June 2013

General considerations:

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

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

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

- If there is any question or doubt about the content of this educational material, it should be done directly to the author by e-mail.

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June 2013 – content:

- **ADHERENCE TO IMMUNOTHERAPY IN TIMES OF FINANCIAL CRISIS** (González-de-Olano D, Álvarez-Twose I. Ann Allergy Asthma Immunol 2013; 110: 466–468).


SERUM TRYPTASE DETERMINATION IN PATIENTS WITH ACUTE ALLERGIC REACTIONS (Vitte J, Bongrand P. J Allergy Clin Immunol 2013; 131: 1714).


• **ADHERENCE TO IMMUNOTHERAPY (IT) IN TIMES OF FINANCIAL CRISIS** (González-de-Olano D, Álvarez-Twose I. Ann Allergy Asthma Immunol 2013; 110: 466–468):

  - Reasons for nonadherence to allergen IT: (i) inconvenience, (ii) high costs, (iii) lack of efficacy.
  - Authors show in Spain that adherence to IT (especially to sublingual IT) ↓ during financial crisis.
  - Factors associated with ↑ adherence to IT: (i) prescription before economic recession (OR=1.89); (ii) patient age <12 yrs (OR=3.06).

• **ALLERGIC REACTIONS AFTER IMMUNIZATION** (Kelso GM. Ann Allergy Asthma Immunol 2013; 110: 397–401):

  - Vaccines: ↓ morbidity and mortality of many infectious diseases (eg. eradication of smallpox).
  - Considerations regarding adverse reactions to vaccines: (i) confirm the adverse reaction; (ii) if the clinical history suggests an IgE-mediated reaction, perform in vivo and in vitro tests to detect specific IgE (slgE) against the vaccine or its components; (iii) patients with negative vaccine skin tests will usually tolerate the vaccine; (iv) patients with positive vaccine skin tests may tolerate the vaccine, in these cases the vaccine should be gradually administered; (v) it is prudent to observe the patient 30 min after the immunization; (vi) it is prudent to be prepared for anaphylaxis; (vii) consider assessing patient’s immune status to the vaccine (prior doses, including the suspected culprit dose, may have generated enough immunity, so further doses could be withheld or delayed); (viii) if an IgE-mediated reaction to the vaccine is confirmed, try to detect the specific culprit allergen because other vaccines could contain the same allergen (eg. a patient with gelatin allergy may react to MMR, varicella or influenza vaccines); (ix) in most cases, patients with suspected allergy to vaccines can receive subsequent vaccinations safely.

  - **How to confirm an IgE-mediated allergy to a vaccine?** (i) Suggestive clinical history: manifestations of mast cell degranulation within 4 hrs after immunization; (ii) IgE detection by skin testing (use the same vaccine brand that caused the reaction): SPT with undiluted vaccine, intradermal reaction with 1/100 diluted vaccine (nonirritating concentration).

  - **How to confirm an IgE-mediated allergy to a vaccine component?** (i) Suggestive clinical history: signs of mast cell degranulation within 4 hrs after using a vaccine component (eg. egg, gelatin, yeast, latex); (ii) slgE detection to the vaccine component: SPT, in vitro testing; (iii) OFC.

  - **Gelatin:** (i) stabilizer (µg to mg quantities) of many vaccines; (ii) bovine or porcine origin (extensively cross-reactive); (iii) most frequent culprit allergen in vaccines.

  - **How to diagnose gelatin allergy?** (i) Clinical history: ask for reactions after gelatin ingestion, a negative history does not exclude gelatin allergy; (ii) slgE detection in vitro; (iii) SPT with an office-made extract (not approved by the FDA): dissolve 1 teaspoon of sugared gelatin powder (any flavor) in 5 mL of normal saline (unsugared gelatin tends to gel at room temperature).

  - **How to approach a patient with IgE-mediated gelatin allergy?** Perform skin testing with gelatin-containing vaccines → (i) negative results → vaccinate the patient, observe 30 min afterward; (ii) positive results → consider vaccination in graded doses under observation.

  - **Egg protein (ovalbumin):** present in influenza vaccine (very low amounts) and yellow fever vaccine (higher amounts).
• **How to diagnose egg allergy?** (i) **Clinical history:** ask for reactions after egg ingestion; (ii) **sIgE detection** by skin and serum tests; (iii) **oral food challenge.**

• **How to approach a patient with IgE-mediated egg allergy who needs influenza vaccine?** (i) Administer an **entire dose** without previous skin tests, even in patients with anaphylaxis to egg; (ii) **observe 30 min** after vaccination; (iii) **be prepared to manage anaphylaxis;** (iv) **injectable trivalent vaccine** is preferred over nasal live attenuated vaccine because its safety in egg-allergic patients has been studied more extensively; (v) **2 new influenza vaccines (not grown in eggs)** were recently approved for patients ≥18 yrs of age (Flucelvax and Flublok).

• **How to approach a patient with IgE-mediated egg allergy who needs yellow fever vaccine?** Perform **skin tests with the vaccine** → (i) negative results → vaccinate the patient, observe 30 min afterward; (ii) **positive results** → consider vaccination in graded doses under observation.

• **Yeast protein** (Saccharomycyes cerevisiae; common baker’s or brewer’s yeast): present in hepatitis B vaccines (up to 25 mg per dose) and quadrivalent human papillomavirus vaccine (<7 µg per dose); **yeast allergy** is rare.

• **How to diagnose yeast allergy?** (i) **Clinical history:** ask for reactions after yeast ingestion; (ii) **sIgE detection** by skin and serum tests to Saccharomyces cerevisiae.

• **How to approach a patient with confirmed IgE-mediated yeast allergy?** Perform **skin testing with yeast-containing vaccines** → (i) negative results → vaccinate the patient, observe 30 min afterward; (ii) positive results → consider vaccination in graded doses under observation.

• **Natural rubber latex:** present in the **packaging** of many vaccines (vial stopper, syringe); very low risk of vaccine contamination with latex → minimal risk of allergic reactions in patients with IgE-mediated latex allergy.

• **How to approach a patient with IgE-mediated latex allergy?** (i) Use a vaccine without latex stopper; (ii) if not possible, remove the stopper and take the vaccine directly from the vial; (iii) if latex packaging cannot be avoided (eg. a prefilled syringe), vaccinate and observe the patient 30 min afterward.


• **Risk factors for asthma** in young children (<4 yrs old) with recurrent wheeze: (i) **IgE-sensitization** to aeroallergens; (ii) parental history of allergies.

• **Diagnosis of IgE-sensitization to aeroallergens:** (i) **skin prick tests** (SPT); (ii) specific IgE (sIgE) determination in vitro; (iii) **challenge tests.**

• A recent study showed ~80% **concordance** between SPT and sIgE testing results in adults with rhinitis (Allergy Asthma Proc. 2009; 30: 386-396).

• Authors performed SPT (ComforTen device) and sIgE testing (Immulite 2000 3gAllergy® system) to 7 aeroallergens (dog, grass, cockroach, cat, dust mite, ragweed, mouse) in 40
children (<4 yrs old) with recurrent wheezing and family history of asthma and/or eczema → (i) in 80% of children ≥1 sensitizations would have been missed if only SPT had been done; (ii) in 38% of children ≥1 sensitizations would have been missed if only sIgE testing had been done; (iii) children with total IgE ≥300 kU/L were more likely to have only positive sIgE test results.

- Author’s commentaries: (i) there was a significant discordance between SPT and sIgE testing results (possible reasons: antigenic differences between testing materials, variability between testing instruments, immaturity of immune system in young children [eg. mast cells may not have trafficked to the epidermis in sufficient numbers to elicit a typical wheal-and-flare response; mast cells may be less reactive]); (ii) both SPT and sIgE testing should be performed to diagnose IgE-sensitization in young children at high risk of asthma.

  - Omalizumab: (i) anti-IgE mAb → binds to free IgE → ↓ IgE binding to its 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; alternative formula when the chart is not suitable: ≥0.016 mg/kg per IgE unit every 4-wk period; suggested maximum dose: 750 mg every 4 wks.
  - Authors retrospectively studied 26 asthmatic patients (12-67 yrs old) with IgE levels >700 IU/mL who received omalizumab for ≥6 months → omalizumab efficacy was similar compared with a matched group of patients with IgE between 30 and 700 IU/mL: (i) ↑ asthma control; (ii) ↓ ED visits; (iii) ↓ systemic corticosteroid use; (iv) no change in mean FEV1; (v) good safety profile.

  - Oxytocin: drug that ↑ uterine contractility; adverse effects: cardiovascular side effects, bronchoconstriction (asthma worsening), rare cause of anaphylaxis during delivery.
  - Latex allergy: risk factor for anaphylaxis to oxytocin (homology between oxytocin epitopes and latex allergens Hev b 7.01 and Hev b 7.02 [patatin]).
  - Authors report 2 latex-sensitized women (37 and 43 yrs old) with severe anaphylaxis after oxytocin infusion during delivery → diagnosis: positive SPT with Syntocinon 5UI /mL; positive SPT and sIgE in vitro testing with latex.
  - Author’s commentaries: (i) in this case, not testing to oxytocin could have led to an incomplete diagnosis of latex allergy → after an intraoperative anaphylaxis it is recommended to test all drugs or substances that were used; (ii) latex-allergic women should be carefully managed during delivery (latex-free materials, oxytocin alternative agents, appropriate asthma control).

**PEARLS IN ALLERGY AND IMMUNOLOGY  June 2013**

- **Allergen immunotherapy:** only therapy with the potential to modify the natural history of allergic diseases; objectives: restore tolerance, prevent new sensitizations, stop ‘atopic march’; SLIT route of administration: safer, avoids injection pain, more suitable for children.

- Authors analyzed (by the GRADE tool) 29 recent (2009-2012) clinical trials (2469 patients) about SLIT efficacy in children (≤18 yrs old) with respiratory and/or food allergies → (i) grass pollen SLIT is effective in seasonal allergic rhinitis and may be effective in asthma; (ii) HDM SLIT seems to be effective, especially in asthma; (iii) there is not enough evidence to recommend Alternaria SLIT; (iv) food oral IT is more promising than food SLIT; (v) SLIT has good safety profile in respiratory allergies; (vi) be careful with side effects during food IT; (vii) further high-evidence research is needed.

- **AN ALTERNATIVE EXPLANATION FOR THE INVERSE RELATIONSHIP BETWEEN ATOPY AND MYOCARDIAL INFARCTION** (Varner A. J Allergy Clin Immunol 2013; 131: 1715):

  - A recent report showed an inverse relationship between allergen-specific IgE and myocardial infarction. Proposed mechanisms: (i) ↑ specific IgE → ↑ TH2 inflammation → ↓ TH1 inflammation → ↓ CV disease; (ii) atopic patients may have platelet dysfunction and ↑ bleeding times → ↓ CV disease.

  - By the other side, ↑ total IgE has been related to ↑ myocardial infarction. Proposed mechanism: ↑ total IgE → IgE occupies FcεRI and FcεRII on platelets → platelets are activated by allergens → ↑ CV disease.

  - Recently, the FDA reported that omalizumab was related to ↑ risk of thrombotic and CV events.


  - Immunoglobulin: (i) replacement therapy for immunodeficiencies, (ii) immunomodulatory therapy for autoimmune and inflammatory diseases. Approved and off-label indications include >150 different conditions.

  - Authors describe the use of immunoglobulin therapy in Iceland during years 2001 to 2009 → (i) 389 patients received IVIG, 13 received SCIG; (ii) approved indications = 264, unapproved = 110, unclear = 28; (iii) most common indications: PIDs, multiple myeloma, leukemias, lymphomas, demyelinating diseases, multiple sclerosis, idiopathic thrombocytopenia, Kawasaki disease, systemic lupus erythematosus, asthma.

- **EFFECT OF BARRIER MICROBES ON ORGAN-BASED INFLAMMATION** (Garn H, Neves JF, Blumberg RS, Renz H. J Allergy Clin Immunol 2013; 131: 1465-1478):

  - Intestinal microbiota (>100 trillion microorganisms; Firmicutes and Bacteroidetes phyla predominate) → development and regulation of the immune system, mostly in the neonatal period (eg. TLR2 activation by microbes in a ‘tolerogenic’ environment promotes Treg development; ‘tolerogenic’ microbiota promotes IgA production) → local homeostasis (tolerance), distal homeostasis? (eg. in the lung).

  - Factors that may disturb microbiota: (i) Cesarean delivery; (ii) no breastfeeding; (iii) inadequate diet; (iv) early use of antibiotics; (v) low exposure to farms; (vi) certain infections.
• Modern/industrialized lifestyle → **dysbiosis** (qualitative and quantitative disturbance of the microbiota) → dysfunctional immune responses (loss of tolerance) → ↑ risk of **allergic** (eg. asthma), **autoimmune and inflammatory disorders** (eg. IBD).

• **Inflammatory bowel disease (IBD):** altered gut microbiota (↓ Bacteroidetes and Firmicutes, ↑ Actinobacteria and Proteobacteria) → exaggerated immune response against commensal microbiota and potentially against host tissues → **chronic inflammation.**

• **Allergic diseases:** altered gut and/or respiratory microbiota (less diversity, altered predominance of species) → loss of tolerance to foreign allergens → **TH2** inflammation.

• It’s not fully defined: (i) which microbes protect from inflammatory diseases (*lactobacilli* and *bifidobacterium* seem to have beneficial effects); (ii) the direction of causality between inflammatory diseases and altered microbiota.

• How can we correct dysbiosis? (i) Natural delivery; (ii) breastfeeding; (iii) adequate nutrition; (iv) correct use of antibiotics; (v) probiotics and prebiotics; (vi) short-chain fatty acids.


  • Sinusitis rarely occurs in the absence of rhinitis.

  • **Rhinosisinusitis (RS):** inflammation of nasal and paranasal mucosa; **diagnosis:** (i) nasal blockage or nasal discharge (anterior or posterior) + facial pain/pressure or hyposmia, (ii) objective clinical, endoscopic or radiologic evidence of sinonosal inflammation (polyps, mucopurulent discharge, edema). **Acute RS:** <12 wks. **Chronic RS (CRS):** ≥12 wks.

  • **Pathogenesis of CRS:** (i) **Anatomic/structural problems:** nasal septal deviation, nasal valve dysfunction, concha bullosa (enlarged nasal turbinate caused by internal ethmoid air cell), adenoid hyperplasia (mainly in children), nasal choanal narrowing, nasal or sinus mucoceles, scarring from prior nasal or sinus surgery, septal perforations, nasal foreign body, malignancies.

  • (ii) **Altered immunity:** altered epithelial barrier (↓ epithelial tight junctions [occludins, claudins, etc], ↑ epithelial shedding, ↓ repairing proteins [psoriasin, calgranulin A and B, SPINK5]); ↓ ciliary clearance (cystic fibrosis, primary ciliary dyskinesia); ↓ antimicrobial peptides (defensins, psoriasin, PLUNC family, lysozyme, lactoferrin); ↓ TLR responses (especially TLR2 and TLR9); ↓ STAT3 function; ↑ immune activation (T-cell responses [TH2, TH17, TH22], IgE, IgA, effector cells [mast cells, eosinophils], autoantibodies, IL-32); **immunodeficiencies** (eg. agammaglobulinemia); **inflammatory diseases** (eg. Wegener’s granulomatosis, sarcoidosis, aspirin-exacerbated respiratory disease); ↑ remodeling (TGF-β, MMPs, TIMPs).

  • (iii) **Infections** (bacteria, fungi, virus, biofilms): role is not fully defined → antibiotics may help (macrolides and doxycycline have been suggested due to antibacterial and antiinflammatory properties); biofilm-destabilizing agents may help; some patients respond to antifungals.

  • (iv) **Pollutants and drugs:** cigarette smoke, pollutants, cocaine, topical vasoconstrictors.
• **Treatment of CRS:** (i) nasal irrigation/douching; (ii) intranasal and oral corticosteroids; (iii) antibiotics; (iv) surgery; (v) other therapies: antihistamines, LTRA, 5-lipoxygenase inhibitors, allergen immunotherapy, biological agents (monoclonal antibodies, soluble receptors, cytokines), aspirin desensitization, topical and oral antifungals, decongestants, mucolytics (eg. n-acetylcysteine), phototherapy, MTX, protein pump inhibitors, capsaicin, furosemide, vit D, Manuka honey, bromelain, quercetin, undecylenic acid, urtica dioica, massage of the sinus ostea with swabs of botanical essential oils, air purifiers, diets.

• **Phenotype:** observable characteristics of a disease. **Endotype:** pathophysiologic mechanisms of a disease.

• **Modern medicine:** determination of specific phenotypes and endotypes of a disease → personalized therapy → improved outcomes.

• **Advantages of endotyping:** (i) facilitates development of biomarkers for diagnosis and prognosis; (ii) facilitates association to genetic and environmental factors; (iii) improves personalized therapy.

• **CRS phenotypes:** (i) CRS with nasal polyps (CRSsNP): 4% of the population, TH2 environment, responds better to intranasal corticosteroids; (ii) CRS without nasal polyps (CRSsNP): ↑ remodeling (TGF-β, MMP, TIMP, collagen).

• **Possible CRS endotypes:** (i) fungal-induced endotype (eg. allergic fungal RS); (ii) S. aureus-induced endotype (superantigens favor TH2 milieu; IL-4 and IL-13 ↓ immunity to S aureus); (iii) mucosal barrier defect endotype; (iv) innate immune defect endotype; (v) TH2/IgE/eosinophilic endotype; (vi) TH17/neutrophilic endotype; (vii) autoimmune endotype; (viii) drug-induced endotype (eg. AERD); (ix) remodeling endotype.

• **EXPANDING THE PARADIGM OF EOSINOPHILIC ESOPHAGITIS: MAST CELLS AND IL-9**


  • **Eosinophilic esophagitis (EoE):** eosinophil infiltration into esophageal mucosa → inflammation (vomiting, dysphagia, abdominal pain, failure to thrive, low response to acid-suppressive therapy); probable cause: exaggerated immune response to food allergens or aeroallergens; pathogenic factors: (i) ↑ CCL26 (eotaxin-3) → action through CCR3 → ↑ eosinophil attraction; (ii) ↑ IL-5 → ↑ eosinophil production, attraction, activation and survival.

  • **Otani et al** (J Allergy Clin Immunol 2013; 131: 1576-82): beneficial effect of anti–IL-5 treatment in EoE was related to ↓ in mast cell/eosinophil couplets (esophageal eosinophils and adjacent tryptase-positive mast cells).

  • **New contribution to EoE pathogenesis:** eosinophils produce IL-9 → ↑ mast cell infiltration and activation → interplay between eosinophils and mast cells can be associated with EoE severity.

  • **Which cells produce IL-9?** (i) TH2 cells; (ii) TH9 cells (transcription factors: GATA3, PU.1, IRF4); (iii) type 2 cytokine–producing innate lymphoid cells (ILC2, natural helper cells or nuocytes); (iv) eosinophils.
• Stimulus for IL-9 production: TGF-β (produced by mast cells, eosinophils, Tregs) + IL-4 (produced by TH2 cells, ILC2, basophils) → TH9 cell differentiation; IL-9 production by eosinophils and ILC2.


  • GOF mutations in STAT1 → ↑ response to interferons and IL-27 → TH17-cell deficiency, chronic mucocutaneous candidiasis (CMC), susceptibility to certain bacterial infections, autoimmunity. New described phenotypes include IPEX-like syndrome and disseminated coccidioidomycosis and histoplasmosis.

  • Authors report 4 related subjects with a novel GOF mutation in the coiled-coil domain of STAT1.

  • **Patient 1** (60 yrs old): CMC; lung infections by P aeruginosa, S pneumoniae, Serratia sp, M avium and RSV; HPV-positive squamous cell carcinoma of palate; basal cell carcinoma; shingles; fibromuscular dysplasia with carotid and celiac/splenic artery dissection; IgG2 subclass deficiency that progressed into frank hypogammaglobulinemia; B-cell lymphopenia.

  • **Patient 2** (30 yrs old, daughter of patient 1): CMC; pneumonia; chronic bronchitis; otitis media; sinusitis; B-cell lymphopenia; IgG2 subclass deficiency.

  • **Patients 3** (6 wks old) and **4** (24 months old): children of patient 2; both carry the GOF STAT1 mutation but have no manifestations of immunodeficiency.

  • **Remarkable laboratory findings:** (i) STAT1 hyperphosphorylation in T cells after stimulus with IL-21; (ii) ↓ IL-17A–secreting CD4+ cells; (iii) overexpression of PD-L1 on naive CD4+ T cells; (iv) ↑ B-cell apoptosis (Annexin V and 7-AAD staining; caspase activity); (v) humoral deficiency.

  • **Hypothesis:** STAT1 GOF mutations → ↑ response to IL-27 → overexpression of PD-L1 on naive T cells after stimulation with IL-27 → ↑ PD-1/PD-L1 interaction → ↓ TH17 commitment, ↓ TFH help to B cells?


  • SCID requires urgent therapy with HSCT → (i) ideally, HSCT should be performed with an HLA-identical donor; (ii) if an identical donor is not available, T-lymphocyte–depleted (TCD) HSCT from an HLA-mismatched donor can be performed (75-87% survival); (iii) T-cell depletion ↓ risk of GVHD; (iv) B-cell depletion ↓ risk of EBV-related lymphoproliferation.

  • Authors report 5 virus-infected SCID patients who received parental HLA-haploidentical TCD HSCT (2 received CD34+–selected marrow; 3 received CD3/CD19-depleted peripheral blood stem cells) → 4 patients achieved immunoreconstitution and viral clearance; 1 patient died.

  • **TCD HSCT** can quickly restore immunity to achieve viral clearance in SCID patients.
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**PEARLS IN ALLERGY AND IMMUNOLOGY**  June 2013

• **INHIBITION OF HUMAN B-CELL DEVELOPMENT INTO PLASMABLASTS BY HISTONE DEACETYLASE INHIBITOR VALPROIC ACID** (Kienzler AK, Rizzi M, Reith M, Nutt SL, Eibel H. J Allergy Clin Immunol 2013; 131: 1695-1699):

- Naive B cells encounter microbial antigen for the 1st time and differentiate into: (i) short-lived plasmablasts, which produce early protective immunoglobulins; (ii) long-lived plasma cells, which maintain long-term immunoglobulin production; (iii) memory B cells, which quickly activate after repetitive infection.

- B cell differentiation is strictly linked to proliferation.

- Histone deacetylase (HDAC) inhibitors: novel anticancer drugs (regulate proliferation and apoptosis of tumor cells); immunomodulatory properties at low doses (↓ T-cell proliferation, ↑ TH2 cytokine production, ↑ Treg function).

- Valproic acid (VPA): antiepileptic drug; inhibits class I (including HDAC1 and HDAC2) and class IIa HDACs → ↓ migratory capacity of dendritic cells, ↓ T-cell activation → ↓ experimental autoimmune diseases.

- Authors studied the in vitro effect of VPA (at low therapeutic concentration: 0.25 mmol/L = 42 mg/L) in human B-cell activation and differentiation → (i) without VPA, during 9 days of cultivation with CD40L + IL-21, naive B cells gradually differentiated into plasmablasts (CD27$^{\text{high}}$ CD38$^{\text{high}}$); (ii) VPA ↓ naive B-cell proliferation and differentiation into plasmablasts in a dose-dependent manner; (iii) VPA did not ↓ memory B-cell reactivation and differentiation into plasmablasts; (iv) VPA did not ↓ naive B-cell survival; (v) VPA ↓ IgM, IgG and IgA production from stimulated naive B cells, but not from stimulated memory B cells; (vi) VPA did not change CD40, IL-21R, CD86, AICDA, JAK3, STAT3 or STAT5 expression or phosphorylation in activated naive B cells; (viii) VPA ↓ T-cell proliferation induced by CD3 and CD28 stimulation.

- Author’s commentaries: (i) previous reports showed antibody defects in children, but not adults, taking VPA → hypothesis: adults have more memory B cells, children have more naive B cells (VPA affects proliferation and differentiation of naive B cells, but not memory B cells); (ii) B-cell responses against new encountered microbes and vaccines may be ↓ in children taking VPA; (iii) HDAC inhibitors may help in autoimmune diseases (eg. in SLE, 60% of the autoantibodies against nuclear antigens are produced by autoreactive short-lived plasma cells).

• **LESS SEVERE CLINICAL MANIFESTATIONS IN PATIENTS WITH HEREDITARY ANGIOEDEMA (HAE) WITH MISSENSE C1INH GENE MUTATIONS** (Bors A, Csuka D, Varga L, Farkas H, Tordai A, Füst G, Szilagyi A. J Allergy Clin Immunol 2013; 131: 1708-1711):

- HAE → type I: ↓ level of C1 inhibitor (C1INH); type II: ↓ function of C1INH → recurrent attacks of bradykinin-mediated angioedema, potentially life-threatening.

- Authors studied 106 subjects with type I HAE confirmed by genetic sequencing (mutations of the SERPING1 gene) → a) patients with missense mutations had: (i) onset of symptoms at older age, (ii) fewer total angioedema attacks, (iii) fewer severe angioedema attacks, (iv) less use of C1INH concentrate; b) a polymorphism in factor XII gene was associated with higher factor XII levels and earlier onset of symptoms in type I HAE patients.

- Author’s commentary: the type of mutation in SERPING1 gene may influence the clinical course of patients with type I HAE → more personalized therapy?
• **MICROBIAL INFLUENCE ON TOLERANCE AND OPPORTUNITIES FOR INTERVENTION WITH PREBIOTICS/PROBIOTICS AND BACTERIAL LYSATES** *(Pfefferle PI, Prescott SL, Kopp M. J Allergy Clin Immunol 2013; 131: 1453-1463)*:

  - Exaggerated immune responses: (i) to self antigens: autoimmune diseases; (ii) to beneficial or innocuous foreign antigens: allergic diseases.
  
  - Microbiota: all microorganisms colonizing epithelial surfaces.
  
  - ‘Tolerogenic’ microbiota: microorganisms that: a) regulate immune system development and homeostasis; b) promote tolerance in the early life to: (i) self antigens; (ii) beneficial or innocuous foreign antigens.
  
  - *Factors that influence microbiota in the offspring*: (i) during pregnancy: maternal diet, maternal environment, maternal microbiota; (ii) during partum: type of delivery, use of antibiotics; (iii) during postnatal period and infancy: breastfeeding, diet, use of antibiotics, microbial environment (eg. exposure to farms), pets.
  
  - Which microbes are ‘tolerogenic’? Not well defined; likely Lactobacillus and Bifidobacterium sp.
  
  - Factors that may disturb ‘tolerogenic’ microbiota: (i) altered microbiota in the mother; (ii) Cesarean delivery; (iii) insufficient breastfeeding; (iv) inadequate diet; (v) antibiotic use.
  
  - How do maternal environmental exposures increase allergy risk in the offspring? Hypothesis: (i) epigenetic modifications (eg. ↑ methylation of FOXP3 in germinal cells); (ii) altered cytokine balance (eg. TH2 predominance, Treg deficiency); (iii) altered immune responses in the placenta (eg. ↑ methylation of FOXP3 in the placenta).
  
  - Products that may promote or restore ‘tolerogenic microbiota’ and tolerance: (i) probiotics: ‘tolerogenic’ bacteria (eg. Lactobacillus rhamnosus, Bifidobacterium sp); (ii) prebiotics: nutrients that promote ‘tolerogenic’ bacteria (eg. FOS, GOS).
  
  - Evidence about probiotics: (i) around half of the studies using probiotics (during pregnancy and/or early postnatal period) show ↓ eczema incidence (25-50% reduction); other studies show no benefit, even with similar probiotic strains and protocols; (ii) probiotics have not shown consistent effects on allergic sensitization or respiratory allergies; (iii) several meta-analyses agree that probiotics ↓ eczema risk but not other allergic outcomes; (iv) effects of maternal probiotic use on cord blood immune responses are conflicting; (v) good safety profile.
  
  - Limitations to analyze study results about probiotics: (i) methodological differences between studies; (ii) different probiotic strains were used, including mixes; (iii) different ways of administration; (iv) different timing (prenatal, postnatal or both); (v) different doses; (vi) different clinical outcomes; (vii) different population characteristics; (viii) limited follow-up of the patients; (ix) high dropout rate in several studies.
  
  - Benefits of prebiotic use during pregnancy: (i) possible ↓ in some allergic manifestations; (ii) probable benefit in chronic metabolic diseases (obesity, diabetes); (iii) ↓ in constipation.
  
  - Current evidence shows that prebiotics and probiotics might contribute to prevention of atopic eczema but not asthma, allergic rhinitis or allergic sensitization. A combined antenatal and postnatal use of probiotics has been the most promising approach in high-risk children.
• **Uncertainties for research:** (i) which probiotic strain or prebiotic product should be used? (so far, L rhamnosus had the best results) (ii) when? (iii) how much? (iv) for how much time?

• **Bacterial lysates:** lyophilized extracts from single-strain or mixed bacterial cultures (aeropathogenic or endotoxin-containing gut bacteria) through chemical or mechanical lysis.

• **Evidence about bacterial lysates from aeropathogenic bacteria:** (i) may ↑ secretory IgA levels against bacteria; (ii) may skew perinatal TH2 milieu to TH1/Treg milieu; (iii) may ↓ acute respiratory infections; (iv) may ↓ asthma initiation and exacerbations; (iv) good safety profile.

• **Evidence about bacterial lysates from endotoxin-containing gut bacteria:** (i) may ↓ eczema risk in children with parental history of allergy.

• **Manipulation of the microbiome** could prevent: (i) allergic and autoimmune phenomena; (ii) metabolic diseases; (iii) mood and behavior diseases.

  
  • **Severe combined immunodeficiencies (SCID):** genetic defects characterized by marked ↓ of T-cell development and function; susceptibility to opportunistic infections; require urgent therapy with HSCT or gene therapy; newborns can be screened for SCID by measuring TREC levels (T-cell receptor excision circles).

  • **Combined immunodeficiencies (CID), also called leaky-SCID or T+ SCID:** profound T-cell dysfunction with significant numbers of circulating T cells.

  • **TREC analysis:** excellent sensitivity to detect SCID; CID may not be detected.

  • **MHC class II deficiency** (bare lymphocyte syndrome): autosomal recessive CID; 4 disease-causing genes (RFXANK, RFXAP, RFX5 and CIITA); CD4 T-cell lymphopenia; fatal course without HSCT; TREC levels in this condition have not been reported.

  • Authors report 2 infants with MHC class II deficiency who had normal TREC levels at birth (142 and 97 copies; normal values ≥40 copies).

  • **Patient’s characteristics:** (i) early presentation (3 and 6 months of age) with failure to thrive, intractable diarrhea and severe respiratory infections; one patient had severe neurologic impairment (likely associated with a homozygous deletion in CTNND2 on chromosome 5p15.2); (ii) profound hypogammaglobulinemia; (iii) ↓ CD4 T-cells; (iv) ↓ lymphocyte proliferation; (v) ↓ HLA-DR expression on peripheral blood lymphocytes; (vi) genetic mutations associated with MHC class II deficiency; (vii) one patient died after HSCT, the other patient was not candidate for HSCT because of severe lung and neurologic disease.

  • **Author’s commentary:** patients with MHC class II deficiency and other CID may not be detected by newborn screening using TREC levels.

• **PRIMARY PREVENTION OF ALLERGY BY USING PROTEIN HYDROLYSATE: AN ACHIEVABLE OBJECTIVE?** (Arshad SH. J Allergy Clin Immunol 2013; 131: 1574-1575):
• **Allergic diseases** have dramatically increased. Proposals to stop this trend: (i) avoid allergen; (ii) give allergen at an early age; (iii) restore tolerance to allergens; (iv) create a ‘tolerogenic environment’ (probiotics, prebiotics, vit A, vit D, breastfeeding, omega-3 fatty acids).

• Some **high-risk infants** (parent or sibling with a history of allergy) cannot receive enough breastfeeding at their first months of life → how to feed them to prevent allergy? Proposals: (i) cow’s milk; (ii) partially hydrolyzed formulas (HFs): most peptides with molecular weights <10 kDa; (iii) extensively HFs: 95% of peptides with molecular weights <1.5 kDa; (iv) soy formulas.

• **German Infant Nutritional Intervention (GINI):** largest RCT investigating the primary preventive effect of HFs on allergic manifestations → 2252 high-risk infants were assigned to 1 of 4 formulas in the first 4 months of life if breastfeeding was not feasible: (i) cow’s milk (CM), (ii) partially hydrolyzed whey formula (pHF-W), (iii) extensively hydrolyzed whey formula (eHF-W), (iv) extensively hydrolyzed casein formula (eHF-C) →

  • **Results:** (i) at 1 yr of age: eHF-C group had ↓ atopic dermatitis (AD), GI food allergy and allergic urticaria compared with CM group; pHF-W group had ↓ AD compared with CM group; (ii) at 3 yrs of age: eHF-C and pHF-W groups had ↓ AD compared with CM group; no effect on asthma; (iii) at 6 yrs of age: similar preventive effect on AD; (iv) at 10 yrs of age: no ongoing protective effect on AD between the ages of 7 and 10 yrs; eHF-C and pHF-W groups had ↓ cumulative incidence of AD, primarily driven by the protective effect observed in the first 6 yrs of life.

  • **Conclusions:** (i) eHF-C advantages: most effective (7 infants need to be treated to prevent 1 case of AD); (ii) pHF-W advantages: less expensive and more palatable; (iii) no evidence that HFs are better than maternal milk; (iv) no evidence on prevention of asthma, allergic rhinitis or allergen sensitization; (v) protective mechanisms of HFs are not clear.

  • **Limitations of the trial:** (i) high dropout rate (64.4%); (ii) data at 1 and 3 yrs was based on investigator’s evaluations; data at 6 and 10 yrs was based on parent’s reporting.

• **REDUCED SEROLOGIC RESPONSE TO MUMPS, MEASLES, AND RUBELLA (MMR) VACCINATION IN PATIENTS TREATED WITH INTRAVENOUS IMMUNOGLOBULIN (IVIG) FOR KAWASAKI DISEASE (KD)** (Tacke CE, Smits GP, van der Klis FRM, Kuipers IM, Zaaijer HL, Kuijpers TW. J Allergy Clin Immunol 2013; 131: 1701-1703):

  • KD: high risk of coronary aneurisms if untreated; therapy includes high-dose IVIG.

  • IVIG is taken from thousands of donors to amplify the antibody repertoire → passively acquired antibodies may interfere with immune response to vaccines.

  • Authors evaluated the antibody response to MMR vaccination in 198 patients (1-9 yrs old) treated with IVIG for KD (protective antibody levels: ≥0.2 IU/mL for measles, ≥10 IU/mL for rubella, ≥45 RU/mL for mumps) → (i) compared to healthy controls, patients vaccinated within 6 months after IVIG had ↓ antibody levels against measles, mumps and rubella; (ii) patients vaccinated between 6 and 9 months after IVIG had ↓ levels only against measles; (iii) patients vaccinated >9 months after IVIG had similar antibody responses than healthy controls.

  • **Author’s commentaries:** (i) MMR vaccination should be postponed at least 9 months after IVIG use; (ii) the 11-month interval recommendation by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics may be longer than strictly necessary.
• **SERUM TRYPTASE DETERMINATION IN PATIENTS WITH ACUTE ALLERGIC REACTIONS** (Vitte J, Bongrand P. J Allergy Clin Immunol 2013; 131: 1714):

  - How to diagnose anaphylaxis? (i) clinical criteria; (ii) laboratory criteria: serum mediators (tryptase, histamine, platelet-activating factor [PAF]) produced by allergy effector cells.

  - Authors discuss the limitations of a recent study (Vadas et al. J Allergy Clin Immunol 2013; 131: 144-9), which concluded that PAF levels correlated better with anaphylaxis severity than tryptase or histamine levels.

  - Author's commentaries: (i) each patient's peak tryptase level must be compared with his/her own basal tryptase level (anaphylaxis may ↑ serum tryptase levels as little as 135% or 2 mg/L); (ii) tryptase levels should be measured between 30 to 120 min after anaphylaxis onset (serum tryptase half-life is about 2 hrs); (iii) food-induced anaphylaxis may not ↑ tryptase levels.

• **TREATMENT OF HYPOGAMMAGLOBULINEMIA IN ADULTS: A SCORING SYSTEM TO GUIDE DECISIONS ON IMMUNOGLOBULIN REPLACEMENT** (Agarwal S, Cunningham-Rundles Ch. J Allergy Clin Immunol 2013; 131: 1699-1701):

  - B-cell defects: (i) severe defects (eg. agammaglobulinemia) → replacement with IV or SC immunoglobulin; (ii) modest defects → which patients should receive immunoglobulin?

  - Limitations of immunoglobulin substitution: (i) expensive products; (ii) lifelong therapy.

  - Authors describe a retrospectively-designed scoring system based on laboratory (IgG, IgA, IgM, specific antibody responses) and clinical data (infections, lymphoproliferation, autoimmune and inflammatory diseases, failure to thrive, bronchiectasis, lung function tests), which may help to decide which adult patients with modest humoral defects should receive immunoglobulin.

  - Author's commentaries: (i) this score requires validation, standardization and proof of concept in larger populations of patients with hypogammaglobulinemia; (ii) this score might need modifications before applying to a pediatric population.


  - Risk factors for allergic contact dermatitis (ACD): (i) atopic dermatitis; (ii) skin barrier defects (eg. filaggrin defects?); (iii) repetitive contact with potential allergens.

  - When to suspect ACD? Chronic recurrent or therapy-resistant eczema, even in young children.

  - Contact allergens in children: (i) metals: nickel (most common contact allergen), cobalt, chromate; (ii) preservatives, solvents, emulsifiers; (iii) rubber chemicals; (iv) topical drugs (chlorhexidine, neomycin, steroids, emollients, natural remedies); (v) fragrances.

  - Where are contact allergens frequently encountered? (i) shoes: potassium dichromate, p-phenylenediamine (PPD), p-tert-butylphenol-formaldehyde (PTBF) resin; (ii) perfumes; (iii) jewelries: nickel; (iv) cosmetics; (v) temporary or permanent tattoos: PPD; (vi) shin guards: rubber chemicals, thiourea derivates; (vii) hair dyes: PPD; (viii) clothing: dyes (often involve thighs), formaldehyde ('wrinkle resistant'), rubbers; (ix) diapers: ‘Lucky Luke’ dermatitis...
(sensitization to rubber components → affection of outer buttocks and hips, similar to a cowboy’s gun belt holsters), miliaria-like rash under the stickers; (ix) toys: especially toy-cosmetic products (lipstick, eye shadow).

- **Diagnosis:** patch tests (gold standard) → (i) include all relevant allergens according to the clinical history; (ii) patch tests with topical corticosteroids should be read at ≥7 days; (iii) negative patch test results do not fully exclude ACD.

- **Treatment:** (i) topical steroids (be careful with sensitization); (ii) emollients (be careful with sensitization); (iii) allergen avoidance (be careful with product’s labeling).

- **Prevention:** (i) avoid repetitive contact with potential allergens (eg. nickel-containing jewelries, PPD-containing tattoos); (ii) promote laws about product’s manufacturing (eg. nickel content in jewelries); (iii) correct skin barrier in patients with atopic dermatitis; (iv) improve labeling of manufactured products (eg. cosmetics).

- **Causes of perioral dermatitis in children:** (i) atopic dermatitis; (ii) lip licking; (iii) inhaled steroids; (iv) ACD: sunscreens with a high protection factor, toothpaste, dental fillings, chewing gum.

- **Products that may contain or cross-react with PPD:** hair dyes, azo dyes, tattoos, sulfonamides, p-aminobenzoic acid sunscreens, benzocaine, procaine.

### BARLEY’S LIPID TRANSFER PROTEIN: A NEW EMERGING ALLERGEN IN PEDIATRIC ANAPHYLAXIS


- Barley (Hordeum vulgare): grain commonly used in alcoholic beverages (mostly whiskey and beer); most important allergens: prolamins (Hor v 21), alpha- or beta-amylase inhibitors (Hor v 15, Hor v 16, Hor v 17), lipid transfer protein (LTP, Hor v 14); amylase inhibitors are involved in baker’s asthma induced by barley flour; LTP is involved in allergy to barley’s beer.

- Authors report the case of a 7-yr-old girl with barley allergy → (i) clinical history: anaphylactic shock after ingestion of cow’s milk and cereals containing barley malt; (ii) laboratory: negative SPT and sIgE to cow’s milk, wheat, corn, lupine, buckwheat, honey, rye, oat and soy; positive SPT to barley (3 mm to pearl barley, 2 mm to a heavily malted beer, 10 mm to purified barley and barley malt); positive sIgE to barley (1.47 kU/l); SDS-PAGE immunoblotting and mass spectrometry revealed IgE binding to barley’s LTP.

- **Author’s commentaries:** (i) 1st reported case of barley allergy in children; (ii) barley is frequently used in the agro-food chain → avoidance is difficult because of hidden barley allergens in ‘cereal-based’ products; (iii) consider barley’s LTP allergy in children with severe reactions to cereals → allergen tests should include barley and/or barley’s LTP.

### COMPARISON BETWEEN TWO MAINTENANCE FEEDING REGIMENS AFTER SUCCESSFUL COW’S MILK ORAL DESENSITIZATION


- Cow’s milk allergy: 2-3% of infants; often resolves at childhood or adolescence; conventional therapy: avoidance (↓ QoL, does not prevent accidental exposure), epinephrine autoinjectors; novel treatment: oral immunotherapy (main risk: adverse effects).
After desensitization to cow’s milk, it has been recommended a daily intake to maintain tolerance. Limitation: this maintenance regimen is not suitable for some families.

Authors performed a RCT in 32 children (4–13 yrs old) after successful desensitization to cow’s milk (IgE-mediated allergy) → group A (n=16) received 150–200 ml of cow’s milk twice a week; group B (n=16) received 150–200 ml daily → both maintenance regimens (follow up: 1 yr) had similar efficacy and safety; most adverse reactions occurred during concurrent exercise or infection.


How to prevent allergy initiation? Most proposals over the last 25 yrs have failed or remain controversial: (i) early or late food introduction in infants; (ii) extension of breastfeeding over the first 4 months; (iii) ↓ exposure to indoor allergens; (iv) use of bacterial products.

How to prevent asthma initiation? Most proposals have failed: (i) antihistamines (cetirizine, levocetirizine and desloratadine) in patients with atopic dermatitis; (ii) pimecrolimus in patients with atopic dermatitis; (iii) inhaled corticosteroids in children with recurrent wheeze.

Current recommendations: (i) exclusive breastfeeding for at least 4 months; (ii) use hydrolyzed formulas in high-risk infants when breastfeeding is not available (may ↓ cow’s milk allergy; may ↓ atopic dermatitis); (iii) supplement prebiotic oligosaccharides to infant formulas; (iv) avoid tobacco smoke during pregnancy and infancy; (v) consider specific allergen immunotherapy to prevent allergy progression.

How to improve research on allergy prevention? Focusing on specific allergic diseases (eg. targeting respiratory viruses [RSV, rhinovirus] and allergens to prevent allergic asthma).


Factors that may ↓ risk of atopic dermatitis and asthma: older siblings, natural delivery, farm exposure, certain infections, attending childcare, tolerogenic microbiota, prebiotics, probiotics.

Food allergy burden has ↑ worldwide; origin may involve genetic and environmental factors.

Authors performed a systematic review of 46 studies to identify the association between food allergy and several factors that likely influence microbial exposure → (i) study heterogeneity precluded metaanalysis; (ii) factors that showed association with ↑ food allergy: Cesarean delivery; (iii) factors that showed association with ↓ food allergy: having siblings, attending childcare, farm exposure, endotoxin exposure, certain infections, probiotic use, tolerogenic microbiota; (iv) further prospective studies using DBPCFCs as an outcome are required.


Lentil (Lens culinaris): legume; important protein source in many countries; lentil seeds are a frequent cause of IgE-mediated allergy in several countries.
Authors studied 30 children (1.3-16.1 yrs old) with IgE-mediated lentil allergy (diagnosis: consistent clinical history + positive SPT and/or sIgE + positive open OFC in some patients; the best cutoff level of sIgE to predict clinical reactivity was 4.8 kU/l [sensitivity: 50%, specificity: 100%, PPV: 100%, NPV: 56%] → (i) median age at onset of symptoms: 1.5 yrs; (ii) most frequent symptoms: cutaneous (97%), respiratory (30%); (iii) anaphylaxis was reported in 27% of patients; (iv) 4 patients also had symptoms after exposure to steam from cooked lentils; (v) 17% of children were only sensitized to lentils; (vi) most common concomitant food allergies: chickpea, peanut, pea, sesame, hazelnut, walnut, egg, milk; (vii) 50% of patients outgrew lentil allergy by 3.5 yrs old; (viii) children with an initial lentil sIgE <4.9 kU/l were more prone to outgrow allergy; (x) risk of anaphylaxis was remarkably high if lentil sIgE >23 kU/l.

* I suggest revising the journal AllergyWatch, it is a very useful tool to keep updated in the specialty of Allergy and Clinical Immunology:

http://www.acaai.org/Pages/allergy-watch.aspx