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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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
January 2014 – content:


- **APPROACH TO DESENSITIZATION IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE** (Scott DR, White AA. Ann Allergy Asthma Immunol 2014; 112: 13-17).

- **ASTHMA ADHERENCE: HOW CAN WE HELP OUR PATIENTS DO IT BETTER?** (Shams MR, Fineman SM. Ann Allergy Asthma Immunol 2014; 112: 9-12).

- **EFFICACY AND SAFETY OF SULFASALAZINE IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA** (Orden RA, Timble H, Saini SS. Ann Allergy Asthma Immunol 2014; 112: 64-70).

- **REVISITING FATAL ASThma** (Traister R, Wenzel S. Ann Allergy Asthma Immunol 2014; 112: 4-5).


- **VITAMIN D STATUS AT BIRTH: AN IMPORTANT AND POTENTIALLY MODIFIABLE DETERMINANT OF ATOPIC DISEASE IN CHILDHOOD?** (Bacharier LB. J Allergy Clin Immunol 2014; 133: 154-155).


- **MODULATION OF MUCOSAL/SYSTEMIC ANTIBODY RESPONSE AFTER SUBLINGUAL IMMUNOTHERAPY IN MITE-ALLERGIC CHILDREN** (Queirós MGJ, Silva DAO, Siman IL, Ynoue LH, Araújo...
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.


• THE EDITOR RECOMMENDS THIS ISSUE’S ARTICLES TO THE READER (Pediatr Allergy Immunol 2013: 24: 719).


ANNALS OF ASTHMA, ALLERGY & IMMUNOLOGY:


  • Anaphylaxis: (i) definition: acute severe multisystemic allergic reaction, potentially fatal; (ii) lifetime prevalence: 0.05-2%; (iii) incidence: 1/10,000 patient-yr (incidence is increasing; 0-4 yr-old children have higher incidence rates); (iv) mechanisms: release of mediators from mast cells and basophils (mainly IgE-mediated reactions; IgG-mediated mechanisms have been shown in mice); (v) most common culprits: foods, drugs, hymenoptera venom, latex; (vi) factors that influence severity: pathogenic mechanism, allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors; (vii) important comorbidities: asthma, allergic rhinitis, atopic dermatitis, food allergy.

  • 2 groups of aminoglycoside antibiotics (depending on the aminocyclitol nucleus): (i) streptidine (streptomycin), (ii) deoxystreptomyccin (neomycin, kanamycin, gentamicin, and tobramycin).

  • Streptomycin: (i) uses: antibiotic, antituberculous drug; (ii) main adverse effects: ototoxicity, nephrotoxicity, neuromuscular paralysis; (iii) does not share antigenic structures with other aminoglycoside antibiotics.

  • Authors report the case of a 64-yr-old man with suspected allergy to aminoglycoside antibiotics (generalized urticaria after use of aminoglycosides 10 yrs earlier) → allergy testing with streptomycin: positive intradermal test (concentration=1 mg/mL in 0.9% NaCl) complicated with anaphylactic reaction 10 min later (ear itching, facial erythema, generalized urticaria, dyspnea, chest discomfort, dizziness; successfully treated with epinephrine, methylprednisolone and chlorpheniramine); positive basophil activation test [BAT] (concentration=0.01 mg/mL).

  • Author’s commentaries: (i) 1st report of streptomycin-induced anaphylaxis confirmed by BAT; (ii) skin testing with aminoglycosides may trigger anaphylaxis in allergic subjects; (iii) risk factors for systemic reactions after skin testing: uncontrolled asthma; concomitant use of drugs (e.g. ACE inhibitors); testing with foods, drugs or Hymenoptera venom, (iv) deaths after intradermal testing have been reported; (v) after skin testing, patients should be educated on symptoms of anaphylaxis; (vi) BAT might be a useful tool to diagnose allergy to aminoglycosides.

• APPROACH TO DESENSITIZATION IN ASPIRIN-EXACERBATED RESPIRATORY DISEASE (Scott DR, White AA. Ann Allergy Asthma Immunol 2014; 112: 13-17):

  • Hypersensitivity to NSAIDs: (i) intolerance: pharmacologic mechanism (inhibition of cyclooxygenase-1 [COX-1]); cross-reactivity between COX-1 inhibitors; 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 (frequently effective but requires continuous therapy; tolerance disappears within 2 to 5 days after NSAID discontinuation).

  • Aspirin-exacerbated respiratory disease (AERD; Samter’s triad): (i) prevalence: 0.5% of the general population, 5-15% of asthmatics, 35% of asthmatics with nasal polyps; (ii) pathophysiology: NSAIDs block COX-1 activity → ↓ synthesis of prostaglandin E2 (PGE2) and thromboxane A2 → ↑ activity of 5-lipoxygenase and LTC4 synthase → ↑ production of
cysteinyl leukotrienes (LTs) → ↑ airway inflammation; (iii) clinical manifestations: intolerance to COX-1 inhibitors (selective COX-2 inhibitors and salicylate-containing foods are nearly always well tolerated), nasal polyposis, chronic eosinophilic pansinusitis (anosmia is prominent), severe asthma (not always present), peripheral eosinophilia (frequently present); (iv) main onset of symptoms: 20-40 yrs of age (can also occur in children and old adults); (v) diagnosis: clinical history, drug challenge with acetylsalicylic acid (ASA), ↑ urinary LTE4; (vi) treatment: topical/oral corticosteroids, LABAs, antileukotrienes, antihistamines, sinonasal surgery, desensitization to ASA (effective in up to 87% of patients [improves asthma and sinusitis outcomes]; optimal maintenance dose is usually ≥325 mg bid [risk of GI bleeding]; case reports have shown that 100-300 mg/day can be effective; ASA-desensitized patients may take any other NSAID; desensitization is lost after 2-3 days of NSAID suspension).

- Drug challenge with ASA: (i) usually safe (be careful in patients with uncontrolled asthma); (ii) ideally it should be done in a double-blind placebo-controlled way (practically difficult); (iii) before testing, suspend use of oral anti-H1, SABA and anticholinergics; (iv) premedication with anti-LTs can ↓ bronchospasm risk without ↑ false-negative results; (v) starting ASA dose=20-40 mg; (vi) interval between doses=90-180 min; (vii) positive reactions usually occur at doses of 45-100 mg and within 30-60 min of dosing (reactions can occur up to 3 hrs after dosing); (viii) typical sequence of oral ASA dosing: 30, 45, 60, 100, 150, 325 mg; (ix) a modified protocol (safe, effective, less time-consuming) uses nasal ketorolac (1.26 mg spray) before oral ASA.

- ASTHMA ADHERENCE: HOW CAN WE HELP OUR PATIENTS DO IT BETTER? (Shams MR, Fineman SM. Ann Allergy Asthma Immunol 2014; 112: 9-12):

  - Adherence to medication (WHO definition): “the extent to which a person’s behavior (including taking medication, following diet plans and executing lifestyle modifications) correspond with the agreed recommendations from a health care provider”.

  - Compliance to medication: “the extent to which patients follow physician instructions, prescriptions and proscriptions”.

  - Patients with asthma have low adherence to therapy: (i) 30-70% of adherence to controller therapies; (ii) <50% of adherence to environmental control measures (e.g. 20% of families accept to remove pets; up to 55% of patients still have frequent exposure to nicotine).

  - Importance of adherence to asthma medication: ↑ disease control, ↓ exacerbation risk, ↓ costs.

  - Reasons for low adherence to asthma therapy: (i) patient issues (e.g. low perception of symptoms, low confidence in the physician, fear of side effects, poor health literacy, language barriers); (ii) physician issues (e.g. prescription of complex medication regimens, illegible indications, bad relation with the patient); (iii) administrative or financing issues (e.g. high costs, limited access to appointments).

  - How to assess adherence to asthma therapy? (i) use asthma diaries; (ii) use validated clinical scores in every appointment (do not rely only on patient reports because they tend to overestimate disease control); (iii) observe inhaler technique in every appointment; (iv) use objective lung function tests; (v) count pills and weigh canisters; (vi) use pharmacy refill records or electronically monitored metered dose inhalers.

  - How to improve adherence to asthma therapy? (i) improve physician-patient communication, confidence and motivation (e.g. the Medication Communication Index assess the quality of
• **EFFICACY AND SAFETY OF SULFASALAZINE IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA** (Orden RA, Timble H, Saini SS. Ann Allergy Asthma Immunol 2014; 112: 64-70):

  • Chronic urticaria (CU): (i) definition: recurrent wheals for >6 wks (concomitant angioedema may occur); (ii) lifetime prevalence: up to 20% of the population; (iii) impact: significant morbidity, ↓ QoL, high costs; (iv) main classification: spontaneous (no clear triggers; 50% of cases are ‘autoimmune’), inducible (triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise); spontaneous and inducible urticaria can co-occur in the same patient; (v) 1st-line treatment: anti-H1 at usual dosing (50% of patients may not respond); (vi) 2nd-line treatment: up to quadruple dose of anti-H1 (50% of patients may not respond → antihistamine-refractory CU); (vii) other reported therapies: 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, calcineurin inhibitors, mycophenolate, pseudoallergen-free diet, anticholinergic agents, androgens, selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants; (viii) prognosis: 50% of cases may resolve spontaneously within 1 yr; 75% of cases within 5 yrs.

  • Authors studied 31 patients with antihistamine-resistant idiopathic CU who were treated with sulfasalazine → (i) 26 patients (83.9%) showed symptom improvement within 3 months; (ii) 16 patients (51.6%) became asymptomatic within 6 months; (iii) 11 patients (35.4%) achieved complete symptom relief after tapering off sulfasalazine; (iv) 5 patients (16.1%) failed treatment; (v) 6 patients (19.4%) had a modified course of sulfasalazine therapy owing to abnormal hematologic parameters; (vii) 2 patients (6.5%) discontinued sulfasalazine owing to severe adverse events (drug-induced leukopenia, rhabdomyolysis).

  • Author’s commentaries: (i) sulfasalazine should be considered in patients with antihistamine-resistant CIU (similar efficacy and safety to cyclosporine); (ii) patients who receive sulfasalazine should be monitored for adverse events (headache, rash, nausea, vomiting, dyspepsia, anorexia, reversible oligospermia, leukopenia, rhabdomyolysis).

• **REVISITING FATAL ASTHMA** (Traister R, Wenzel S. Ann Allergy Asthma Immunol 2014; 112: 4-5):

  • Severe asthma: (i) includes untreated asthma, difficult-to-treat asthma (DTT) and therapy-resistant asthma; (ii) occurs in up to 10% of asthmatics; (iii) impact: high morbidity, significant mortality, high costs; (iv) often associated to persistent airway inflammation and remodeling.

  • Risk factors for severe asthma: (i) genetic susceptibility (e.g. genetic variants affecting epithelial barrier, innate immunity or adaptive immunity; genetic variants that ↑ asthma risk in one environment may ↓ risk in another environment), (ii) respiratory infections, (iii) comorbidities (e.g. severe nasosinusal disease, obesity, GERD), (iv) pollutants (e.g. smoking, particulate matter), (v) sensitization to fungi (e.g. severe asthma with fungal sensitization).
• A patient with uncontrolled asthma may have: (i) unawareness of disease severity; (ii) a physician who is undertreating asthma or not recognizing comorbidities; (iii) low adherence to therapy (80% of patients with DTT); (iv) treatment-resistant disease; (v) a wrong diagnosis.

• Futuristic approach in asthma/wheezing: use of clinical data and biomarkers to identify specific asthma/wheezing phenotypes and endotypes → give individualized therapy (e.g. leukotriene-induced asthma → give antileukotrienes).

• Oda et al (Ann Allergy Asthma Immunol. 2014; 112: 23-28) → fatal asthma was associated to: (i) ↑ IL-18 and IL-18 receptor expression in inflammatory cells, epithelial cells and smooth muscle; (ii) ↑ CD8+ T cells (hypothesis: virus or allergens → IL-18 overproduction in genetically susceptible individuals → activation of CD8+ T cells → secretion of Th1 and Th2 cytokines → severe inflammation, bronchoconstriction, mucous plugging → fatal asthma).

• Author’s commentary: (i) IL-18 might have a pathogenic role in fatal asthma; (ii) IL-18 pathway is a potential target for asthma therapy.

• SPICE ALLERGIES IN CHILDREN (Fiocchi A, Dahdah L, Martelli A, Mazzina O, Manzotti G. Ann Allergy Asthma Immunol 2013; 112: 72-73):
  • Adverse reactions to spices: (i) non-IgE mediated: due to irritant effect; (ii) IgE-mediated: urticaria, angioedema, bronchospasm, anaphylaxis.
  • Allergy to spices: (i) rare in adults, very rare in children; (ii) usually occur due to sensitization to profilins (present in members of the Apiaceae family [anise, fennel, coriander, cumin]).
  • Saffron (from the Arabic word zafaran=yellow): (i) spice of the Iridaceae family; (ii) derived from the dried stigma of the flower of the saffron crocus (Crocus sativus); (iii) 3 allergic molecules: Cro s 1 (an Ole 1-like protein), Cro s 2 (a profilin), Cro s 3 (an LTP); (iv) saffron allergy: only described in adults (generally in occupational settings due to Cro s 3).
  • Authors report the case of a 12-yr-old boy with saffron allergy → (i) clinical history: allergic rhinitis to grass pollen, cat and house dust mite; oral allergy syndrome to apple, watermelon and fennel; immediate severe sneezing after smelling and eating a small amount of risotto alla Milanese → (ii) allergy testing: total IgE=2,872 kU/L; positive prick test to saffron powder; ↑ serum specific IgE to saffron (ImmunoCAP=10.1 kU/L), positive DBPCFC with saffron (sneezing, rhinorrhea, nasal obstruction and conjunctivitis 10 min after ingestion of 1 coffee-spoon of saffron cream); molecular testing suggested Cro s 2 as the responsible allergen → (iii) successful treatment: avoidance (no unintentional exposure has occurred within 3 yrs).

• SUCCESSFUL DESENSITIZATION TO AGALSIDASE BETA AFTER ANAPHYLAXIS (Talreja N, Butt A, Lopez Del Valle R, Fox RW, Lockey RF. Ann Allergy Asthma Immunol 2013; 112: 71-72):
  • Fabry disease: (i) X-linked lysosomal storage disorder; (ii) pathogenesis: mutations of the GLA (α-galactosidase) gene → deficiency of the enzyme α-galactosidase → accumulation of globotriaosylceramide and other neutral glycolipids → inflammation and fibrosis of the skin, kidney, nervous system and heart; (iii) life expectancy: 50 yrs for males, 70 yrs for females; (iv) treatment: enzyme replacement with agalsidase (alfa or beta isoforms).
• **Agalsidase beta (Aβ):** (i) produced in Chinese hamster ovary cells (undergoes nonhuman glycosylation); (ii) IgG antibodies to Aβ are present in ~80% of patients; (iii) IgE responses to Aβ resulting in anaphylaxis have been reported in 1% of patients receiving Aβ therapy.

• Authors report the case of a 50-yr old man with Fabry disease and anaphylaxis to Aβ (rash, angioedema and hypotension during infusion) → (i) diagnosis: positive serum IgE and IgG to Aβ, positive prick test to Aβ (0.0014 mg/mL) → (ii) successful treatment: desensitization to Aβ after premedication (oral prednisone, intravenous diphenhydramine, famotidine).

• **X-LINKED AGAMMAGLOBULINEMIA PRESENTING AS POLYMICROBIAL PNEUMONIA, INCLUDING PNEUMOCYSTIS JIROVECII** (Jongco AM, Gough JD, Samataro K, Rosenthal DW, Moreau J, Ponda P, Bonagara VR. Ann Allergy Asthma Immunol 2013; 112: 74-75):

  • **Bruton’s tyrosine kinase (BTK):** (i) essential protein for B-cell development; (ii) expressed in all hematopoietic cells except T cells and plasma cells; (iii) BTK inhibitors are being developed for clinical use in malignant tumors and autoimmune diseases.

  • **X-linked agammaglobulinemia (XLA):** mutations in BTK gene (>600 mutations have been described) → block in B-cell maturation at pre-B stage → ↓ circulating B cells (<2% of peripheral blood lymphocytes) → ↓ production of immunoglobulins → recurrent infections.

  • **Pneumocystis jirovecii:** (i) opportunistic microorganism that causes pneumonia mainly in patients with T-cell defects; (ii) B cells and *Pneumocystis*-specific antibodies may contribute to defence against this microbe.

  • Author’s report the case of a 4-month-old boy with XLA (undetectable IgG, IgA, IgM and IgE; B cells <1%; ↑ CD4+CD45RO+ T cells, ↓ CD4+CD45RA+ T cells; novel BTK gene mutation within the kinase domain causing a frameshift and a premature stop codon) who presented with polymicrobial pneumonia (bronchoalveolar lavage results positive for *Pneumocystis jirovecii*, K pneumonae and P aeruginosa) → successful treatment: piperacillin-tazobactam, cotrimoxazole, methylprednisolone, immunoglobulin replacement therapy, azithromycin.

  • Why did the patient develop *Pneumocystis* pneumonia? Hypothesis: BTK deficiency → antigen-presenting cell (APC) dysfunction, ↓ T-cell maturation and function.

  • Author’s commentaries: (i) *P jirovecii* pneumonia should be considered in XLA patients with respiratory distress; (ii) BTK deficiency may ↓ APC function, T-cell maturation and activation.
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JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:

  - Authors review 4 areas of childhood asthma: (i) natural history and pathophysiology; (ii) diagnostics and biomarkers; (iii) outcome measures; (iv) therapeutics.
  - Natural history of asthma: (i) asthma has several ‘endotypes’ (e.g. IL-13-mediated, leukotriene-mediated, etc.) and ‘phenotypes’ (e.g. allergic asthma, adult-onset asthma, obesity-associated asthma, etc.); (ii) asthma typically begins in childhood (mainly allergic asthma) but can also initiate in adulthood (especially nonallergic asthma); (iii) asthma results from the interaction between the host’s genetics, epigenetics and environment; (iv) risk factors for asthma: family history of IgE-mediated allergies, personal history of food allergy, atopic eczema or allergic rhinitis, prematurity, Cesarean delivery, growing in urban areas, lack of siblings, lack of breastfeeding, sensitization to aeroallergens, wheezing during viral infections (e.g. respiratory syncytial virus, human rhinovirus, influenza virus, metapneumovirus), exposure to pollutants (e.g. cigarette smoke), inadequate diet, psychological issues.

- Pathogenesis of allergic asthma: (i) disruption of airway epithelial tight junctions and activation of epithelial cells by allergens (e.g. house dust mite proteases, fungal spores, pollen germination), pollutants (e.g. cigarette smoke) and virus (e.g. respiratory syncytial virus) in a genetically susceptible subject → (ii) entry of allergens through the disrupted epithelium or intact epithelial cells (transcytosis) → (iii) secretion of TSLP, IL-25 and IL-33 from activated epithelial cells → (iv) activation of type 2 innate lymphoid cells (ILCs) by TSLP, IL-25 and IL-33 → (v) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from type 2 ILCs → (vi) activation of dendritic cells (DCs) by cytokines (TSLP, IL-25, IL-33) and PRR-mediated signalling → (vii) maturation of DCs (expression of TH2-favoring costimulatory molecules [OX-40L]; secretion of TH2-attracting cytokines [CCL17, CCL22]; presentation of allergen-derived peptides in MHC-II molecules) → (viii) attraction and differentiation of TH2 cells via antigen presentation, costimulatory molecules (OX40L, CD80/86) and cytokine signalling (IL-4) → (ix) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from TH2 lymphocytes → (x) IgE production from B cells; attraction and activation of effector allergy cells (mast cells, eosinophils, basophils); mucus secretion by epithelial cells → (xi) airway inflammation, epithelial injury, bronchoconstriction, air trapping, airway remodeling (goblet cell hyperplasia, thickening of the reticular basement membrane, subbasement fibrosis, smooth muscle hypertrophy/hyperplasia, angiogenesis).

- Diagnosis of asthma: (i) clinical history; (ii) lung function studies (difficult to perform in young children): spirometry, plethysmography, impulse oscillometry, provocation tests; (iii) allergy testing: detection of specific IgE (in vivo and in vitro tests); (iv) imaging studies: chest X-ray, CT and MRI; (v) markers of airway inflammation: sputum eosinophils, FENO, exhaled CO, proteomic analysis (e.g. serum periostin, urinary LTE4), metabolomic analysis; (vi) novel biomarkers for diagnosis, prognosis and follow-up are needed, especially in young children.

- Extending the benefits of novel asthma therapies to young children has been slow.
• No asthma treatment has shown to alter progressive loss in pulmonary function (especially in severe asthma).

• PHARMACOGENETICS: IMPLICATIONS OF RACE AND ETHNICITY ON DEFINING GENETIC PROFILES FOR PERSONALIZED MEDICINE (Ortega VE, Meyers DA. J Allergy Clin Immunol 2014; 133: 16-26):
  
  - Futuristic approach in allergic diseases: use of clinical, laboratory, histologic and genetic biomarkers to identify specific genotypes/endotypes/phenotypes → give individualized therapy.
  
  - Subjects from different ethnic groups have variable responses to specific therapies (efficacy, safety) → pharmacogenetics has the goal to develop personalized therapies for subjects from different ethnic groups based on their genetic profile (pharmacogenomic biomarkers).
  
  - Example: asthma patients may respond differently to β2-adrenergic receptor agonists depending on genetic variants of the β2-adrenergic receptor.

• PREDICTING THE FUTURE FOR RECURRENT RESPIRATORY SYMPTOMS IN YOUNG CHILDREN: APPLYING A DASH OF SCIENCE TO THE ART OF MEDICINE (Turner S. J Allergy Clin Immunol 2014; 133: 119-120):
  
  - Asthma: (i) usually presents before 5 yrs of age; (ii) frequently underdiagnosed or misdiagnosed in early childhood (inappropriate labels: chronic bronchitis, wheezy bronchitis, reactive airway disease, recurrent pneumonia, recurrent upper respiratory tract infections, GERD); (iii) not every wheezing infant will develop asthma (40% of children wheeze within 1st yr of life but only 30% of preschoolers with recurrent wheezing will have asthma at 6 yrs); (iv) there is no accurate single screening test to predict which young children with recurrent wheezing will develop asthma.
  
  - It is difficult to diagnose asthma in children <5 yrs old because at this age: (i) clinical manifestations are variable, nonspecific and difficult to describe; (ii) differential diagnosis is broad (e.g. acute viral wheeze, cystic fibrosis, ciliary dyskinesia, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, foreign-body aspiration); (iii) it is difficult to assess airflow limitation and airway inflammation (e.g. routine lung function tests are difficult to perform).
  
  - Factors that may predict asthma development in infants <3 yrs of age: (i) 3 episodes of wheezing per year, (ii) wheezing without colds, (iii) parental atopy, (iv) personal history of eczema or allergic rhinitis, (v) ↑ total IgE, (vi) IgE-sensitization to aeroallergens, (vii) exposure to high levels of indoor allergens, (viii) peripheral eosinophilia ≥4%.
  
  - Pescatore et al (J Allergy Clin Immunol 2014; 133: 111-118) present a simple 10-item questionnaire that may help to predict asthma outcome in 1- to 3-yr-old children with respiratory symptoms (predictors: shortness of breath, wheeze frequency, wheeze without colds, exertional wheeze, cough, male sex, age >1 yr, eczema, parental asthma, aeroallergen-induced cough).
  
  - Take-home message: young children with frequent wheezing (≥3 times/yr), wheezing without colds and no alternative diagnosis → give a therapeutic trial with inhaled corticosteroids for 3 months (usually safe and effective in asthma).

- **HSCT:** (i) procedure that can cure many severe primary immunodeficiency diseases (PIDs); (ii) has never been reported in patients with complement deficiencies (most complement factors are produced in the liver, however, C1q is synthesized by bone marrow-derived monocytes).

- **C1q deficiency:** (i) severe autosomal recessive PID; (ii) ↓ activation of the classical complement pathway; (iii) high risk of death from fulminant bacterial infections or systemic lupus erythematosus (SLE)-like autoimmunity (C1q is the strongest disease susceptibility gene for severe SLE in human subjects [90% risk of skin disease, 50% risk of renal disease]).

  Authors report the case of a 16 yr-old patient with C1q deficiency and severe clinical course (S pneumoniae-induced meningitis, central nervous system vasculopathy, persistent lupus-like facial rash) incompletely controlled by immunosuppressive therapy → treatment: reduced-conditioning HSCT from his healthy HLA-matched brother → 6 months post-transplantation: full donor chimera, no GvHD, marked clinical improvement, normalization of CH50 and serum C1q levels, restoration of hematopoiesis and myelopoiesis, ↓ autoantibodies.

  **Author’s commentaries:** (i) 1st report of a complement PID successfully treated with HSCT; (ii) patients with C1q deficiency may have high risk of morbidity and mortality → HSCT is a considerable therapeutic option.


- **Risk factors for asthma:** family history of IgE-mediated allergies, personal history of food allergy, atopic eczema or allergic rhinitis, prematurity, Cesarean delivery, growing in urban areas, lack of siblings, lack of breastfeeding, sensitization to aeroallergens, wheezing during viral infections (e.g. respiratory syncytial virus, human rhinovirus, influenza virus, metapneumovirus), exposure to pollutants (e.g. cigarette smoke), inadequate diet, psychological issues.

- **Guxens et al → Maternal psychological distress** during pregnancy was associated with childhood wheezing until 4 yrs of age.

- **Uses of intravenous immunoglobulin (IVIG):** (i) replacement therapy in primary and secondary immunodeficiencies; (ii) immunomodulatory therapy in autoimmune and inflammatory diseases.

- **Séité et al → IVIG induces B-cell anergy** by reducing B-cell receptor-mediated activation.

- **Allergen immunotherapy:** only therapy that can alter the natural history of IgE-mediated allergy.

- **Sublingual immunotherapy (SLIT):** (i) mechanisms: antigen presentation by tolerogenic mucosal dendritic cells (it is important to keep the allergen 2 to 3 min under the tongue) → induction of T regulatory responses, downregulation of TH2 responses → ↓ production of IgE, ↑ production of IgG4, IgG1 and IgA, (ii) advantages: self-administration, convenience, safety; (iii) disadvantages: very low adherence (56% of patients discontinue SLIT during the 1st year; only 15% of patients complete 3 years of SLIT); (iv) reasons for SLIT discontinuation: cost, side-effects, no perception of efficacy.

- **Phleum species SLIT tablets:** (i) clinically efficient treatment for grass pollen–induced rhinoconjunctivitis; (ii) therapy’s beneficial effects persist for at least 2 yrs after treatment.
• **Suárez-Fueyo et al →** A 1- to 4-month-treatment period with Phleum species SLIT tablets can provide valuable information regarding therapy outcome (increased specific IgE production at 1 month predicts a specific IgG4 response; reduction in IL-4+ cell frequency correlates with generation of putative regulatory T cells).

• **Pulmonary macrophages:** (i) patrol the lung and clear inhaled matter, pathogenic microbes and dying cells; (ii) release cytokines and proteases that regulate inflammation; (iii) can change their activity depending on their environment.

• **Chana et al →** Pulmonary macrophages acquire a new phenotype in COPD patients (↑ numbers, ↓ phagocyte function, ↑ inflammatory activity, ↓ response to glucocorticosteroids) → therapeutic target in patients with COPD.

• **Rhinovirus respiratory infections:** (i) recognized risk factor for asthma development and exacerbation; (ii) induce TH2-skewed cytokine responses.

• **Lukkarinen et al →** Human bocavirus 1 (HBoV1) respiratory infections: (i) not associated with ↑ asthma risk; (ii) induce TH1-skewed cytokine responses; (iii) suppress rhinovirus-induced cytokine responses.

• **Übel and Sopel et al →** Basic leucine zipper transcription factor ATF-like (BATF): (i) important for TH2, TH17 and B-cell differentiation in allergic asthma patients; (ii) increased expression in asthma children not treated with steroids; (iii) potential therapeutic target in allergic asthma.

• **UNSUSPECTED MILD EMPHYSEMA IN NONSMOKING PATIENTS WITH CHRONIC ASTHMA WITH PERSISTENT AIRWAY OBSTRUCTION** (Gelb AF, Yamamoto A, Mauad T, Kollin J, Schein MJ, Nadel JA. J Allergy Clin Immunol 2014; 133: 263-265):

  • Authors show that emphysema (confirmed by imaging, lung function and histology) can occur in nonsmoking adult patients with chronic moderate-severe asthma.

  • Hypothesis: recurrent asthma attacks → bronchiolar inflammation → persistent activation of proteolytic cascades → cleavage and disruption of lung parenchymal-terminal bronchiole attachments → emphysema.

• **VITAMIN D STATUS AT BIRTH: AN IMPORTANT AND POTENTIALLY MODIFIABLE DETERMINANT OF ATOPIC DISEASE IN CHILDHOOD?** (Bacharier LB. J Allergy Clin Immunol 2014; 133: 154-155):

  • Effects of vit D on immune system: (i) ↑ skin barrier function; (ii) ↑ production of antimicrobial peptides (β-defensins, cathelicidin); (iii) ↑ phagocytic activity of macrophages; (iv) ↓ maturation of dendritic cells; (v) ↓ production of TH1 and TH17 cytokines; (vi) ↑ differentiation of Treg cells; (vii) ↓ function of B-lymphocytes; (viii) ↓ production of IgE; (ix) ↑ IL-10 production by mast cells.

  • Hypovitaminosis D has been associated (frequently but not uniformly) with ↑ occurrence or severity of allergy (allergic sensitization, recurrent wheezing, asthma, allergic rhinitis, food allergy, atopic dermatitis).

  • Factors that influence vit D status (and may confound results): skin color, altitude, latitude, sun exposure, sunscreen use, season, adiposity, diet, use of vit D supplements, chronic diseases, genetic factors.
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.

- Baiz et al → (i) cord blood 25-hydroxy-vitamin D levels were inversely correlated to early transient wheezing (but not late-onset or persistent wheezing) and atopic dermatitis; (ii) no association was found between cord blood 25-hydroxy-vitamin D levels and parent-reported doctor-diagnosed asthma or allergic rhinitis at age 5 yrs.

- What is needed? Randomized controlled trials studying the effect of vit D supplementation on allergy outcomes.

- Factors that determine vit D status in early childhood: (i) most important factors: vit D supplementation, cow’s milk intake; (ii) less important factors: skin pigmentation, season.

- American Academy of Pediatrics → give vit D supplementation (400 IU/day) to: (i) exclusively and partially breast-fed infants; (ii) all non–breast-fed infants receiving <32 oz/day vit D–fortified milk or formula.
PEDiatric allergy and Immunology:

  • Babies grab everything and put it in their mouth → (i) disadvantages of this behaviour: ↑ risk of infections, infestations and poisoning; (ii) possible biologic advantage of this behaviour: ‘antigen scavenging’ (early oral exposure to antigens during infancy and childhood appears to favor immune tolerance and ↓ risk of allergic diseases).
  • Analogy to Psalms 8:3: ‘Out of the mouth of babes and sucklings hast thou founded strength….that thou mightest still the enemy and the avenger…’ → enemy: pathogens; avenger: immune response.

  • Immune tolerance: nonresponsiveness of the adaptive immune system or active Treg cell response to antigens; mechanisms: generation of Treg cells, anergy/deletion of reactive lymphocytes.
  • 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 (e.g. exposure to aeroallergens via the nasopharyngeal mucosa in genetically susceptible subjects → specific TH2 responses to aeroallergens → IgE-mediated allergic respiratory diseases).
  • Allergen immunotherapy: only therapy that can alter the natural history of IgE-mediated allergy.
  • Sublingual immunotherapy (SLIT): (i) mechanisms: antigen presentation by tolerogenic mucosal dendritic cells (it is important to keep the allergen 2 to 3 min under the tongue) → induction of T regulatory responses, downregulation of TH2 responses → ↑ production of IgG4, IgG1 and IgA, ↓ production of IgE; (ii) advantages: self-administration, convenience, safety; (iii) disadvantages: very low adherence (56% of patients discontinue SLIT during the 1st year; only 15% of patients complete 3 years of SLIT); (iv) reasons for SLIT discontinuation: cost, side-effects, no perception of efficacy.
  • Why allergic disease can improve with placebo SLIT? (i) psychological effect; (ii) ↑ visit frequency to physician; (iii) ↑ adherence to environmental measures and pharmacotherapy.
  • Low levels of salivary IgA have been associated with the development of allergy.
  • Authors studied the effect of SLIT (Dermatophagoides pteronyssinus allergens ± bacterial extracts (cell wall antigens from S pneumoniae, S pyogenes, S aureus, K pneumoniae, M catarrhalis) in mite-allergic Brazilian patients with allergic rhinitis and asthma → results: (i) significant long-term improvement in total symptom/medication scores, (ii) important modulation of mucosal/systemic antibody responses; (iii) good safety profile (only mild local and systemic reactions).
THE EDITOR RECOMMENDS THIS ISSUE’S ARTICLES TO THE READER (Pediatr Allergy Immunol 2013: 24: 719):

- Hoskin-Parr L et al. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: A dose-dependent relationship. Pediatr Allergy Immunol 2013: 24: 762–771 → (i) there was a strong, dose-dependent correlation between ↑ antibiotic exposure during infancy (<2 yrs of age) and reported asthma at 7 yrs of age (weaker association with reported eczema and hay fever; lack of association with skin-test sensitization); (ii) hypothesis: ↑ antibiotic use in infancy → altered gut microflora → abnormal development of immune tolerance → ↑ risk of asthma.

- Trønnes H et al. The association of preterm birth with severe asthma and atopic dermatitis: a national cohort study. Pediatr Allergy Immunol 2013: 24: 782–787 → (i) preterm birth was associated with ↑ risk of severe asthma and ↓ risk of atopic dermatitis.


- Allergic diseases have dramatically increased → proposals to stop this trend: (i) avoid early contact with allergens (e.g. food); (ii) ↓ contact with allergens (e.g. house dust mite); (iii) give allergens at an early age (e.g. food); (iv) promote 1st contacts with allergens in a more ‘tolerogenic environment’ (e.g. use of probiotics, prebiotics, vit A, vit D, breastfeeding, omega-3 fatty acids); (v) restore tolerance to allergens (e.g. immunotherapy).

- Cow’s milk protein (CMP) hydrolysate formulas (HFs) can be classified dependent on: (i) the degree of hydrolysis: partial (pHFs) or extensive (eHFs); (ii) the protein source: whey (W) or casein (C).

- Some high-risk infants (parent or sibling with a history of allergy) cannot receive enough breastfeeding at their 1st months of life → how to feed them to prevent allergy? Proposals: (i) intact CMP (not indicated for children with existing CMP allergy); (ii) pHFs (most peptides with molecular weights <10 kDa; pHFs are not indicated for children with existing CMP allergy); (iii) eHFs (>90% of peptides with molecular weights <1.5 kDa); (iv) soy formula.

- Arguments that favor the use of CMP-HFs for allergy prevention in high-risk children when breastfeeding is not sufficiently feasible in the 1st 4-6 months of life: (i) avoid early exposure to intact CMP; (ii) active induction of immune tolerance to CMP; (iii) >25 yrs of clinical experience with HFs; (iv) good evidence (e.g. the German Infant Nutritional Intervention [GINI] study) that feeding with eHF-C (Nutramigen) can ↓ prevalence and cumulative incidence of atopic eczema and food allergy; (v) evidence (the GINI study) that feeding with pHF-W (NAN-HA) can ↓ the prevalence of atopic eczema; (vi) HFs appear to be nutritionally adequate; (vii) HFs appear to be cost-effective; (viii) AAAAI recently stated: ‘pHF-W and eHF-C have a preventive effect on atopic dermatitis and CMP allergy when used instead of intact CMP formula in high-risk children’ (advantage of eHF-C: slightly more protective activity than pHF-W; advantage of pHF-W: better taste and price than eHF-C).

- Arguments against the use of CMP-HFs for allergy prevention in high-risk children when breastfeeding is not sufficiently feasible in the 1st 4-6 months of life: (i) biologic mechanism of action of HFs are not well understood; (ii) intervention with HFs has not shown a protective effect on respiratory allergies and allergic sensitization at 10 yrs of age; (iii) the Cochrane systematic review about HFs effect has not yet included recent large information that does not support the use of HFs (outcomes of the Melbourne Atopic Cohort Study [MACS] and long-term outcomes of the German Infant Nutritional Intervention [GINI] study); (iv) promoting use of HFs may ↓ breastfeeding (breastfeeding has several nonallergy benefits: protection from infections, ↑ infant-maternal bonding, inexpensive).