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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August 2013 – content:

• A CASE OF RELAPSING POLYCHONDRI TIS AND HYPOGAMMAGLOBULINEMIA (Gavrilova T, Capitle E. Ann Allergy Asthma Immunol 2013; 111: 147–148).

• ADVANCES IN DIAGNOSIS AND MANAGEMENT OF INSECT STING ALLERGY (Golden DBK. Ann Allergy Asthma Immunol 2013; 111: 84-89).

• ATTENTION-DEFICIT/HYPERACTIVITY DISORDER STIMULANT MEDICATION REACTION MASQUERADING AS CHRONIC COUGH (Leibel S, Bloomberg G. Ann Allergy Asthma Immunol 2013; 111: 82-83).


• ERTAPENEM-INDUCED ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS WITH CROSS-REACTIVITY TO OTHER BETA-LACTAM ANTIBIOTICS ON PATCH TESTING (Fernando SL. Ann Allergy Asthma Immunol 2013; 111: 138-139).

• FERTILITY AND HUMAN SEMINAL PLASMA HYPERSENSITIVITY (Tan J, Bernstein JA. Ann Allergy Asthma Immunol 2013; 111: 145-146).


• XENON VENTILATION COMPUTED TOMOGRAPHY RULES: NEW TECHNOLOGY MAY OPEN UP FURTHER UNDERSTANDING IN ASTHMA (Phipatanakul W, Teague WG. Ann Allergy Asthma Immunol 2013; 111: 81).


• BRIDGING IMMUNITY AND LIPID METABOLISM BY GUT MICROBIOTA (Greer RL, Morgun A, Shulzhenko N. J Allergy Clin Immunol 2013; 132: 253-262).

• EOSINOPHILIC ESOPHAGITIS TREATED WITH IMMUNOTHERAPY TO DUST MITES (Ramirez RM, Jacobs RL. J Allergy Clin Immunol 2013; 132: 503-504).


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• A CASE OF RELAPSING POLYCHONDRTIS AND HYPOGAMMAGLOBULINEMIA (Gavrilova T, Capitle E. Ann Allergy Asthma Immunol 2013; 111: 147–148):

  - Relapsing polychondritis (RP): recurrent immune-mediated inflammation and destruction of the cartilage; 30% of patients have other autoimmune or hematologic diseases; typical onset = 40-60 yrs of age; female/male ratio = 3/1; affected areas: cartilage of the ears (most frequent), respiratory tract, joints, heart, blood vessels; diagnosis: 3 out of 6 criteria (chondritis of pinna, nasal chondritis, nonerosive inflammatory polyarthritis, ocular inflammation, respiratory tract chondritis, cochlear or vestibular dysfunction); treatment: corticosteroids (1st line), immunosuppressants, biologic agents (anti-TNFα, IL-1R antagonists, anti-IL-6, anti-CD20).

  - Authors report the case of a 37-yr-old man with RP (3-yr history of recurrent ear inflammation, several courses of prednisone) and hypogammaglobulinemia (↓ IgG, ↓ IgM, normal IgA, ↑ IgE, normal B-cell and T-cell counts, no severe infections) of ‘unknown origin’ (no monoclonal disease, no autoimmune disease, no proteinuria, no enteropathy) → significant improvement of RP with prednisone (15 mg/day) and methotrexate (20 mg/wk).

  - Own commentary: frequent corticosteroid use could have caused the hypogammaglobulinemia?

• ADVANCES IN DIAGNOSIS AND MANAGEMENT OF INSECT STING ALLERGY (Golden DBK. Ann Allergy Asthma Immunol 2013; 111: 84-89):

  - Epidemiology of insect sting allergy: (i) large local reactions: >5% of the population; (ii) systemic reactions: 1% of children, 3% of adults; (iii) sensitization is more frequent than allergy (↑ specific IgE in 20% of adults; often transient; persistent sensitization is associated with ~15% chance of systemic reaction to a subsequent sting); (iv) 50% of fatal sting reactions occur in individuals with no prior history of a reaction.

  - Low-risk patients: (i) previous large local sting reactions (risk of subsequent systemic reaction: 5-10% [mainly mild], risk of requiring epinephrine in subsequent reactions <3%); (ii) children with skin-limited reactions (risk of subsequent severe systemic reaction <3%)

  - High-risk patients: (i) prior rapid and severe sting reactions; (ii) advanced age; (iii) ↑ serum tryptase levels (>11.4 ng/mL) [always look for mast cell disorders in these patients]; (iv) ↑ serum PAF levels; (v) honeybee allergy; (vi) underlying medical conditions.

  - Diagnostic tests: (i) purposes: confirm allergic sensitization, define risk of future reactions (level of sIgE [skin or in vitro testing] correlates with frequency [but not severity] of subsequent systemic reactions); (ii) indications: history of systemic reaction and high risk for subsequent reactions (a positive test in a low-risk patient may lead to unnecessary fear and VIT use).

  - Diagnostic pitfalls of conventional tests (skin testing and serum sIgE testing): (i) inaccurate to screen general population for venom allergy (limited negative and positive predictive value); (ii) levels of sIgE [skin or serum testing] do not correlate with severity of reactions; (iii) up to 30% of subjects with a history of systemic reaction may have negative skin test results (potential reasons: refractory period [4-6 wks after the reaction], low potency extracts, inherent variability of venom skin tests); (iv) 15% of subjects with a history of systemic reaction may have no detectable serum sIgE (~6% of such individuals have a systemic reaction to a challenge sting); (v) a positive test result reflects IgE-sensitization but not always clinical allergy.
• novel diagnostic advances: (i) basophil activation testing (had higher sensitivity than intradermal skin testing in patients with negative serum slgE and SPT results; predicted efficacy and risk of VIT); (ii) use of recombinant venom allergens (distinguished cross-reactivity from dual specific sensitization to honeybee and vespid venom).

• treatment: (i) insect avoidance, (ii) epinephrine autoinjectors, (iii) venom immunotherapy (VIT).

• treatment should be personalized according to: age, severity of previous reactions, results of allergy testing, risk of insect exposure, patient fears and preferences (QoL is very important).

• Authors discuss important issues about VIT: indications, dosing (initiation and maintenance phases), duration, predictors of efficacy and risk.

• prognosis: (i) the single best predictor of a sting reaction is the history of reaction to a previous sting; (ii) it is not possible to assure ‘zero’ risk of a systemic sting reaction.

• chance of requiring epinephrine for a sting reaction: 1% in random adults; 2-3% in large local reactors, children with cutaneous systemic reactions, patients undergoing VIT, patients who discontinue VIT after 5 yrs and have no high-risk factors.

• attention-deficit/hyperactivity disorder stimulant medication reaction masquerading as chronic cough (Leibel S, Bloomberg G. Ann Allergy Asthma Immunol 2013; 111: 82-83):

  • chronic cough in children: daily cough >4 wks; frequent consult to allergists; most common causes: asthma, protracted bacterial bronchitis, chronic rhinosinusitis, GERD; unusual causes: tic disorders (e.g. Tourette syndrome).

  • Authors report the case of an 8-yr-old girl with chronic dry cough and tics (7 months of duration, daily basis, occasional worsening at nights, no nasal symptoms, no wheezing, negative allergy testing, normal chest radiograph, no response to therapeutic trials [azithromycin, loratadine, inhaled albuterol, oral prednisolone]) related to initiation of dextroamphetamine therapy (a stimulant medication for attention-deficit/hyperactivity disorder) → successful treatment: discontinuation of dextroamphetamine (cough and tics resolved within 48 hrs).


  • anaphylaxis: potentially fatal severe allergic reaction; treatment: epinephrine (1st line, recommended as intramuscular injection); at-risk patients are indicated to carry epinephrine autoinjectors (limitations: low rates of carrying, underuse, incorrect injection technique, unintentional injections).

  • epinephrine autoinjectors: EpiPen (most known), Auvii-Q (novel autoinjector designed to ↓ use-related mistakes [safety guard on the same end as the needle, audible and visual instructions, retractable needle to minimize time beneath the skin]).

  • Authors compared the bioavailability, safety and tolerability of 0.3 mg of epinephrine injected with Auvii-Q and EpiPen in 71 healthy adults (18-45 yrs old) → (i) both autoinjectors had no significant differences in epinephrine peak concentration and epinephrine total exposure; (ii) similar safety profiles; (iii) most adverse events were mild (98%), all resolved spontaneously.
• **CONGENITAL NEPHROTIC SYNDROME AND AGAMMAGLOBULINEMIA: A THERAPEUTIC DILEMMA** (Payne KM, Nelson MR, Petersen MM. Ann Allergy Asthma Immunol 2013; 111: 142-143):

  - **Uses of intravenous immunoglobulin (IVIG):** replacement therapy in primary and secondary immunodeficiencies; immunomodulatory therapy in autoimmune and inflammatory diseases.
  - **No consensus on IVIG replacement in protein-losing diseases.**
  - **Congenital nephrotic syndrome:** protein loss through urine → ↓ IgG → ↑ infection risk → antibiotic prophylaxis is recommended.
  - **Is it appropriate to use IVIG in patients with congenital nephrotic syndrome?** Controversial because: (i) within 30 hrs, 55% of the IVIG could be found in the urine, (ii) IVIG is expensive, (iii) previous reports show that IVIG can be beneficial (↓ infections, ↓ proteinuria, ↑ kidney function) in pediatric and adult nephrotic syndrome.
  - **Authors report the case of a 1-month-old boy with congenital nephrotic syndrome (mutation in NPHS1 [nephrin gene]) and secondary agammaglobulinemia (IgG <70 mg/dL, normal B-cell count) unresponsive to subcutaneous immunoglobulin (up to 1 g, 3 times/week) → complications: sepsis by Klebsiella oxytoca (responded to antibiotics), severe bronchiolitis by RSV → treatment: bilateral nephrectomy, dialysis → no significant infections after nephrectomy, patient is waiting for kidney transplant.

• **DRESS SYNDROME WITH SUSPECTED STRONGYLOIDES INFECTION IN A PATIENT TREATED FOR HEPATITIS C** (Rampur L, Jariwala S, Amin B, Patel P, Rosenstreich DL. Ann Allergy Asthma Immunol 2013; 111: 138-139):

  - **Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome:** severe hypersensitivity reaction to drugs (e.g. allopurinol, sulfonamides, phenobarbital, carbamazepine, phenytoin, abacavir, telaprevir); clinical manifestations: rash, fever, lymphadenopathy, eosinophilia, multiorgan affection.
  - **Strongyloides stercoralis:** soil-transmitted helminth; affects ~30 million people worldwide; may cause autoinfection and persist for decades; clinical manifestations: vague GI or pulmonary symptoms, eosinophilia, adult respiratory distress syndrome, hyperinfection syndrome in immunocompromised patients (invasive filariform larvae carrying gut flora invade tissues → severe complications [e.g. meningitis, pneumonia, sepsis] → high mortality [as high as 87%]); diagnosis: serum IgG to Strongyloides (does not differentiate between current or previous infection, cross reacts with other helminth infections [e.g. filariasis, ascariasis, acute schistosomiasis], stool examination (low sensitivity).
  - **Authors report the case of a 55-yr-old man with DRESS syndrome** (erythematous maculopapular rash, fever, lymphadenopathy, eosinophilia, hepatitis, lymphopenia, positive IgG to HHV-6, ↑ IgE) associated with hepatitis C virus treatment (6 wks after starting peg-interferon alpha-2a, telaprevir and ribavirin, which cleared viral load) and suspected Strongyloides infection (positive IgG to Strongyloides, two negative stool examinations for ova and parasites) → successful treatment: oral prednisone, ivermectin (200 mg/kg/day for 2 days).
  - **Author’s commentary:** (i) be careful to use corticosteroids in patients with suspected Strongyloides infection (risk of hyperinfection syndrome).
• **ERTAPENEM-INDUCED ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS WITH CROSS-REACTIVITY TO OTHER BETA-LACTAM ANTIBIOTICS ON PATCH TESTING** (Fernando SL. Ann Allergy Asthma Immunol 2013; 111: 138-139):

  - **Acute generalized exanthematous pustulosis (AGEP):** rare drug-induced skin hypersensitivity (penicillins are frequent culprits; 2 previous case reports of carbapenem-induced AGEP); mortality rate=5%; treatment: stop culprit drug, corticosteroids.

  - Authors report the case of a 47-yr-old man with ertapenem-induced AGEP (fever, generalized pustular rash and marked neutrophilia 2 days after starting ertapenem for clindamycin-resistant erysipelas) confirmed by skin biopsy (intraepidermal and subcorneal spongiform pustules with papillary edema) and positive patch testing (ertapenem, meropenem, penicillin and cephalothin) → successful treatment: linezolid instead of ertapenem, no need for corticosteroids → AGEP resolved in 2 wks.

  - **Author’s commentary:** this case likely represents a type IVd hypersensitivity to the common β-lactam ring.

• **FERTILITY AND HUMAN SEMINAL PLASMA HYPERSENSITIVITY** (Tan J, Bernstein JA. Ann Allergy Asthma Immunol 2013; 111: 145-146):

  - **Seminal plasma hypersensitivity (SPH):** local or systemic allergic reactions minutes after vaginal exposure to semen; clinical manifestations: vaginal inflammation, urticaria, angioedema, wheezing, anaphylaxis; major allergen: PSA (other antigens have also been implicated); diagnosis: prevention of symptoms using condom, positive specific IgE by skin or in vitro testing (especially in systemic SPH); treatment: intravaginal graded challenge or subcutaneous desensitization using whole seminal fluid or seminal plasma proteins from sexual partner.

  - **Response to treatment:** (i) women with systemic SPH: usually successfully treated, no problems with infertility; (ii) women with localized SPH: variable responses to treatment, infertility is a common concern.

  - Authors performed a retrospective study to assess fertility in 12 women with localized SPH who were treated with subcutaneous immunotherapy to seminal plasma proteins → (i) 7 women had successful treatment (complete ↓ of symptoms), 2 'somewhat successful' (improvement of symptoms compared with baseline), 3 unsuccessful (no improvement of symptoms); (ii) 8 women were able to conceive (5 had term pregnancies), 2 were not able to conceive, 2 were not interested in conceiving.

  - **Author’s commentary:** infertility does not appear to be an inherent complication of localized SPH, regardless of treatment success.

• **SUCCESSFUL ORAL DESENSITIZATION TO LEVOTHYROXINE** (Fevzi D, Mustafa G, Ozgur K, Cetin T, Abdullah B, Sait Y, Ugur M, Osman S. Ann Allergy Asthma Immunol 2013; 111: 146-147):

  - **Previous reported reactions to levothyroxine:** urticaria, angioedema, eczematiform rash, fever, liver dysfunction. One patient was successfully desensitized with intravenous levothyroxine.

  - Authors report the case of a 35-yr-old woman (history of multiple ‘drug allergies’, including radiocontrast agent and NSAIDs) with Hashimoto’s disease and immediate reactions to oral levothyroxine (generalized itchy rash, dyspnea and palpitations 30 min after a 100 µg dose) →
atopy testing (solution of 25 µg levothyroxine in 1 mL of 0.09% phosphate-buffered saline): negative SPT (undiluted solution), positive intradermal reaction (1/100 wt/vol concentration) → successful treatment: oral desensitization (13 doses every 30 min).

- **XENON VENTILATION COMPUTED TOMOGRAPHY RULES: NEW TECHNOLOGY MAY OPEN UP FURTHER UNDERSTANDING IN ASTHMA** (Phipatanakul W, Teague WG. Ann Allergy Asthma Immunol 2013; 111: 81):
  - Assessment of asthma control is a challenge. Current methods: (i) clinical scores (e.g. ACT), (ii) lung function tests (e.g. spirometry); (iii) tests to assess inflammation (e.g. sputum eosinophils).
  - Air trapping indicates ventilation heterogeneity and predicts asthma exacerbation risk.
  - Jung et al (Ann Allergy Asthma Immunol. 2013; 111: 90-95) present a novel method to assess ventilation abnormalities in adults with asthma based on hyperpolarized xenon computed tomography (CT) → ventilation abnormalities correlated with metrics of asthma control, methacholine bronchoconstriction test results, sputum eosinophilia and distal airway obstruction (no correlation with large airway obstruction).
  - Author’s commentaries: (i) asthma does not uniformly affect the airways; (ii) structural and functional changes as identified by xenon CT can be highly predictive of asthma outcomes.

  - Allergic fungal rhinosinusitis (AFRS): noninvasive form of fungal disease (mainly by Aspergillus sp); clinical history: chronic rhinosinusitis with nasal polyps (CRSwNP), ↑ total IgE, ↑ specific IgE to Aspergillus sp (skin or in vitro testing), eosinophilic mucous plugs with fungal hyphae ('allergic mucin'); complications: inflammation/erosion/compression of contiguous structures (e.g. bone, orbits, brain).
  - Authors evaluated 17 patients with AFRS (Schubert diagnostic criteria) → compared to patients with only CRSwNP and healthy controls, patients with AFRS had: (i) ↑ serum total IgE; (ii) ↑ serum specific IgE to S aureus superantigens (which correlated with total IgE) → sinusal tissue samples from 3 AFRS patients showed biofilms carrying Aspergillus and S aureus together.
  - Hypothesis: colonization by Aspergillus sp → TH2 response to Aspergillus sp → ↓ epithelial barrier, ↓ TH17 inflammation, ↑ alternative macrophage activation → superimposed S aureus infection/colonization → superantigenic activity → polyclonal B- and T-cell activation → markedly ↑ IgE production.
  - Author’s commentaries: (i) in patients with AFRS, S aureus superantigens may ↑ TH2 responses to fungal allergens and ↑ production of polyclonal IgE and IgG; (ii) this process may also happen in patients with allergic bronchopulmonary aspergillosis (ABPA); (iii) patients with AFRS or ABPA may benefit from antibiotics to S aureus or anti-IgE therapies.

  - Telomeres: terminal regions of chromosomes that protect DNA from damage. Shortened telomeres → ↑ cellular senescence (↓ capacity to proliferate), ↑ cell apoptosis.
Leukocytes from patients with COPD have shorter telomeres than those from healthy controls.

Telomerase ↓ shortening of telomeres → ↑ cell life and proliferation. Telomerase has 2 main subunits: (i) telomerase RNA component (TERC); (ii) telomerase reverse transcriptase (TERT, the functional component of telomerase activity).

Authors studied 14 nonsmoker adults (25-60 yrs old) with asthma (6 mild, 8 severe) → compared to healthy controls, asthmatic patients had: (i) ↓ telomere length in peripheral leukocytes (significant in patients with severe asthma); (ii) ↓ TERT expression in submucosal cells from bronchial biopsies.

Hypothesis: asthma → ↑ systemic inflammation → ↑ systemic oxidative stress → ↑ leukocyte turnover, ↓ telomerase activity → ↑ shortening of telomeres → ↑ leukocyte aging.

BRIDGING IMMUNITY AND LIPID METABOLISM BY GUT MICROBIOTA (Greer RL, Morgun A, Shulzenko N. J Allergy Clin Immunol 2013; 132: 253-262):

Gut functions: (i) nutrition/metabolism (enzyme secretion, digestion, absorption); (ii) immunity (effector or tolerogenic responses). It is essential to maintain immune and metabolic functions balanced.

Normal gut function requires cross-regulation between: (i) intestinal epithelium, (ii) immune system, (iii) gut microbiota.

Authors: (i) describe several diseases that alter this cross-regulation (e.g. immunodeficiency-associated enteropathies, celiac disease, inflammatory bowel disease, obesity), (ii) propose microbiota-oriented therapies to prevent/restore gut homeostasis and function (e.g. novel antibiotics that do not affect microbiota, prebiotics, probiotics).

EOSINOPHILIC ESOPHAGITIS TREATED WITH IMMUNOTHERAPY TO DUST MITES (Ramirez RM, Jacobs RL. J Allergy Clin Immunol 2013; 132: 503-504):

Eosinophilic esophagitis (EoE): infiltration of eosinophils into esophageal mucosa → chronic inflammation → esophageal dysfunction. Food and aeroallergens are frequent culprits.

Authors report the case of a 4-yr-old boy with EoE (recurrent vomiting; >25 eos/hpf in esophageal biopsies; suboptimal response to food elimination diet and oral fluticasone), allergic rhinitis and IgE-mediated sensitization to several foods and dust mites → successful treatment: high-dose immunotherapy to D farinae and D pteronyssinus (clinical and histologic improvement within 2 yrs).

Hypothesis: aeroallergens are swallowed in postnasal drainage → esophageal inflammation.

INNATE SENSORS OF PATHOGEN AND STRESS: LINKING INFLAMMATION TO OBESITY (Jin Ch, Flavell RA. J Allergy Clin Immunol 2013; 132: 287-294):

Obesity → excessive nutrients, ‘metabolic stress’ → ↑ DAMPs → ↑ activation of innate immune receptors (PRRs, such as TLR and NLR) → chronic low-grade systemic inflammation (e.g. in the brain, pancreatic islets, liver, muscle, adipose tissue), also called metabolic inflammation or ‘metainflammation’ → metabolic and inflammatory diseases (e.g. metabolic syndrome, type 2 diabetes, atherosclerosis, stroke, cardiovascular diseases, allergies, asthma).
• Protective actions of commensal gut microbiota: (i) production of short-fatty acids (SCFAs) from dietary fiber → regulation of lipid metabolism; (ii) metabolism of choline and bile acids → regulation of lipid metabolism; (iii) immune regulation.

• Altered commensal gut microbiota → altered immune regulation, altered lipid metabolism, ↑ pathogenic microorganisms → ↑ PAMPs and DAMPs → ↑ activation of innate immune receptors → ↑ inflammatory diseases (e.g. autoimmune diseases, allergies, asthma), ↑ metabolic diseases (e.g. obesity, type 2 diabetes).

• Strategies to protect/restore commensal gut microbiota: (i) novel antibiotics that do not affect commensals; (ii) probiotics; (iii) prebiotics; (iv) fecal transplantation.


• IgE-mediated allergic reactions to mites usually occur when mite allergens are breathed (e.g. allergic rhinitis, asthma).

• Ingestion of mites (e.g. mite-contaminated wheat flour) in mite-allergic patients may cause systemic reactions (urticaria, angioedema, gastrointestinal symptoms, bronchospasm, anaphylaxis [called oral mite anaphylaxis or OMA]).

• How to prevent OMA? (i) Store flour (sealed plastic or glass containers) in the refrigerator; (ii) use air purifiers; (iii) decrease intradomiciliary humidity; (iv) clean and disinfect furniture and floors; (v) use acaricides.

• PATIENTS INFORMING IMMUNOBIOLOGY: HOW DISORDERS OF IL-21 RECEPTOR SIGNALING UNRAVEL PATHWAYS OF CD8 T-CELL FUNCTION (Milner JD. J Allergy Clin Immunol 2013; 132: 412-413):

• IL-21 → signalling through IL-21R, STAT3 and STAT1 → pleiotropic effects on immune cells.

• Effects of IL-21 on CD8+ T cells (mouse studies): ↑ proliferation, ↑ survival, ↑ cytotoxicity, memory acquisition.

• Is IL-21 essential for immunity against virus? Let’s study patients with defects in IL-21R, STAT3 and STAT1.

• IL-21R deficiency → mild viral infections, invasive cryptosporidiosis (related to CD8+ T-cell defects?).

• STAT1 deficiency (dominant negative or loss-of-function mutations) → significant viral infections (related to CD8+ T-cell defects? type I interferon defects? both?).

• STAT3 deficiency (dominant negative mutations) → severe viral infections are infrequent (STAT3 defect may be compensated by TCR signalling, residual STAT3 activity and alternative pathways of IL-21 signalling [MAPK, Akt]); patients may suffer complicated/chronic herpesvirus infections [e.g. EBV, VZV, HSV] (hypothesis: STAT3 defects → ↓ activity of SOCS3 and Bcl-6 → ↓ differentiation to central and effector memory CD8+ T cells).

• Author’s commentaries: (i) IL-21 requires normal signaling through STAT3, but not STAT1, to induce CD8 cytotoxicity; (ii) IL-21 seems to be required for maximal CD8 proliferation.
• **SPICING DEFECT OF CD33 AND INFLAMMATORY SYNDROME ASSOCIATED WITH OCCULT BACTERIAL INFECTION** (Balmer ML, Trüeb B, Zhuang L, Slack E, Beltraminelli H, Villiger PM. J Allergy Clin Immunol 2013; 132: 490-493):

  • **Autoinflammatory diseases**: genetic defects in the regulation of innate immunity → ↑ activation of innate immunity (e.g. ↑ IL-1 production) → recurrent inflammation (fever, rash, arthritis, ↑ inflammatory markers, etc.).

  • Many autoinflammatory diseases can be successfully treated with **IL-1 blockage** (e.g. anakinra).

  • Authors report the case of a **26-yr-old woman** (unremarkable history except for hip surgery 9 yrs ago) with a **clinical picture** that suggested autoinflammatory syndrome (recurrent fever, maculopapulous nonpruritic skin rash, lymphadenopathy, rheumatic pains, ↑ serum inflammatory markers) → **molecular testing**: splicing defect in CD33 (↓ CD33M [long-splicing variant], ↑ CD33m [short-splicing variant]) → good response to anakinra for 1.5 yrs, when septic arthritis by S aureus was diagnosed (infection occurred in the site of the previous hip surgery) → **successful treatment**: antibiotics, surgical removal of the 2 infected screws → no recurrence of episodic inflammation (without further treatment with anakinra).

  • **Hypothesis**: CD33 (Siglec-3) defect (↓ CD33M [isoform that interacts with sialic acid]) → ↓ regulation of innate immunity → ↑ inflammatory response to occult S aureus infection → recurrent inflammatory episodes → initial good response to anakinra until S aureus infection was severe.


  • **Rituximab**: anti-CD20 chimeric mAb → profound B-cell depletion → therapeutic option in B-cell neoplasms and certain autoantibody-mediated diseases.

  • **Immediate hypersensitivity (IHS) reactions to rituximab**: pruritus, urticaria, angioedema, bronchospasm, hypotension, anaphylaxis.

  • **Desensitization to rituximab**: may be used for IgE-mediated and non-IgE-mediated IHS reactions; molecular basis is not completely elucidated.

  • Authors report the case of a **16-yr-old boy** with steroid-resistant nephrotic syndrome and anaphylaxis-like reaction (urticarial rash, angioedema, throat tightness, cough, abdominal pain, vomiting, tachycardia) 90 min after 1st rituximab infusion (dose=180 mg) → negative SPT (10 mg/mL) and intradermal tests (1:100 and 1:10 dilution) with Rituximab → **successful approach**: 12-step rapid desensitization to rituximab (performed thrice at 1-week intervals) → ↑ Tregs (CD4+CD25+FoxP3+ T cells) in peripheral blood 24 hrs after the 1st and 3rd desensitizations.

  • **Author’s commentaries**: (i) desensitization to rituximab may be useful in rituximab-allergic patients who do not have acceptable therapeutic alternatives; (ii) Treg cells may have a role in the mechanism of desensitization to rituximab.

• Outdoor air pollution: risk factor for development and worsening of respiratory allergic diseases.

• Authors followed (for 18 months) 22 children (16-85 months old) with atopic dermatitis (AD) → ↑ levels of outdoor air pollutants (toluene, PM<sub>10</sub>, PM<sub>2.5</sub>, TVOC) were associated with ↑ AD symptoms.

• Hypothesis: ↑ outdoor air pollutants → ↓ epidermal barrier function, ↑ skin inflammation.

• Author’s commentaries: (i) outdoor air pollution is an aggravating factor for AD; (ii) control of outdoor air pollution may improve management of AD patients.


  • Many infants with eczema are IgE-sensitized to egg by 4 months of age (even with no previous exposure) → be careful when egg is 1st introduced.

  • Early introduction of egg (4 months of age) does not appear to ↑ risk of egg allergy in infants with eczema.

  • Severe adult-onset asthma appears to be a distinct asthma phenotype.

  • IL-4 and IL-13 stimulate TH2 cells to produce IL-31 (an inflammatory cytokine that mediates pruritus.

• Intrinsic atopic dermatitis (AD): greater immune activation (particularly TH17 and TH22) compared to extrinsic AD.

• AD: ↓ neutrophil activity and TH17 axis (compared to psoriasis) → ↑ susceptibility to S aureus infections.

• S. aureus infection in patients with AD → ↑ neutrophil counts in the skin.

• TSLP plays an important role in allergic asthma → anti-TSLP therapy may benefit patients with allergic asthma.


  • Nuclear receptors: ligand-activated transcription factors that link lipid signaling to gene expression; important for regulating functions of macrophages and dendritic cells (DCs).

  • Authors review: (i) the role of retinoid X receptor, retinoic acid receptor, peroxisome proliferator-associated receptor γ, liver X receptor and vit D receptor in shaping immune and metabolic functions of macrophages and DCs; (ii) the contribution of macrophage- and DC-expressed nuclear receptors to various immunopathologic conditions (e.g. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, asthma).

• Waldeyer’s ring: component of the mucosa-associated lymphoid tissue (MALT); main function: generate adaptive immune responses; major components: adenoids and tonsils; minor components: tubal tonsils and lateral pharyngeal bands.

• Adenotonsillar hypertrophy (ATH): frequent problem in childhood; complications: obstructive sleep apnea, chronic rhinosinusitis, otitis media with effusion.

• What is the influence of allergy on ATH?

• Authors evaluated the presence of specific IgE (ImmunoCAP) in the serum and adenotonsillar tissue of children (6.68 ± 3.30 yrs of age) with ATH → (i) allergic inflammation had an important role in ATH; (ii) many patients had local atopy (positive sIgE in adenotonsillar tissue with negative serum sIgE).


  FPIES: non-IgE-mediated allergy to food proteins; clinical history (usually starts in the 1st yr of life, typically resolves by 3 yrs of age): vomiting, diarrhea, dehydration, electrolyte disbalance (2-6 hrs after eating culprit food); frequent culprits: cow’s milk, soy, grains; diagnosis: clinical history, oral food challenge; treatment: allergen avoidance.

  Lysinuric protein intolerance (LPI): ↓ transport of cationic aminoacids (e.g. lysine, arginine, ornithine) through the basolateral membrane of epithelial cells in gut and kidney; variable clinical manifestations (usually start at weaning): vomiting and diarrhea 1-6 hrs after eating protein-rich foods; aversion to protein-rich foods, failure to thrive, hepatosplenomegaly, renal insufficiency, pulmonary alveolar proteinosis, hematologic and immunologic abnormalities; diagnosis: ↑ cationic aminoacids in urine, ↓ cationic aminoacids in blood, mutations in SLC7A7 gene (autosomal recessive inheritance); treatment: protein-restricted diet, oral supplementation of citrulline, life-long follow-up.

• Authors present the case of a 1-yr-old infant with LPI misdiagnosed as FPIES → (i) clinical manifestations: vomiting and diarrhea within 1–3 h after eating meat, chicken, fish or eggs; mild hepatosplenomegaly; (ii) laboratory: ↑ ferritin, ↑ LDH, negative allergy tests (prick, patch, sIgE) to the suspected foods, ↑ cationic aminoacids in urine, ↓ cationic aminoacids in blood; (iii) genetic analysis: homozygous missense mutation in SLC7A7 gene; (iv) successful treatment: low-protein diet (1.5 g/kg/day), oral citrulline supplementation (100 mg/kg/day).

• Important differences between FPIES and LPI: (i) children with LPI typically react to any protein-rich food, children with FPIES typically react to one or few foods; (ii) LPI presents with ↑ inflammatory markers (e.g. ferritin, LDH).


  IgE-mediated egg allergy: frequent food allergy; conventional treatment: egg avoidance, autoinjectable epinephrine.
• Children ≥2 yrs of age: if sIgE to egg ≥6 kUa/l or SPT to egg white >7 mm → >95% likelihood of clinical reactivity to egg.

• Children <2 yrs of age: if sIgE to egg ≥2 kUa/l or SPT to egg white >5 mm → >95% likelihood of clinical reactivity to egg.

• Many egg-allergic children tolerate baked egg; regular ingestion of baked egg (in this group of children) can accelerate acquisition of tolerance to non-baked egg and ↑ QoL.

• Authors performed an open food challenge (OFC) to extensively heated egg in 236 egg-allergic children → (i) 150 children (64%) passed the OFC and incorporated baked egg into their diet; (ii) 86 children (36%) reacted to the OFC (12 children [14%] had anaphylaxis); (iii) SPT, asthma or prior egg anaphylaxis did not predict OFC outcome.

• Author’s commentary: OFC to baked egg should be performed under medical supervision.


  • Immune system in the fetus: (i) T cells appear in the gut at 11 wks gestation; (ii) Peyer’s patches appear at 16 wks gestation (CD4αβ T cells at 19 wks gestation, CD8αβ T cells in the perinatal period); (iii) B cells appear in the gut lamina propria in the post-natal period; (iv) macrophages appear in the gut mucosa at 11–12 wks gestation; (v) there is a TH2 bias (to prevent fetus rejection by the mother immune system); (vi) fetus receives maternal IgG by transplacental transfer.

  • Intrauterine environment → fetus is normally not exposed to microorganisms.

  • Delivery → newborn immature gut immune system is exposed to a vast array of microorganisms (e.g. maternal microbiota, environmental microbes) → cross-talk between gut epithelial cells, gut immune system and microbiota → commensal microbiota and beneficial molecules (e.g. food) must be tolerated; pathogenic microbes must be blocked or repelled.

  • Immune system in the 1st months of life [‘hybrid’ maternal–infant immune system]: (i) serum IgG is mainly maternal derived; (ii) mother provides IgG and IgA in the colostrum and breast milk; (iii) maternal IgG may affect active newborn response to infections and vaccines; (iv) maternal microbiota influences newborn gut microbiota; (v) newborn gut microbiota regulates development of gut epithelium and mucosal immune system; (vi) gut immune system must tolerate commensal microbiota (proposed mechanisms: ↓ TLR expression, ↑ inhibitory factor kappa B (iκB) → ↓ NF-κB-mediated responses).

  • Composition of newborn gut immune system is not well defined (normal newborn gut tissue is difficult to obtain for research).

  • Factors that influence newborn gut microbiota and immune system: maternal microbiota, mode of delivery, gestational age at birth, breastfeeding, diet, probiotics, prebiotics, antibiotics.

  • Gut commensal bacteria → ↑ production of IL-25, TSLP, retinoic acid and TGF-β from gut epithelial cells → ↑ IL-10 and ↓ IL-23 production from DCs, ↑ activity of CD103+DCs → ↓ TH17 inflammation, ↑ Treg differentiation → regulation of immune system.
• Lipopeptides from commensal bacteria → signalling through TLR2 on epithelial cells → apical tightening and sealing of tight junctions by ZO-1 → maintenance of epithelial barrier.

• Distribution of adult gut mucosal immune system: (i) epithelium; (ii) lamina propria; (iii) Peyer’s patches.

• Intraepithelial lymphocytes (IELs) include: (i) conventional CD4+ or CD8+ TCRαβ T cells (function: lifelong protection against specific gut pathogens), (ii) TCRγδ T cells, (iii) CD8αα TCRαβ T cells, (iv) double negative [CD4- CD8-] TCRαβ T cells (functions from i to iv: rapid response to microbes, maintenance of homeostasis).

• IL-15 promotes IEL growth and survival; IL-7 stimulates development of TCRγδ IELs; CXCL9, CXCL10, CCL1, CCL17 and CCL22 attract T cells; CCL25, CCL28, CXCL12 and CXCL13 attract B cells; CX3CL1 promotes antigen sampling by DCs.

• Risk factors for necrotizing enterocolitis (NEC): prematurity, immature gut epithelium, immature gut immune system, abnormal gut microbiota, ↑ bacterial translocation through gut, cesarean section, ↓ breastfeeding, parenteral nutrition, antibiotic use.

• Probiotics (Lactobacillus spp., Bifidobacteria spp) may ↓ gut permeability, ↑ mucosal IgA and ↓ gut inflammation → may ↓ NEC incidence in extremely preterm infants (the Probiotic in Preterm Babies Study [PiPS] is running to address this hypothesis).

• Benefits of breastfeeding: (i) provides antimicrobial molecules (IgA, IgM, lysozyme, lactoferrin, complement); (ii) provides immunoregulatory molecules (EGF, IL-10, TGF-β, sCD14); (iii) ↑ beneficial gut bacteria (e.g. Bifidobacterium spp); (iv) ↓ incidence of GI infections, respiratory infections, otitis media, sudden infant death syndrome (SIDS), type I and type II DM, atopic dermatitis, asthma, obesity, NEC.

• Adjuvants to replicate beneficial effects of breastfeeding: extrinsic EGF, butyrate.

• Further research is needed to clarify: (i) the organization of the newborn gut immune system; (ii) factors that influence its development; (iii) how to promote/restore normal gut immune system functions; (iv) how to better treat gut infections in newborns; (v) how to design better mucosal vaccines; (vi) diagnostic markers and targeted immunotherapies for necrotizing enterocolitis; (vii) protective mechanisms of breastfeeding and analogues of breastfeeding.


• Authors performed a longitudinal cohort study to evaluate the association between reported sun exposure (at 1 month, 8 yrs and 16 yrs of age) and the occurrence of allergic diseases or sensitization at 16 yrs of age → (i) ↑ sun exposure during summer days in adolescence was associated with ↓ eczema and ↓ rye-grass rhinitis (independently of vit D levels) but not with asthma or inhalant allergen sensitization; (ii) sun exposure in infancy or childhood was not associated with occurrence of eczema, rye-grass rhinitis, asthma or inhalant allergen sensitization at 16 yrs of age.

• Author’s commentary: sun exposure may benefit patients with allergic diseases, independently of effects on vit D or allergen sensitization.