL-13, IL-5, IgE, IL-31 → promote skin barrier dysfunction and pruritus), ↑ TH22 inflammation (promotes acanthosis), altered TH1 responses (predisposition to viral and bacterial infections), altered TH17 responses (predisposition to bacterial and fungal infections), ↓ Treg responses.

- (iv) exaggerated immune responses to food allergens (e.g. milk, egg), aeroallergens (e.g. house dust mites), microbial molecules (e.g. from S aureus or Malassezia sp) or self antigens (e.g. human thioredoxin).

- (v) abnormal skin colonization by microbes: S aureus colonizes the skin in 90% of AD patients (staphylococcal enterotoxins induce polyclonal T-cell and B-cell activation).

- 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).

- Filaggrin: important role in the integrity of skin barrier; expressed by keratinocytes; not expressed by nasal, bronchial or esophageal epithelium; loss-of-function genetic mutations occur in 30% of AD patients (however, 8% of healthy subjects also carry those mutations).

- Desmoglein 1 deficiency → ↓ epidermal intercellular adhesion → severe dermatitis, multiple allergies, metabolic wasting.

- Tmem79 (MATT in humans) deficiency → abnormal lamellar granule secretory system in the epidermis → altered stratum corneum formation → pathogenic factor in atopic dermatitis.

- ‘Futuristic’ therapy of AD: determine specific AD phenotypes using clinical, laboratory, histologic and genetic biomarkers → individualize therapy.

- X-linked agammaglobulinemia (XLA): mutations in BTK gene → block in B-cell maturation at pre-B stage → ↓ circulating B cells (<2% of peripheral blood lymphocytes) → ↓ production of immunoglobulins → recurrent infections.
- Authors show that variants in the BTK gene can be nonpathogenic.
- Author’s commentaries: (i) measure B-cell numbers in every male patient with ↓ serum immunoglobulin levels (even with mild infectious history); (ii) consider an alternative diagnosis when B-cell numbers are ≥2% (even if there is a coding region variation in the BTK gene).


- IL-5: main cytokine that stimulates eosinophil production, migration and survival.
- Eosinophil-depleting mAbs (anti-IL-5 [mepolizumab, reslizumab], anti-IL-5Rα [benralizumab, which also depletes basophils]): therapeutic options in patients with eosinophilic diseases (hypereosinophilic syndrome, eosinophilic esophagitis, eosinophilic asthma); no significant side effects (eg. patients with HES who have received mepolizumab for 6 yrs).
- Compared to bone marrow and circulating eosinophils, the tissue eosinophil might be less responsive to certain antieosinophil agents, including corticosteroids.


- Glucocorticoids (GC): cornerstone of management of allergic and autoimmune diseases.
- Glucocorticoid-induced osteoporosis (GIO): (i) most common iatrogenic cause of osteoporosis (corticosteroids affect osteoclasts, osteoblasts and osteocytes); (ii) risk factor for fragility fractures; (iii) most frequent due to oral GC administration (>5 mg/d prednisone for >3 months) (iv) may also occur with high-dose GC topical therapy; (v) effective detection and management of GIO is encouraged (main recommendations: adequate intake of calcium and vit D, pharmacologic osteoporosis therapy in high-risk patients).

OUTCOMES OF THE CHILDHOOD ASTHMA PREVENTION STUDY AT 11.5 YEARS (Toelle BG, Garden FL, Ng KKW, Belousova EG, Almqvist C, Cowell CT, Tovey ER, Webb KL, Leeder SR, Marks GB. J Allergy Clin Immunol 2013; 132: 1220-1222):

- Effectiveness of environmental interventions (e.g. allergen avoidance, breast feeding, maternal diet) for the primary prevention of asthma is controversial.
- Authors report the outcomes of The Childhood Asthma Prevention Study at 11.5 yrs of patient follow up → (i) HDM avoidance and omega-3 fatty acid supplementation for the first 5 yrs of life in high-risk children did not ↓ the prevalence of atopy, asthma or other atopic disorders at age 11.5 yrs; (ii) identifying effective interventions to prevent asthma remains an elusive challenge.

  - Innate immune system: (i) barriers: physical (e.g. skin, mucosal epithelium, cilia), chemical (e.g. gastric acid), biological (e.g. commensal bacteria); (ii) soluble molecules (e.g. antimicrobial peptides, complement system); (iii) cells (e.g. neutrophils, macrophages, NK lymphocytes).

  - Nasal mucosal epithelial cells and glands: (i) barrier against the entry of airborne substances and pathogens; (ii) secrete mucous, which immobilize pathogens and other harmful substances; (iii) produce dozens of antimicrobial peptides (e.g. defensins, cathelicidin, S100A7, SPLUNC1, lactoferrin): deleterious effect against bacteria, fungi, virus and parasites.

  - Abnormal expression of host defense molecules has been linked to many airway diseases.

  - Authors show that expression of antimicrobial peptides differed between the inferior region (inferior turbinate [IT]) and the superior region (uncinate tissue [UT]) of the sinonasal mucosa in healthy human subjects.

  - Causal hypothesis for these findings: (i) maxilloturbinal (IT) vs ethmoturbinal (UT) tissues have different embryonic origins; (ii) IT vs UT may have different environmental exposures (pathogens, microbiota, pollutants, allergens); (iii) UT is located at a point of drainage of various sinuses, so it might need special defense mechanisms (e.g. SPLUNC1 has surfactant properties and may promote mucociliary clearance).

• **RHINOVIRUS SPECIFIC IGE CAN BE DETECTED IN HUMAN SERA** (Tam JS, Jackson WT, Hunter D, Proud D, Grayson MH. J Allergy Clin Immunol 2013; 132: 1241-1243):

  - Respiratory viral infections (mainly by respiratory syncytial virus [RSV] or human rhinovirus [HRV]): important pathogenic factor in asthma development and exacerbations.

  - HRV: (i) nonenveloped, single-stranded RNA virus (Picornaviridae family); (ii) >150 serotypes with many more distinct strains that can infect humans; (iii) 3 genetic clades (A, B, C); (iv) HRV infection is ubiquitous.

  - Authors show that human subjects can develop specific IgE against HRV after exposure → important implication in the pathogenesis of asthma exacerbations.

  - Author’s commentaries: (i) specific IgE has also been shown against RSV or influenza virus; (ii) whether antiviral-specific IgE is a purposeful or maladaptive immune response, it appears to contribute to the exacerbation and perhaps development of atopic disease.

• **THE BIOLOGY OF THE GLUCOCORTICOID RECEPTOR: NEW SIGNALING MECHANISMS IN HEALTH AND DISEASE** (Oakley RH, Cidlowski JA. J Allergy Clin Immunol 2013; 132: 1033-1044):

  - Glucocorticoids (GCs): (i) stress hormones necessary for life; (ii) synthetic GCs are potent antinflammatory drugs (cornerstone of management of allergic and autoimmune diseases).

  - Mechanism of action of GCs: diffusion across the cell membrane → binding to the glucocorticoid receptor α (GRα) in the cytoplasm → GRα liberates from chaperone proteins (HSP90) → GRα enters the nucleus through nuclear import proteins (importin α) → GRα
homodimerizes → GR complex binds to gene promoters and induces or represses the transcription of thousands of genes (e.g. switches off many activated inflammatory genes [cytokines, chemokines, adhesion molecules, etc.]).

- **GR:** (i) there are many isoforms, with unique expression, gene-regulatory and functional profiles; (ii) GR isoforms derive from a single gene by alternative splicing of the primary transcript, alternative translation initiation of the mature mRNA, and posttranslational modifications of the encoded protein → ↑ diversity of glucocorticoid responses both in healthy and diseased tissues.

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

- **Strategies for managing GC resistance:** (i) anti-inflammatory drugs: phosphodiesterase 4 inhibitors (e.g. oral roflumilast for COPD), p38MAPK inhibitors, NF-κB inhibitors, macrolides; (ii) drugs that ↑ HDAC2 expression: theophylline, nortriptyline, PI3Kδ inhibitors; (iii) LABA: ↑ PP2A, ↓ GRα phosphorylation, ↑ GRα translocation to the nucleus; (iv) antioxidants: Nrf2 activators.

- **Many factors affect sensitivity and specificity to GCs:** (i) GR isoform; (ii) GC type; (iii) GC concentration; (iv) GC target genes; (v) target cell/tissue.

- **Dissociated or selective glucocorticoid receptor agonists (SEGRAs) (in research):** (i) retain the antiinflammatory effects of GCs; (ii) lose the adverse effects of GCs.

  - 73% of patients with cow’s milk–mediated eosinophilic esophagitis (CMME) tolerated significant amounts of baked milk products without recurrence of symptoms or esophageal inflammation → this finding could improve adherence to diet, QoL and nutrition in patients with CMME.
  - **Tiotropium bromide:** add-on therapy for asthma control; (i) factors associated with a positive response to tiotropium in uncontrolled asthmatic patients: higher cholinergic tone, positive immediate response to albuterol, airway obstruction; (ii) factors not associated with a positive response to tiotropium: ethnicity, sex, atopy, IgE level, sputum eosinophil count, FENO, asthma duration, body mass index.
  - **Long-acting β2-agonists** → ↑ nuclear translocation of the activated glucocorticoid receptor in sputum macrophages (equivalent to that seen with a 5-fold higher dose of ICS) → ↑ corticosteroid sensitivity in patients with COPD.
  - **Tmem79 (MATT):** novel skin barrier–related gene involved in the pathogenesis of atopic dermatitis.
  - **Futuristic approach in asthma/wheezing:** use of clinical data and biomarkers to identify specific asthma/wheezing phenotypes → give individualized therapy (e.g. leukotriene-induced asthma → give antileukotrienes).

- **THE LONG ROAD TO OPTIMAL MANAGEMENT FOR CHRONIC GRANULOMATOUS DISEASE** (Notarangelo LD. J Allergy Clin Immunol 2013; 132: 1164-1165):
• **Chronic granulomatous disease (CGD):** genetic defects of the phagocyte NADPH oxidase complex → phagocyte dysfunction (impaired production of microbicidal ROS) → severe bacterial and fungal infections, granuloma formation, inflammatory manifestations (e.g. colitis [mimicking Crohn disease], interstitial pneumonitis, nodular pneumonia, neutrophilic dermatosis, granulomatous hepatitis, cystitis) → high early mortality in the absence of treatment (disease severity reflects the degree of residual [if any] NADPH oxidase activity).

• **Forms of CGD:** (i) X-linked CGD (the most frequent): mutations of the CYBB gene encoding for the gp91phox subunit of the NADPH oxidase complex; (ii) autosomal recessive CGD: mutations of the genes that encode for the p22phox, p47phox, p67phox, and p40phox subunits.

• **NADPH oxidase activity:** (i) can be measured by the dihydrorhodamine test; (ii) might help to predict outcomes in CGD patients.

• **Treatment of CGD:** (i) curative treatment: HSCT (for which patients and when is still matter of debate), gene therapy; (ii) supportive treatment to prevent infections: antibacterial and antifungal prophylaxis, IFN-γ; (iii) supportive treatment for granulomas and inflammatory manifestations: immunosuppressive agents (corticosteroids, azathioprine, anti-TNF-α, thalidomide; significant side effects; ↑ infection risk).

• Koker et al (J Allergy Clin Immunol 2013; 132: 1156-63): patients with p47phox deficiency had more NADPH oxidase residual activity compared to patients with gp91phox, p22phox or p67phox deficiency → clinical course in patients with p47phox deficiency was less severe.


• Comparing outcomes of conservative versus curative treatment in CGD patients with similar levels of oxidase activity is of outmost importance.


• **FPIES:** (i) non-IgE-mediated allergy to food proteins (potentially severe); (ii) clinical history (usually starts in the 1st yr of life): vomiting, diarrhea, dehydration, electrolyte disbalance, hypotension, shock, acidemia, methemoglobinemia (2-6 hrs after eating the culprit food); (iii) frequent culprits: cow’s milk, soy, grains; (iv) diagnosis: clinical history, oral food challenge; (v) treatment: allergen avoidance; (vi) prognosis: FPIES typically resolves by 3-5 yrs of age (medically supervised OFCs are usually performed to confirm FPIES resolution); (vii) breast-fed infants with FPIES can typically continue lactating without maternal avoidance (FPIES is very rare in exclusively breast-fed infants).

• **Ondansetron hydrochloride:** (i) highly potent and selective serotonin 5-HT3 receptor antagonist (peripheral and central receptors); (ii) approved to prevent and treat nausea/vomiting induced by chemotherapy or radiation; (iii) low risk of adverse effects (be cautious in children with underlying heart disease, as QT prolongation has been observed); (iv) used successfully off-label in emergency room settings to control vomiting (such as in acute gastroenteritis).

• Authors report the rapid efficacy of ondansetron in 5 children who had FPIES reactions during oral food challenges.
• Author’s commentaries: (i) ondansetron may have great value in treating FPIES reactions; (ii) the apparent efficacy of ondansetron raises questions as to whether inflammation is the central mechanism underlying FPIES and whether corticosteroids truly have a role in FPIES treatment; (iii) ondansetron should be routinely used in the treatment of FPIES reactions, both in the food challenge setting and in the emergency room.