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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August 2014 – content:


• ANAPHYLAXIS TREATMENT: CURRENT BARRIERS TO ADRENALINE AUTO-INJECTOR USE (Song TT, Worm M, Lieberman P. Allergy 2014; 69: 983–991).


• A CASE OF ANAPHYLAXIS TO PALIVIZUMAB (Savitz J, Geaney C, Banks TA. Ann Allergy Asthma Immunol 2014; 113: 236-237).


• **MOLECULAR CHARACTERIZATION OF REDOX MECHANISMS IN ALLERGIC ASTHMA** (Jiang L, Diaz PT, Best TM, Stimpfl JN, He F, Zuo L. Ann Allergy Asthma Immunol 2014; 113: 137-142).

• **SPECIAL CHALLENGES IN TREATMENT AND SELF-MANAGEMENT OF OLDER WOMEN WITH ASTHMA** (Baptist AP, Hamad A, Patel MR. Ann Allergy Asthma Immunol 2014; 113: 125-130).


• **RISKS FOR INFECTION IN PATIENTS WITH ASTHMA (OR OTHER ATOPIC CONDITIONS): IS ASTHMA MORE THAN A CHRONIC AIRWAY DISEASE?** (Juhn YJ. J Allergy Clin Immunol 2014; 134: 247-257).


ALLERGY:


  • **Anaphylaxis:** (i) **definition:** acute, severe, life-threatening systemic hypersensitivity reaction; (ii) **lifetime prevalence:** 0.0582%; (iii) **mechanisms:** release of mediators from mast cells and basophils (IgE-mediated, IgG-mediated, complement-mediated, idiopathic); (iv) **most common culprits:** foods, drugs, hymenoptera venom, latex (in up to 20% of cases the elicitor is not identified); (v) **factors that influence severity:** patient’s age, pathogenic mechanism, allergen properties, allergen dose, route of exposure, degree of sensitization, affinity of specific IgE, presence of cofactors, basal tryptase level, comorbidities (uncontrolled asthma, mast cell disorders, cardiovascular disease), concomitant use of drugs (β-blockers, ACE inhibitors); (vi) **augmentation factors:** exercise, alcohol, infections, NSAIDs, drugs, menses, stress; (vii) **diagnosis:** clinical history (NIAID/FAAN criteria: sensitivity=96.7%, specificity=82.4%; anaphylaxis can present without cutaneous signs in ~15% of patients), measurement of allergy mediators (e.g. serum tryptase, serum/urinary histamine or metabolites, serum PAF), allergy testing (e.g. sIgE detection by skin and in vitro tests); (viii) **biphasic anaphylactic reactions** (recurrent anaphylactic symptoms after resolution of the primary event) may occur in up to 20% of reactions; (ix) **treatment in the acute setting:** intramuscular epinephrine (1st line therapy; no absolute contraindications), trigger removal, correct positioning of the patient (hypotension → lying on back with lower extremities elevated; pregnant → semirecumbent on the left side with lower extremities elevated; respiratory distress without hypotension → sitting up), intravenous fluids (crystalloids are the 1st choice, given in boluses of 20 ml/kg), inhaled β2-agonists, oxygen, systemic H1- and H2- antihistamines (intravenous antihistamines may cause hypotension), systemic corticosteroids (may prevent biphasic reactions), nebulized adrenaline (for laryngeal edema), nebulized budesonide (for airway edema), adrenaline infusion (in refractory cases), glucagon (in cases of resistance to epinephrine), cardiopulmonary resuscitation; (x) **long-term management:** allergen avoidance, epinephrine autoinjectors, immunotherapy, anaphylaxis management plan, medical identification, psychological evaluation, group support.

  • **Adrenaline** acts on: (i) **α1 receptors** → peripheral vasoconstriction, ↑ blood pressure, ↓ mucosal edema; (ii) **β-1 receptors** → ↑ rate and force of cardiac contractions, ↑ blood pressure; (iii) **β-2 receptors** → bronchodilation, ↓ release of inflammatory mediators.

  • **Augmentation factors (cofactors) for anaphylaxis** (↓ anaphylaxis threshold; appear in up to 30% of anaphylactic episodes; >1 cofactor may be needed to elicit anaphylaxis): (i) **Physical exercise:** most frequent cofactor (e.g. ‘food-dependent exercise-induced anaphylaxis’, which only occur in the presence of exercise; described for wheat, shrimps, meat, pistachio, spinach, etc.; most frequent with hard exercise and high degree of food sensitization; may also occur with minimal exercise [e.g. ironing]); differential diagnosis: cholinergic urticaria, exercise-induced asthma, physical urticaria. (ii) **Alcohol:** relevant factor in up to 15% of anaphylactic episodes. (iii) **Infections (mild or severe):** relevant factor in up to 11% of episodes; may complicate venom or pollen immunotherapy (SIT must be paused or ↓ during infections. (iv) **NSAIDs:** relevant factor in up to 9% of episodes. (v) **Other drugs:** mast cell-activating drugs
(iodinated RCM [most frequently iomeprol and iopromide], muscle relaxants [most frequently suxamethonium], quinolones, opioids), drugs that ↑ bradikinin levels (e.g. ACE inhibitors), drugs that ↓ gastric acid (proton pump inhibitors, H2-receptor blockers [↑ risk of anaphylaxis in patients with oral allergy syndrome due to acid-sensitive allergens]), drugs that block counteracting mechanisms during anaphylaxis (β-adrenergic antagonists, ACE inhibitors, angiotensin receptor blockers, MAO inhibitors).


• Mechanisms underlying cofactor-induced anaphylaxis: (i) ↑ gut permeability (exercise-induced, alcohol-induced, infection-induced, NSAID-induced [e.g. NSAIDs ↓ expression of the tight junction protein claudin-7]) → ↑ allergen bioavailability; (ii) ↓ activation threshold of mast cells and basophils (exercise-induced, NSAID-induced, infection-induced, drug-induced); (iii) ↑ synthesis of leukotrienes (NSAID-induced); (iv) ↓ gastric acid (drug-induced) → ↑ allergen bioavailability; (v) immune system stimulation (infection-induced): formation of IgG/IgM immune complexes, release of complement anaphylotoxins (C5a is more potent than C3a for mast cell degranulation; mucosal mast cells do not express anaphylatoxin receptors), cell activation through innate immune receptors (e.g. peptidoglycan can induce mast cell degranulation).

• Median times to cardiovascular and/or respiratory collapse during anaphylaxis: (i) 5-10 min for IV drugs, (ii) 15 min for field insect stings and IM drugs, (iii) 30 min for food and oral drugs.

• Allergists must know: (i) how to treat acute anaphylaxis (it may occur after immunotherapy application, skin testing [especially with food or drugs], or food/drug challenges); (ii) how to evaluate and manage a patient with a suspected history of anaphylaxis (confirm diagnosis, determine the etiology, give a treatment plan to prevent and treat further episodes).

• Approach to a patient with a history of anaphylaxis: (i) evaluate all potential triggers (e.g. food, drugs, insect stings, latex, exercise [or food + exercise], temperature changes, menstruation) within 6 hrs before symptom onset (idiopathic anaphylaxis can account for 60% of adult cases); (ii) assess severity by taking a thorough history of all signs and symptoms (place and time of onset, duration, recurrence, response to treatment); (iii) exclude differential diagnosis (e.g. mastocytosis, mast cell activation disorder [risk factor for anaphylaxis], carcinoid syndrome, neuroendocrine tumors, drug-induced flush [niacin, nicotine, ACE inhibitors, corticosteroids, cathecolamines], alcohol-related flush [alone or in combination with drugs such as disulfiram, griseofulvin or cephalosporins], acute coronary syndrome, pulmonary embolism, postprandial syndromes [ingestion of monosodium glutamate or sulfites, scombroidosis], hereditary angiodema, vocal cord dysfunction syndrome, panic attack, somatoform disorder); (iv) perform proper laboratory tests (serum tryptase, plasma histamine, urinary histamine metabolites, serum PAF, serum PGD2, in vivo and in vitro allergy tests, allergen challenges, tests to exclude differential diagnosis [e.g. imaging studies if suspicion of neuroendocrine tumors, neuropeptide levels if suspicion of carcinoid syndrome, bone marrow biopsy if suspicion of mastocytosis]); (v) give detailed written indications to prevent and quickly-treat further anaphylaxis episodes (e.g. trigger avoidance, use of medical identification, use of autoinjectable epinephrine [>1 dose is needed in up to 30% of episodes], correct positioning, avoidance of some drugs [β-blockers and MAO inhibitors can ↓ epinephrine action; ACE inhibitors can ↓ angiotensin action and ↑ bradykinin levels]); (vi) consider use of immunotherapy (e.g. for hymenoptera sting or food allergy).

• Absolute indications for an adrenaline auto-injector: (i) previous anaphylaxis with food, latex, aeroallergens and other unavoidable triggers; (ii) previous exercise-induced anaphylaxis; (iii)
previous idiopathic anaphylaxis; (iv) co-existent unstable or moderate to severe, persistent asthma with food allergy; (v) venom allergy in adults with previous systemic reactions (unless on maintenance venom immunotherapy) or children with more than systemic cutaneous reactions; (vi) underlying mast cell disorder and any previous systemic reaction.

• **ANAPHYLAXIS TREATMENT: CURRENT BARRIERS TO ADRENALINE AUTO-INJECTOR USE** (Song TT, Worn M, Lieberman P. Allergy 2014; 69: 983–991):

  - Anaphylaxis: (i) potentially fatal severe hypersensitivity reaction; (ii) 1st-line acute treatment: intramuscular adrenaline into the anterolateral portion of the midthigh (middle of vastus lateralis muscle); (iii) failure or delay in adrenaline administration can ↑ death risk; (iv) a high proportion of individuals with fatal anaphylaxis have had no previous anaphylactic episodes.

  - Adrenaline autoinjectors (AAIs): (i) indicated for patients at risk of anaphylaxis (potentially lifesaving); (ii) no absolute contraindications to use AAIs during an anaphylactic episode; (iii) 5 commercial AAIs currently available and licensed in Europe and/or US (Europe: Anapen, EpiPen, Jext; US: Adrenaclick, Auvi-Q, EpiPen); (iv) mean time to maximum adrenaline concentration (Tmax): EpiPen=8 min, subcutaneous adrenaline=34 min; (v) holding the EpiPen for 1 second was as effective as 10 seconds; (vi) EpiPen propels adrenaline reaching a depth of ~2.78 cm (needle’s length=1.43 cm), enough to reach the muscle even in obese patients.

  - Barriers to AAI use: (i) patient’s factors: low rates of carrying, fear, insecurity, low knowledge; (ii) physician’s factors: low knowledge, low ability to educate, bad relation with the patient; (iii) social/economic factors: cost, local unavailability, unavailability in public places.


  - Food allergy (FA=immunologic reactions to food): (i) IgE-mediated: urticaria, angioedema, bronchospasm, anaphylaxis; (ii) cell-mediated: enterocolitis, proctocolitis, celiac disease, contact dermatitis; (iii) IgE- and cell-mediated: atopic dermatitis, eosinophilic GI diseases.

  - Important points about FA: (i) self-reported FA is ~5 times higher than challenge-proven FA; (ii) several genetic and environmental factors play a role in FA pathogenesis; (iii) diagnosis depends on clinical history and appropriate allergy testing; (iv) food allergen sensitization does not imply clinical reactivity and vice versa; (v) sensitization to food allergens can occur by nonoral routes (e.g. allergy to α-gal after tick bites, allergy to peanut after sensitization through skin); (vi) only trained healthcare professionals, able to interpret results and manage possible adverse reactions, should perform SPTs; (vii) component-resolved diagnosis (CRD) is a promising diagnostic tool that adds sensitivity and specificity to IgE-allergy testing; (viii) management of FA depends on the clinical syndrome; (ix) a “personalized medicine” approach to diagnose and treat FA is likely required but remains elusive.
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- **Factors associated with FA:** (i) genetic susceptibility; (ii) ↓ gut epithelial barrier; (iii) use of gastric acid suppressive drugs; (iv) ↑ intestinal inflammation; (v) ↑ 'proinflammatory' microbiota (e.g. Clostridium, Staphylococci); (vi) ↓ 'tolerogenic' microbiota (e.g. Lactobacillus, Bifidobacterium); (vii) ↑ TH2 responses (including IgE production); (viii) food sensitization through skin; (ix) vitamin D insufficiency; (x) unhealthy dietary fat; (xi) obesity; (xii) increased hygiene; (xiii) "inappropriate" timing of 1st exposure to foods.

- **IgE-mediated FA:** (i) rising prevalence worldwide (6% of children and 4% of adults in the westernized world); (ii) etiology: genetic factors (currently not modifiable), environmental/exposure factors (targets for prevention); (iii) impact: significant morbidity, ↓ QoL, mortality risk, high costs; (iv) >170 foods have been reported to cause allergic reactions; (v) main allergenic foods (comprise 90% of cases): milk, egg, peanut, tree nuts, wheat, soy, seafood; (vi) diagnosis: clinical history, specific IgE detection by SPT or in vitro testing (serum sIgE, component-resolved diagnosis, basophil activation test), elimination diet, food challenge (gold standard); (vii) conventional treatment: allergen avoidance (does not prevent accidental exposure), epinephrine autoinjectors, nutritional counseling, follow up to confirm spontaneous development of tolerance (especially in egg, milk, wheat and soy allergy), ingestion of extensively heated egg or milk products in children who tolerate them (this may accelerate resolution of egg and milk allergy, respectively); (viii) optimal treatment: restore tolerance by exposing patients to gradually increasing doses of allergen (immunotherapy).

- **Importance of component-resolved diagnosis (CRD):** (i) CRD can help to determine patient's sensitization on a molecular basis (e.g. specific IgE to Ara h 2 [main peanut allergen]; specific IgE to prolamins or cupins [plant allergens with high anaphylactic potential]; specific IgE to PR-10 proteins or profilins [heat-labile plant allergens with low anaphylactic potential]; specific IgE to ovomucoid [Gal d 1, an egg-white allergen resistant to heat and digestion, associated with persistent and severe allergic reactions]; specific IgE to ovalbumin, ovotransferrin or lysozyme [heat-labile egg-white allergens, associated with mild and transient allergic reactions]); (ii) CRD can help to define clinical entities (e.g. specific IgE to omega-5-gliadin in patients with wheat-dependent exercise-induced anaphylaxis; specific IgE to galactose-alpha-1,3-galactose in patients with delayed-type immediate allergy to red meat); (iii) CRD can help to identify cross-reactive allergens (e.g. latex-fruit allergy syndrome; mite-cockroach-crustacean allergy syndrome; pork-cat allergy syndrome; allergy to cross-reactive carbohydrate determinants [CCDs] in plants, latex or Hymenoptera venoms; allergy to parvalbumin [a fish panallergen]).

- **Oral immunotherapy (OIT) for FA is under active investigation; potential benefits:** long-lasting acquisition of tolerance, ↑ QoL, ↓ danger of accidental food exposure.

- **Main limitations of OIT:** (i) lack of evidence of long-lasting efficacy (RCT with cow's milk, egg and peanut OIT have reported desensitization in 33–90% of subjects; however, ability for OIT to induce long-lasting tolerance remains uncertain); (ii) allergic reactions during OIT, including reactions to previously tolerated doses (cofactors: concurrent infection, physical activity within 2 hrs, alcohol, NSAIDs, poorly controlled asthma, empty stomach, pollen season, menses); (iii) it should be performed by expert physicians in an appropriate environment; (iv) patient and family should collaborate actively.

- **How to ↑ efficacy and safety of OIT?** (i) adding omalizumab (anti-IgE mAb); (ii) using modified allergens (baked food, recombinant allergens, peptides), (iii) adding immune response modifiers.
(monophosphoryl lipid A [TLR-4 agonist], CpG containing DNA [TLR-9 agonist], probiotics); (iv) personalized OIT schemes.

- **Recommendations for primary prevention of FA:** (i) exclusive breastfeeding for the first 4-6 months of life; (ii) no special dietary restrictions for pregnant or lactating mothers; (iii) use of hypoallergenic formula if breastfeeding is insufficient in high-risk infants up to 4 months of age (then a standard milk can be used); (iv) introduction of complementary foods after 4 months of age, irrespective of atopic heredity; (v) no special dietary restrictions after 4 months for age, irrespective of atopic heredity.

- **Eosinophilic esophagitis (EoE):** (i) prevalence in the general population: ~1/2,000 subjects; (ii) incidence is rising; (iii) male to female ratio=3:1; (iv) impact: significant morbidity, ↓ QoL, high costs; (v) pathogenesis: genetic susceptibility, environmental insults to the esophageal epithelium (e.g. allergens, infections, irritants) → epithelial barrier dysfunction (e.g. ↓ expression of the cell adhesion protein DSG-1), ↑ secretion of TSLP and IL-33 → ↑ allergen entry through the epithelium → immune reaction to food or respiratory allergens → infiltration of eosinophils into esophageal mucosa → chronic inflammatory infiltrate (eosinophils, mast cells, a special basophil population, TH2 cells, iNKT cells) → esophageal fibrosis, remodelling (e.g. transdifferentiation of epithelial cells to a myofibroblast phenotype) and dysfunction; (vi) common causal foods in children: milk, egg, soy, wheat, beef, chicken; (vii) common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg; (viii) frequent association (40-90%) with other atopic diseases (asthma, allergic rhinitis, food allergy, atopic dermatitis).

- **Diagnosis of EoE:** (i) clinical history: abdominal pain, vomiting, dysphagia, heartburn, cough, choking, food aversion; (ii) complications: food impaction, failure to thrive, esophageal perforation, mental affectsation; (iii) esophageal endoscopy: edema, white exudative plaques, mucosal rings (‘trachealization’), strictures, linear furrows, mucosal tearing; (iv) esophageal biopsy (2-4 biopsies from the proximal and distal esophagus; positive result: ≥15 eosinophils per high-power field; other findings: superficial layering, microabscesses, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, lamina propria fibrosis); (v) allergy testing (skin prick test [SPT], serum specific IgE, atopy patch test [APT]) with food and respiratory allergens; (vi) food elimination-reintroduction trials (elimination diets can take up to 6 wks per food); (vii) detection of eosinophil-mediated inflammation (e.g. cationic eosinophil granule proteins) by SPECT imaging.

- **Treatment of EoE:** (i) diet options: 6-food elimination diet (milk, egg, wheat, soy, fish/seafood, peanut/tree nuts), diet guided by allergy tests, aminoacid formula; (ii) topical corticosteroids: low bioavailability, low potential for systemic adverse effects, ↑ risk of local fungal infection; (iii) systemic corticosteroids: effective, severe side effects; (iv) biologic therapies targeting the eosinophil (e.g. anti-IL-5 mAb, anti-IL-5R mAb); (v) esophageal dilation: might provide short-term symptomatic relief, only used if dietary and medical therapy has failed.


  - EAACI provides this guideline to improve the management of patients with food allergy (FA) in the community setting → objectives: (i) ↓ risk of accidental allergic reactions to foods; (ii) improve management of anaphylaxis in the community (e.g. use of epinephrine autoinjectors);
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(iii) improve QoL of food-allergic patients in school or work (↓ discrimination, ↓ stigmatization);
(iv) encourage general awareness about FA (families, schools, restaurants, etc.);
(v) improve education about FA;
(vi) promote organizations and working groups in FA;
(vii) improve legislation at local and national levels regarding FA;
(viii) promote research on these topics.


• Allergic diseases (e.g. asthma, hay fever, eczema, anaphylaxis, food allergy, drug allergy): (i) affect ~1 billion people in the world; (ii) increasing prevalence worldwide; (iii) impact: high costs, ↓ QoL, mortality risk; (iv) there is no established way to prevent or cure them.

• Advances in the field of allergic diseases: (i) novel methods allow measurement of allergen concentration and distribution in indoor and outdoor environments; (ii) innate lymphoid cells are ‘new’ players in allergic disorders; (iii) epithelial functions are important regarding allergy pathogenesis; (iv) tissue/organ responses to environmental stimuli are heterogeneous; (v) novel high-throughput, unbiased approaches allow acquisition of huge data regarding complex biological responses (omics); (vi) microbiomes and pathogens (e.g. S. aureus, rhinoviruses) modify the risk of development, persistence and aggravation of allergic diseases; (vii) molecular-based allergy diagnostics (‘component-resolved’ diagnostics) allow to identify more precisely IgE-mediated sensitization.

• Futuristic approach for allergic patients: discovery of biomarkers to identify specific endotypes and phenotypes → give individualized therapy (optimizing efficacy and safety).

• IMPAIRED NLRP3 INFLAMMASOME EXPRESSION AND FUNCTION IN ATOPIC DERMATITIS DUE TO TH2 MILIEU (Niebuhr M, Baumert K, Heratizadeh A, Satzger I, Werfel T. Allergy 2014; 69: 1058–1067):

• Atopic dermatitis (AD): (i) common chronic skin disease (3% of adults, 20% of children); (ii) prevalence has ↑ globally; (iii) impact: ↓ QoL, high costs, ↑ predisposition to skin infections and other allergies; (iv) multiple pathogenic factors: genetic, epigenetic, environmental; (v) clinical features: eczema, dry skin, pruritus, ↑ predisposition to skin fungal, viral and bacterial infections (e.g. Staphylococcus aureus); (vi) immune abnormalities: defective epithelial barrier, defective innate immune responses, eosinophilia, ↑ IgE, ↑ TH2 and TH22 responses in the skin.

• Authors show that AD patients had impaired NLRP3 expression and function in the skin, which may partially explain the increased susceptibility to colonization and infection with S. aureus.
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

• **A CASE OF ANAPHYLAXIS TO PALIVIZUMAB** (Savitz J, Geaney C, Banks TA. Ann Allergy Asthma Immunol 2014; 113: 236-237):

  • Anaphylaxis: (i) definition: acute life-threatening systemic hypersensitivity reaction; (ii) lifetime prevalence: 0.05-2%; (iii) mechanisms: release of mediators from mast cells and basophils (IgE-mediated, IgG-mediated, complement mediated, idiopathic); (iv) most common culprits: foods, drugs, hymenoptera venom, latex; (v) diagnosis: clinical history, measurement of allergy mediators (e.g. serum tryptase, serum/urinary histamine or metabolites, serum PAF), allergy testing (e.g. sIgE detection by skin and in vitro tests); (vi) treatment in the acute setting: epinephrine (1st-line therapy), antihistamines, corticosteroids, β2-agonists, oxygen, fluids; (vii) long-term management: allergen avoidance, epinephrine autoinjectors, immunotherapy.

• Respiratory syncytial virus (RSV): (i) enveloped RNA virus; (ii) common cause of upper respiratory infections in early childhood; (iii) probable causal role in asthma initiation; (iv) risk factors for severe RSV infection: prematurity, chronic lung disease, congenital heart disease.

• Palivizumab: (i) licensed chimeric monoclonal antibody to prevent RSV infection in high-risk patients; (ii) conformation: human IgG1 framework + murine complementarity determining regions directed to the A antigenic site of the RSV F fusion protein; (iii) form of administration: intramuscularly, once every 30 days for 5 doses; (iv) excellent safety profile.

• Authors report the case of a 28-yr-old girl with DiGeorge syndrome, tetralogy of Fallot and ventilator-dependent chronic lung disease of prematurity who developed an anaphylactic reaction (emesis, dyspnea, cough, urticaria, angioedema, hypoxia, hypotension, tachycardia; good response to epinephrine) minutes after Palivizumab administration (the 2nd dose of the 2nd-year course).

• Author’s commentary: 1st report of anaphylaxis after Palivizumab administration.

• **ASSOCIATION OF SKIN NECROSIS WITH SUBCUTANEOUS IMMUNOGLOBULIN THERAPY** (Datta R, Kuruvilla M, Gill M, de la Morena MT. Ann Allergy Asthma Immunol 2014; 113: 232-233):

  • Patients with immunoglobulin deficiencies → replacement therapy with IgG (intravenous or subcutaneous administration).

  • Subcutaneous IgG (SCIG) therapy: (i) advantages: more stable serum IgG levels, shorter infusion times, fewer systemic adverse effects, increased convenience; (ii) disadvantages: more frequent infusion site reactions (e.g. pain, edema, induration, erythema, heat, itching).

  • Authors report the case of 2 patients with necrotic skin lesions appearing in the injection site of SCIG → **Patient 1**: 13-yr-old boy with common variable immunodeficiency who received weekly SCIG on his thighs since the age of 10 yrs; increasing the needle size prevented new necrotic lesions. **Patient 2**: 11-yr-old girl with trichothiodystrophy and hypogammaglobulinemia who received weekly SCIG on her thighs since the age of 7 yrs.

  • Author’s commentary: 1st report of necrotic ulcers as local adverse effects of SCIG (hypothetic causal factors: needle size, depth of placement, site of infusion, infection, immune-related reactions).
  
  • Patients with cystic fibrosis (CF) need frequent antibiotic use → ↑ risk of drug allergic reactions.

  • Rapid drug desensitization (RDD): (i) procedure that can be performed when a drug-allergic patient obligatorily needs the culprit drug; (ii) risky because allergic reactions can occur, especially in the final steps of desensitization and during the full-dose intermittent treatment.

  • Authors report their experience with successful treatment using RDD followed by a continuous intravenous β-lactam antibiotic infusion (23.5-hour infusion of 9 g/d of ceftazidime or 12 g/d of piperacillin, using a portable pump, for the entire treatment course) in CF patients who could not complete the regular RDD procedure because of severe life-threatening allergic reactions during the full-dose treatment.

  
  • Summary Statement 1: Every patient with asthma should have an asthma action plan (written and/or electronic), including instructions for recognition of loss of control and activation of the yellow zone intervention plan. (Recommendation: B Evidence).

  • Summary Statement 2: Instruct patients to activate the yellow zone intervention plan when there is acute loss of asthma control outside a medical facility, defined as: (i) ↑ asthma symptoms; (ii) ↑ use of reliever medications; (iii) ↓ peak flow rate (PEFR) of ≥15% or PEFR <80% of personal best; (iv) ↑ nocturnal asthma symptoms. (Strong Recommendation: B Evidence).

  • Summary Statement 3: Instruct patients to activate the yellow zone plan at the onset of an upper respiratory tract infection if this is a previously identified trigger. (Strong Recommendation: B Evidence).

  • Summary Statement 4: Instruct patients to escalate asthma therapy when they experience a loss of asthma control that puts them in the yellow zone. (Recommendation: B Evidence).

  • Summary Statement 5: Advise patients to use a short-acting β2 agonist (SABA) for reliever use in the yellow zone (2 to 4 puffs every 4 to 6 hrs) in addition to their escalated yellow zone treatment. If SABA use exceeds 12 puffs per day, advise patients to contact their physician. (Recommendation: C Evidence).

  • Summary Statement 6: Advise patients treated with daily low-to-moderate dose inhaled corticosteroid (ICS) therapy to consider increasing the total ICS dose per 24 hrs (ie, quadrupling) for managing loss of asthma control in the yellow zone. (Option: B Evidence).

  • Summary Statement 7: For children <6 yrs of age with recurrent wheezing and risk factors for subsequent asthma (ie, positive modified asthma predictive index), consider initiating high-dose ICS or oral montelukast at the early signs of wheezing illnesses to decrease intensity of symptoms. (Option: B Evidence).
• **Summary Statement 8**: For patients with mild to moderate asthma, consider recommending symptom-driven use of ICS with concomitant inhaled β agonist for control of yellow zone symptoms. (Option: B Evidence).

• **METAL HYPERSENSITIVITY IN TOTAL JOINT ARTHROPLASTY** (Pinson ML, Coop CA, Webb Ch N. Ann Allergy Asthma Immunol 2014; 113: 131-136):

  - Total joint replacement (TJR): (i) procedure numbers are increasing (hip and knee); (ii) types of hip prostheses: metal-on-polyethylene (advantages: ↓ risk of metal allergy; disadvantages: ↑ risk of bone reaction to plastic and subsequent aseptic joint loosening), metal-on-metal (advantages: high strength and durability; disadvantages: ↑ risk of metal allergy), ceramic-on-ceramic; (iii) knee prostheses can use a cemented fixation (risk of allergy to benzoyl peroxide).

  - Metal hypersensitivity in patients with TJR: (i) increasing incidence (10-15% of the general population have metal hypersensitivity); (ii) impact: prosthesis failure (conflicting evidence), ↑ costs; (iii) pathophysiology: corrosion of metals in contact with other surfaces → release of metal ions or haptons → metal binding to self proteins → cell-mediated hypersensitivity to metal-protein complexes; (iv) more common after hip TJR than after knee TJR (no metal-on-metal contact); (v) more common to stainless-steel prosthesis (contain nickel, chromium, molybdenum, manganese) and cobalt-alloy components than to titanium-alloy components; (vi) polysensitization may occur, mainly with nickel and cobalt; (vii) clinical features: prosthesis dysfunction (joint pain, joint effusion, joint dislocation), localized or systemic contact dermatitis (erythema, induration, warmth, itch, rash); (viii) diagnosis: clinical history, patch testing (currently there are no standardized commercial panels specific for TJR materials), in vitro tests (lymphocyte transformation test, leukocyte migration inhibition factor test, lymphocyte activation test; they are not routinely available); (ix) differential diagnosis: prosthesis infection, mechanical failure; (x) treatment: NSAIDs, physical therapy, topical and systemic corticosteroids, topical calcineurin inhibitors, surgical revision (intraoperative findings include pseudotumor [nonmalignant, noninfectious soft tissue mass associated with the implant] and aseptic lymphocyte-dominated vasculitis-associated lesion), desensitization (potential therapy); (xi) prevention: test for metal allergy before surgery in patients with a reported history of metal sensitivity or a previous unexplained failed TJR (conflicting evidence).

• **Patch testing for metal hypersensitivity**: (i) screening panels should include nickel, cobalt, potassium dichromate, sodium thiosulfate (gold), potassium dicyanoaurate, platinum, mercury, copper, tin, aluminum and palladium; (ii) comprehensive panels should include nickel, cobalt, potassium dichromate, sodium thiosulfate, potassium dicyanoaurate, platinum, mercury, copper, tin, aluminum, palladium, molybdenum, vanadium, titanium, manganese, niobium, zirconium, methyl methacrylate, benzoyl peroxide, gentamycin and mupirocin.

• **Evidence is not conclusive** as to whether metal joint implants increase metal hypersensitivity or if metal hypersensitivity leads to prosthesis failure.

• **MOLECULAR CHARACTERIZATION OF REDOX MECHANISMS IN ALLERGIC ASTHMA** (Jiang L, Diaz PT, Best TM, Stimpfl JN, He F, Zuo L. Ann Allergy Asthma Immunol 2014; 113: 137-142):

  - Asthma: (i) definition: chronic inflammatory respiratory disease characterized by airway inflammation, hyperresponsiveness, obstruction and remodeling; (ii) prevalence: ~300 million people worldwide; (iii) impact: significant morbidity, ↓ QoL, mortality risk (250,000 deaths/year worldwide), high costs; (iv) several endotypes and phenotypes (e.g. TH2/eosinophilic
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- **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, 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.

- **Oxidative stress** appears to play a key role in the pathogenesis of allergic asthma → potential biomarker(s) for diagnosis and monitoring, promising therapeutic target.

**SPECIAL CHALLENGES IN TREATMENT AND SELF-MANAGEMENT OF OLDER WOMEN WITH ASTHMA** (Baptist AP, Hamad A, Patel MR. Ann Allergy Asthma Immunol 2014; 113: 125-130):

- Older asthmatic women: age group with the highest asthma mortality rate.

- Factors that may contribute to the higher burden of asthma among older women: (i) menopause can aggravate asthma; (ii) older woman are more prone to adverse effects of medications (e.g. systemic corticosteroids, adrenergic agonists); (iii) elderly patients have decreased responsiveness to β2-adrenergic agonists; (iv) elderly patients commonly use inhalers incorrectly; (v) older woman have decreased perception of breathlessness; (vi) comorbidities (obesity, depression, cardiovascular disease, GERD, other respiratory diseases); (vii) older women frequently work as caregivers (stressful work); (viii) older women frequently have less economy and education status than men.

- Primary immunodeficiency diseases (PIDs): (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 subjects; (iii) impact: severe complications (infections, autoimmunity, immune dysregulation, allergies, autoinflammation, cancer), ↓ QoL, mortality risk, high costs; (iv) early diagnosis and treatment can be lifesaving; (v) Jeffrey Model Foundation PID warning signs are useful for general alert of PIDs; (vi) recognizing which part of the immune system is primarily affected, even in the absence of a definitive diagnosis, is important for selecting initial treatment; (vii) except for patients with SCID or severe life-threatening immune dysregulation, most cases of PID can be initially treated with immunoglobulin replacement therapy, prophylactic antibiotics or immunosuppressive drugs, while searching for a definitive diagnosis; (viii) genetic diagnosis is usually important for specific therapy (including gene therapy), prognosis, genetic counseling and preimplantation diagnosis; (ix) when indicated, definite therapy of severe PIDs (e.g. HSCT) should not be delayed while waiting for genetic diagnosis.

- The last IUIS update (2013) lists >250 known PIDs, classifying them in 9 categories (some genotypes can lead to phenotypes that fit in >1 category [e.g. CD40 ligand deficiency is classified as both antibody deficiency and CID]); (i) combined immunodeficiencies (CID); (ii) CID with associated or syndromic features; (iii) predominantly antibody deficiencies; (iv) diseases of immune dysregulation; (v) congenital defects of phagocyte number, function, or both; (vi) defects that involve innate immunity; (vii) autoinflammatory disorders; (viii) complement deficiencies; (ix) phenocopies of PIDs (conditions that resemble PIDs and are not due to germline mutations [e.g. autoantibodies against IL817, somatic mutations in FAS]).

- PID diagnosis can be challenging because: (i) >200 different PID-causing genes have been described; (ii) clinical and laboratory presentation of PIDs can be very variable due to gene-gene interactions, environmental influence or epigenetics (e.g. RAG mutations can present with SCID, Omenn syndrome or hyper-IgM syndrome; WASP mutations can present as Wiskott-Aldrich syndrome, X-linked thrombocytopenia or X-linked neutropenia); (iii) current PID diagnostic approach is usually performed by phenotypic and functional characterization (time-consuming); (iv) genetic diagnosis is classically performed since 1977 by Sanger sequencing (laborious, time-consuming, expensive).

- Approaches for identifying PID causative mutations: (i) educated guesses based on known signaling pathways essential for immune cell development and function → targeted gene sequencing (e.g. discovery of CD40 ligand and CD40 deficiency as causes of hyper-IgM syndrome; discovery of IL-2 receptor γ chain, JAK3 and IL-7 receptor α chain deficiency as causes of SCID; discovery of IL-17 pathway defects as causes of CMC); (ii) similarity of clinical phenotypes to mouse models → targeted gene sequencing (e.g. discovery of WIPF1 deficiency in a female patient with a clinical phenotype resembling Wiskott-Aldrich syndrome; discovery of NKX2-5 deficiency as a cause of congenital asplenia); (iii) unbiased genetic approaches: linkage analysis with polymorphic markers (e.g. discovery of LRBA deficiency in patients with hypogammaglobulinemia, ↓ memory B-cell numbers and autoimmunity), next-generation DNA sequencing.
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• **Next-generation sequencing (NGS):** (i) rapid, accurate, low-cost, high-throughput DNA sequencing technology that has identified mutations in novel PID-causing genes (e.g. STAT1 mutations in patients with chronic mucocutaneous candidiasis; PLDN mutations in Hermansky–Pudlak syndrome type 9; IL10R1 mutations as a cause of neonatal-onset Crohn disease); (ii) simultaneously amplify and sequence millions of DNA fragments within few days; (iii) can be used to sequence the whole-genome [WGS] or the whole-exome [WES] (sum of all exons and their adjacent nucleotides; approximately 85% of PID-causing deleterious mutations occur in these regions); (iv) useful diagnostic tool for complex PIDs, particularly for patients with atypical disease presentation; (v) promising tool for early diagnosis and treatment of PID in patients presenting with a 1st episode of severe infection (PID screening); (vi) WGS and WES can be complemented with homozygous mapping (e.g. discovery of LRBA deficiency in a consanguineous family with chronic IBD and combined immunodeficiency; discovery of RHOH deficiency in a consanguineous family with naive T-cell lymphopenia, defective T-cell activation and epidermodysplasia verruciformis; discovery of MALT1 deficiency as a cause of combined immunodeficiency); (vii) advantages of WGS over WES: detection of mutations in noncoding regions (~99% of the genome), greater capacity to detect structural variants.

• **Limitations of NGS:** (i) differentiation between pathogenic mutations and irrelevant variations can be challenging, especially for variations in noncoding regions or mutations with autosomal dominant effect or incomplete penetrance; (ii) insufficient gene coverage (WES might not adequately sequence as much as 10% of genes); (iii) low ability to identify structural variations of the genome such as copy number variations, deletions, inversions and translocations (e.g. WGS was not able to initially detect a heterozygous deletion in PLCG2 in 3 families with dominantly inherited cold-induced urticaria, antibody deficiency and autoimmunity).

• **Human genome=3.2 billion bases. Human exome=30 million bases (1% of the human genome).**

• Any genome will have ~4 million variants differing from the reference genome. ~20,000 will occur in the coding and splice site regions. ~10,000 will be nonsynonymous. 200-1000 will be “novel” (not reported in existing SNP public databases; ~75% existing in heterozygous state) → which of these “novel” mutations is pathogenic? Bioinformatic programs can help to predict the effect in protein function (e.g. Polyphen-2, SIFT, MutationTaster, MAPP) and assess sequence conservation (GERP, Phylo-P SCORE) → if several “possible pathogenic” genes persist, genes essential for immune function are prioritized for Sanger sequencing and functional analysis, while those unrelated to immune function can often be excluded.

• **Mutations in noncoding regions (~99% of the genome):** (i) its pathogenic effect is difficult to establish, a known candidate gene is usually needed (e.g. discovery of intronic UNC13D mutations causing familial HLH type 3; intronic GATA2 mutations in patients with MonoMAC syndrome; intronic SH2D1A mutations causing XLP; a mutation in the 59 untranslated region of NEMO causing X-linked ED-ID); (ii) novel bioinformatic and laboratory tools to predict pathogenicity are necessary.

• A genome has ~69% more heterozygous than homozygous variants → identification of pathogenic mutations with an autosomal dominant effect is challenging (a multiple-generation pedigree with 6 to 12 affected subjects is often necessary to detect a mutation with autosomal dominant effect) → sequencing affected subjects from unrelated families can help (e.g. discovery of heterozygous mutations in GATA2 causing MonoMAC syndrome).
• Mutations with incomplete penetrance are not easily detected by NGS (e.g. an autosomal dominant missense mutation in TRIF causing susceptibility to herpes virus encephalitis with incomplete penetrance).

• Array comparative genomic hybridization can detect copy number variations (e.g. detection of novel deletions in DOCK8 in patients with autosomal recessive hyper-IgE syndrome; detection of large deletions in CYBB causing chronic granulomatous disease).

• MHC CLASS I AND II DEFICIENCIES (Hanna S, Etzioni A. J Allergy Clin Immunol 2014; 134: 269-275):
  
  MHC class I deficiency: (i) genetic defects: TAP1, TAP2, TAPBP (encoding tapasin), undefined genes; (ii) inheritance: autosomal recessive; (iii) few cases have been reported worldwide.

  TAP1 or TAP2 deficiency: (i) patients can be asymptomatic, especially through infancy; (ii) clinical features: bacterial respiratory tract infections, bronchiectasis, sterile necrotizing skin granulomatous lesions (dysregulated immune response?) mainly affecting the legs (midface deformity can occur when the upper respiratory tract is affected); (iii) immunologic findings: normal total lymphocyte counts, ↓ CD8 T-cell counts, normal CD4 T-cell and B-cell counts, normal responses on mitogen stimulation, normal specific immune reactivity to foreign antigens; (iv) diagnosis: serologic HLA typing, HLA homozygosity (TAP and tapasin genes are located within the MHC locus on chromosome 6), flow cytometric analysis of PBMCs labeled with a pan-anti-HLA class I mAb (W6/32), genetic sequencing; (v) differential diagnosis: CGD, CVID, granulomatosis with polyangiitis, sarcoidosis; (vi) treatment: prevention and treatment of respiratory infections, basic antiseptic care for skin ulcers (skin grafting had no positive effects; IFN-α treatment worsened the lesions).

  Tapasin deficiency was reported in only 1 patient who had late-onset chronic primary glomerulonephritis without any of the symptoms associated with TAP deficiencies.

  MHC class I deficiency with unknown genetic defect was reported in 2 brothers; one had unexplained steroid-responsive anemia, the other was completely asymptomatic.

  Why patients with MHC class I deficiency seem to maintain intact immunity to virus and cancer cells? Hypothesis: (i) NK cells, αβ CD8+ cells and γδ T cells might give protection in a TAP-independent manner; (ii) residual MHC class I expression.

  MHC class II deficiency: (i) genetic defects: CIITA, RFX5, RFXAP, RFXANK (transcription factors for MHC class II proteins); (ii) inheritance: autosomal recessive; (iii) ~200 patients reported worldwide; (iv) clinical features: recurrent early-onset severe infections (bacteria, virus, fungi, protozoa), protracted diarrhea, failure to thrive, liver/biliary tract disease (including sclerosing cholangitis), autoimmune cytopenias, dysmorphic features (reported in 3 unrelated patients); (v) immunologic findings: ↓ CD4 T-cell counts, normal CD8 T-cell and B-cell counts, low serum immunoglobulin levels, normal responses on mitogen stimulation, absence of specific cellular and humoral responses to foreign antigens, detectable TREC; (vi) diagnosis: absence of MHC class II molecule expression on cell surface, genetic sequencing (RFXANK deficiency accounts for >70% of all known patients); (vii) treatment: HSCT (earlier HSCT has better prognosis; HSCT does not correct the absence of MHC class II expression on thymic epithelial cells), intravenous immunoglobulin, treatment and prevention of infections and other
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- **RISKS FOR INFECTION IN PATIENTS WITH ASTHMA (OR OTHER ATOPIC CONDITIONS): IS ASTHMA MORE THAN A CHRONIC AIRWAY DISEASE?** (Juhn YJ. J Allergy Clin Immunol 2014; 134: 247-257):
  - Atopic diseases can ↑ predisposition to infection incidence and severity: (i) potential reasons: ↓ epithelial barrier, ↓ innate immunity, dysregulated adaptive immunity; (ii) examples: asthma patients have ↑ susceptibility to severe pneumococcal disease and human rhinovirus infection; atopic dermatitis patients have ↑ susceptibility to S aureus infection and herpesvirus infection.
  - Microorganisms can aggravate atopic diseases: (i) S aureus infection can aggravate atopic dermatitis and chronic rhinosinusitis; (ii) viral respiratory infections can cause asthma initiation and exacerbations; (iii) fungal infections can aggravate bronchial asthma, chronic rhinosinusitis and atopic dermatitis; (vi) Candida infections can aggravate eosinophilic esophagitis.
  - Biomarkers to identify atopic patients with increased susceptibility to infections are necessary.

  - Angioedema: (i) definition: localized and self-limiting edema of subcutaneous and submucosal tissue; (ii) cause: release of vasoactive mediators → temporary increase in vascular permeability; (iii) it can accompany urticaria (wheals) or present alone (no wheals); (iv) EAACI new classification of angioedema (does not include urticaria with angioedema) distinguishes 3 hereditary types and 4 nonhereditary types.
  - Hereditary angioedema (HAE): (i) HAE with C1-inhibitor deficiency (C1-INH-HAE): type I and type II; (ii) HAE with FXII mutation (FXII-HAE): autosomal dominant trait with low penetrance; (iii) HAE of unknown origin (U-HAE): similar to FXII-HAE but with no FXII mutations.
  - Acquired angioedema (AAE): (i) idiopathic histaminergic AAE (IHAAE): improves with antihistamines, no underlying cause is identified; (ii) idiopathic nonhistaminergic AAE (InH-AAE): antihistamine-refractory (4x dose); (iii) AAE related to angiotensin-converting enzyme inhibitors (ACEI-AAE): occurs in <1% of treated subjects; (iv) AAE with C1-INH deficiency (C1-INH-AAE): associated with underlying lymphoproliferative or autoimmune diseases.
  - Drugs to treat angioedema (mostly studied in C1-INH-AAE): (i) plasma-derived or recombinant human C1-INH; (ii) ecallantide (inhibitor of kallikrein); (iii) icatibant (BK type 2 receptor antagonist); (iv) attenuated androgens; (v) tranexamic acid; (vi) freshly frozen plasma.
  - Acquired angioedema with C1-INH deficiency (C1-INH-AAE): (i) recurrent episodes of bradykinin-mediated angioedema due to C1-INH consumption; (ii) estimated prevalence: 1/100,000-1/500,000; (iii) pathophysiology: lymphoproliferative disorders, autoimmune diseases (e.g. SLE, vasculitis), neoplasms, monoclonal gammopathies, infections → autoantibody production (including to C1-INH) → activation of the classical complement pathway → consumption of C1q, C1-INH and C4 → ↑ activity of FXII and kallikrein → ↑ bradykinin production → C1-INH-AAE; (iv) usually presents after 40 yrs of age; (v) clinical manifestations: recurrent swelling of subcutaneous tissues (face, extremities, genitals), abdominal organs...
(stomach, gut, bladder) or upper airways (larynx), unresponsive to antihistamines or corticosteroids; (vi) laboratory: ↓ or normal C1-INH level, ↓ C1-INH activity, ↓ C4 level, ↓ C1q level (70% of cases), autoantibodies to C1-INH (in some patients); (vii) treatment of acute attacks (based on case reports and series): plasma-derived C1-INH, icatibant, ecallantide, fresh frozen plasma; (viii) long-term treatment: therapy of underlying disease, ↓ attack triggers, attenuated androgens, antifibrinolytic agents, plasma-derived C1-INH, rituximab.

• Authors report the case of a 66-yr-old woman with C1-INH-AAE and non-Hodgkin lymphoma (splenic marginal zone type) → treatment: splenectomy, short-term prophylaxis with human C1-INH (plasma-derived or recombinant) before surgeries.

• Author’s commentary: 1st case report on short-term prophylaxis in C1-INH-AAE using recombinant human C1-INH.


  • Primary immunodeficiency diseases (PIDs): (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 subjects; (iii) impact: severe complications (infections, autoimmunity, immune dysregulation, allergies, autoinflammation), ↓ QoL, mortality risk, high costs; (iv) early diagnosis and treatment can be lifesaving.

  • Severe combined immunodeficiencies (SCID): genetic defects causing complete lack of T-cell development → lack of cellular and humoral immunity → early-life severe infections (including opportunistic), fatal course if not treated (HSCT, gene therapy, enzyme replacement therapy).

  • Combined immunodeficiencies (CID): genetic defects causing reduced T-cell function → ↓ cellular and humoral immunity → severe infections (including opportunistic), immune dysregulation, usually fatal course if not treated.

  • Nuclear factor κB (NF-κB): (i) chief regulator of immune cell activation, survival and proliferation; (ii) excessive NF-κB activity is associated with cancer (particularly B-cell malignancy) and autoimmunity; (iii) defective NF-κB activity is associated with immunodeficiency.

  • Caspase recruitment domain family, member 11 (CARD11), B-cell chronic lymphocytic leukemia/lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) form the CARD11-BCL10-MALT1 (CBM) signalosome complex.

  • CBM complex: essential molecular link between the triggering of cell-surface antigen receptors (e.g. TCR, BCR, TLR) and NF-κB activation.

  • CARD11 is only expressed in the hematopoietic system and appears to be specific for signaling through TCR and BCR. BCL10 and MALT1 are much more broadly expressed, along with proteins that replace CARD11 function (e.g. CARD9, CARD10).

  • Certain B-cell lymphomas are associated with chromosomal translocations that increase BCL10 or MALT1 activation.
• Authors review the clinical and immunologic features of novel combined immunodeficiencies due to germline mutations affecting the CBM complex (defining features: abnormal NF-κB activation, dysregulated B-cell development).

• **CARD11 loss-of-function mutations** (OMIM #615206) → severe cellular immunodeficiency, early-onset panhypogammaglobulinemia, ↓ NF-κB activation, normal T-cell counts, ↓ T-cell proliferation, ↓ Treg cells, ↓ TH17 cells, ↑ transitional B cells, ↓ mature B cells, fatal course if untreated (HSCT).

• **CARD11 gain-of-function mutations** (OMIM #606445), also called BENTA (B-cell expansion with NF-κB and T-cell anergy): early-onset massive B-cell lymphocytosis, splenomegaly, lymphadenopathy, ↓ B-cell differentiation, ↓ T-cell activation and proliferation, mild immunodeficiency (recurrent sinopulmonary and viral infections).

• **MALT1 loss-of-function mutations** (OMIM #615468): recurrent sinopulmonary infections, extensive inflammatory gastrointestinal disease, pathologic fractures, ↓ NF-κB activation, normal T-cell numbers, ↓ T-cell proliferation, impaired B-cell differentiation, ↑ transitional B cells, normal numbers of Treg and TH17 T-cell counts, normal immunoglobulin levels, variable ability to produce specific antibodies against protein and polysaccharide antigens, fatal course if untreated (HSCT).

• Why is *Pneumocystis jirovecii* pneumonia so prominent in patients with CARD11 but not MALT1 deficiency? Why is gastrointestinal inflammation a prominent feature of MALT1 mutations?

• Features that should raise suspicion for loss-of-function mutations affecting the CBM complex: CID with normal T-cell numbers, ↓ T-cell proliferation, ↓ NF-κB activation after BCR/TCR and PMA stimulation, defective B-cell development with a transitional B-cell block.

• **Inhibitors of the CBM complex** (e.g. MALT1 protease inhibitors) are potential therapies for immune-mediated diseases (allergy, autoimmunity, cancer, transplant rejection).


  • Caubet et al followed 160 children with food protein-induced enterocolitis syndrome (FPIES) → (i) median age at diagnosis=15 months; (ii) most common triggers: cow’s milk (44%), soy (41%), rice (22.5%), oat (16%); (iii) 65% of children reacted to 1 food, 26% to 2 foods, 9% to multiple foods; (iv) 39 children (24%) had positive specific IgE to the culprit food; (v) among children with cow’s milk-specific IgE, 35% eventually had acute allergic reactions; (vi) median age of tolerance=4 yrs for oat, 4.7 yrs for rice, 6.7 yrs for soy, 5.1 yrs for milk (patients with negative milk-specific IgE); (vii) no patient with detectable milk-specific IgE developed tolerance during the study → conclusion: FPIES might progress to IgE-mediated allergy.

  • Porter et al show that common environmental fungi grew in the upper airway of patients with allergic chronic rhinosinusitis (aggravation of allergic disease?) → eradication of such fungi might improve disease management.

  • Newby et al show that patients with severe asthma had an accelerated rate of lung function decrease if they had variable eosinophilic airway inflammation, in contrast to patients with persistent sputum eosinophilia or patients without airway eosinophilia → variable airway eosinophilia is a potential asthma risk biomarker.
• **Sphingosine-1-phosphate (S1P) receptors** are important for lymphocyte circulation.

• Sic et al show that: (i) different B-cell subsets expressed different combinations of the S1P receptors S1P1, S1P2 and S1P4; (ii) S1P1 induced, but S1P2 inhibited, B-cell migration; (iii) in patients with multiple sclerosis, fingolimod (S1P analog) significantly blocked the circulation of all B-cell subsets except plasma cells; (iv) *DOCK8*, *LRBA* and *WASP* mutations, as well as the Bruton tyrosine kinase inhibitor ibrutinib, prevented S1P-dependent migration.

• **Therapies targeting S1P receptor signaling** might be effective in treating immune-mediated diseases other than multiple sclerosis.

• Dhingra et al studied skin immune responses to patch testing with different contact sensitizers → nickel prominently induced TH1 and TH17 T cells; fragrance and rubber activated TH2 and TH22 T cells → allergic contact dermatitis should not be considered a single entity across all allergens.

• Hong et al show that rhinovirus induced the expansion of IL-13-secreting type 2 innate lymphoid cells (ILC2) in neonatal mice but not in mature mice; anti-IL-25 antibody attenuated ILC2 expansion, mucus hypersecretion and airway responsiveness → early-life rhinovirus infection might contribute to asthma development by provoking IL-25-driven type 2 immune responses.