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.

Juan Carlos Aldave Becerra, MD
Allergy and Clinical Immunology
Hospital Nacional Edgardo Rebagliati Martins, Lima-Peru
jucapul_84@hotmail.com

Juan Félix Aldave Pita, MD
Medical Director
February 2013 – content:


• CHARACTERIZATION OF ASPIRIN ALLERGIES IN PATIENTS WITH CORONARY ARTERY DISEASE (Feng CH, White AA, Stevenson DD. Ann Allergy Asthma Immunol 2013; 110: 92–95).


• SHOULD EXHALED NITRIC OXIDE BE PART OF ROUTINE ASTHMA MANAGEMENT? (Jain, MD Peter Boggs, MD Myron Zitt, MD. Ann Allergy Asthma Immunol 2013; 110: 129-130).


ζ CHAIN–ASSOCIATED PROTEIN OF 70 KDA (ZAP70) DEFICIENCY IN HUMAN SUBJECTS IS ASSOCIATED WITH ABNORMALITIES OF THYMIC STROMAL CELLS (Poliani PL, Fontana E, Roifman CM, Notarangelo LD. J Allergy Clin Immunol 2013; 131: 597-600).

A PROPOSED EXPLANATION FOR INCREASED RISK OF ACTIVE TUBERCULOSIS IN CHILDREN WITH ALLERGIC DISEASE (Eisenhut M. Pediatr Allergy Immunol 2013; 24: 98).


DESENSITIZATION TO ANTIBIOTICS IN CHILDREN (Cernadas JR. Pediatr Allergy Immunol 2013: 24: 3–9).


The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

ALLERGY:

  • Authors report 97 and 94 patients (>18 yr old) with moderate-severe persistent AR who received active or sham acupuncture, respectively (3 times/wk for 4 wks) → both active and sham acupuncture ↓ significantly AR symptoms; effect was greater with active acupuncture.
  • Acupuncture: needles are inserted at specific points in the body, and manipulated or electrically stimulated; ↓ symptoms of several diseases, including osteoarthritis, vomiting and itch.

  • Authors report 88 children (6–17 yr old) with severe therapy-resistant asthma → blood eosinophilia suggested high likelihood of airway eosinophilia; however, normal blood eosinophil levels did not exclude airway eosinophilic inflammation.
  • Blood eosinophil counts rarely reflect airway inflammation in severe asthmatic children.

  • Eosinophil functions: cytotoxicity, repair, remodeling, angiogenesis, immunomodulation.
  • Eosinophils can store cytokines in cytoplasmic granules → immediate availability.
  • Eosinophils do not only express Th2 cytokines, but also Th1 and regulatory cytokines.
  • Secretion of preformed intracellular granules occur in 4 ways: (i) classic exocytosis: granules fuse with cell membrane → total release of single granule's contents; (ii) compound exocytosis: ≥2 granules fuse prior to fusion with cell membrane → simultaneous release of multiple granule contents; (iii) piecemeal degranulation (PMD): cytokines are selectively depleted from granules and transported within secretory vesicles to the cell membrane for release; (iv) cytolysis: intact granules are liberated through a ruptured cell membrane.
  • Most commonly observed mechanisms of eosinophil degranulation in human diseases in vivo: PMD and cytolysis.
  • Receptor-mediated trafficking of cognate cytokines: exogenous stimulation of the eosinophil → specific cytokine receptor chains mobilize to intracellular granules → receptors sequester granule-derived cognate cytokines → the conjugate cytokine-receptor is packaged into secretory vesicles → vesicles are transported to the cell membrane for secretion.

• **EGPA:** usual onset: 40–60 yr old; pediatric cases have been reported.

• **Pathogenesis:** not well defined; association with HLA-DRB4; possibly triggered by infections, allergens or drugs; Th2 responses are prominent; Th1 and Th17 responses are not negligible; increased production, recruitment, activation and survival of eosinophils; humoral immunity is dysregulated (prominent IgG4 and IgE responses).

• 3 phases, which partially overlap: 1) prodromic, allergic phase: asthma (95-100% of patients) and rhinosinusitis; 2) eosinophilic phase: marked peripheral eosinophilia (>1,500/μL), organ involvement (lungs, heart, GI tract); 3) vasculitic phase: systemic small-vessel vasculitis, constitutional symptoms, peripheral neuropathy, renal damage, skin lesions, frequent paradoxical improvement of asthma.

• **Histology:** eosinophilia, necrotizing vasculitis, eosinophil-rich granulomatous inflammation.

• **Laboratory:** marked eosinophilia; ↑ ESR, CRP, IgE and IgG4; ANCA are positive in ~40% of patients (usually p-ANCA, anti-MPO), associated with vasculitis; increased eotaxin-3.

• **Typical case of EGPA:** Patient with adult-onset asthma and rhino-sinusitis, who develops marked eosinophilia and lung infiltrates (peripheral, patchy and migratory).

• **Treatment:** glucocorticoids; immunosuppressants (e.g., cyclophosphamide, azathioprine, methotrexate); new therapeutic options; mepolizumab (anti-IL5 mAb), rituximab (B-cell-depleting agent).

• **UNEXPLAINED RECURRENT FEVER: WHEN IS AUTOINFLAMMATION THE EXPLANATION?**


  • **Differential diagnosis of recurrent fever:** infections, neoplasms, autoimmune diseases, autoinflammatory diseases, drugs, factitious, benign hyperthermia, central fever.

  • **Key questions to a patient with recurrent fever:** 1) At what age did symptoms first appear; 2) What is the duration of the individual fever episodes; 3) What is the time interval between episodes (duration, variable or fixed intervals); 4) What other symptoms are associated with the fever episodes; 5) What can trigger or alleviate a fever episode; 6) How have symptoms developed over time; 7) Which treatments have been used and what was the response; 8) Is there a family history; 9) Does the patient originate from a certain ethnicity?

  • **Authors present beautiful tables and figures to describe and differentiate autoinflammatory syndromes.**
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

• A CASE OF DRESS SYNDROME INDUCED BY THE ANTITUBERCULOSIS DRUGS, PROTHIONAMIDE, AND PARA-AMINOSALICYLIC ACID (Joo-Hee Kim, Seung Hun Jang, Dong Hoon Kim, Sunghoon Park, Dong-Gyu Kim, Ki-Suck Jung. Ann Allergy Asthma Immunol 2013; 110: 118–119):
  • DRESS (drug reaction with eosinophilia and systemic symptoms): rash, fever, lymphadenopathy, eosinophilia, hepatitis; typically develops 2-8 weeks after drug initiation; common culprit drugs: phenobarbital, carbamazepine, phenytoin, lamotrigine, sulfonamides; diagnosis: drug challenge is the gold standard but it has high risk; patch tests, intradermal tests and lymphocyte transformation tests may be useful.
  • Authors report a 33-year-old man with DRESS caused by the second-line antituberculosis drugs prothionamide and para-aminosalicylic acid. Diagnosis was confirmed by drug challenges.
  • Severe reactions to antituberculosis drugs are a great trouble, especially in patients with multidrug-resistant infections, because: 1) patients require prompt therapy; 2) patients need a combination of several drugs; 3) therapy lasts months to years; 3) in some cases it is difficult to find alternative drug regimens; 4) diagnostic tests are not standardized.

  • Drug challenge: gold standard test to diagnose or exclude drug hypersensitivity. Graded challenge is performed when drug allergy is unlikely. Benefits: prevents false labeling of “allergic” patients, eliminates need for drug desensitization, gives confidence to the patient.
  • Many individuals report subjective symptoms after drug intake, which do not suggest a true allergic reaction. Placebo-controlled drug challenge is performed when there is a high suspicion of a nocebo effect (adverse reaction to placebo).
  • Authors report 114 “allergic” patients who underwent 123 drug challenges to the suspected drug or a different drug within the same class) → only 1 patient apparently had a positive reaction (delayed rash reported by phone call, it was not verified); 20 patients reported subjective symptoms (risk factors: female gender, higher number of previous reactions, previous subjective reactions).
  • Low-risk drug challenges: (1) patients with negative penicillin skin test results challenged with a penicillin; 2) penicillin allergic patients challenged with a cephalosporin or a carbapenem; (3) challenges with local anesthetics.
  • High-risk drug challenge: patients with aspirin-exacerbated respiratory disease (AERD) who undergo aspirin challenge.

• **Adherence to therapy** is low among patients with chronic diseases, such as asthma. Reasons: 
  - **patient issues** (eg, low confidence; 
  - **physician issues** (eg, prescribing complex medication regimens; 
  - **administrative or financing issues** (eg, high costs, limited access to appointments).

• Authors report 1,025 patients (5-56 years old) with asthma receiving ICS; patients were considered adherent if ICS use was >80% of prescribed → adherence was low (36%); patients who believed that God determined asthma control were less likely to be adherent.

• **Health locus of control**: individual’s belief about whom or what determines health (doctors, personal behaviour, chance, God, etc.).

• **CHARACTERIZATION OF ASPIRIN ALLERGIES IN PATIENTS WITH CORONARY ARTERY DISEASE** (Feng CH, White AA, Stevenson DD. Ann Allergy Asthma Immunol 2013; 110: 92–95):
  - **Hypersensitivity to aspirin**: 1) respiratory sensitivity (asthma and/or rhinitis), 2) cutaneous sensitivity (urticaria and/or angioedema), 3) anaphylaxis (very rare).
  - Authors report 9,565 patients with coronary artery disease (CAD) → 142 patients (1.5%) had a history of adverse reactions to aspirin; 30 patients (0.3%) had cutaneous and/or respiratory reactions, the other patients had mostly gastrointestinal intolerance or bleeding; 34 patients were receiving daily cardiovascular prophylaxis with aspirin; of 108 patients not receiving aspirin, 25 were prescribed clopidogrel.
  - **Aspirin desensitization** (elimination of pharmacologic and immunologic reactions by exposing a patient to increasing doses of aspirin) was seriously underused in the study population.
  - Since 1988, 87 aspirin desensitizations have been reported. Aspirin desensitization can be performed in the emergency or in the outpatient setting.

• **EFFECT OF MITE ALLERGEN IMMUNOTHERAPY ON THE ALTERED PHENOTYPE OF DENDRITIC CELLS IN ALLERGIC ASTHMATIC CHILDREN** (Chuang-Ming Wang, Jing-Jing Chuang. Ann Allergy Asthma Immunol 2013; 110: 107-112):
  - Effect of mite immunotherapy in dendritic cells of allergic asthmatic children: ↓ expression of CD86 and HLA-DR; ↑ expression of TLR4.
  - CD86, HLA-DR and TLR4 expression may be useful parameters for monitoring SIT efficacy.
  - TLR4 agonists might overcome decreased TLR4 expression in allergic patients, with the potential of improving SIT effects.

  - Many patients with chronic spontaneous urticaria (CSU) do not improve with conventional therapy, such as antihistamines or leukotriene antagonists.
  - Authors report 16 patients with severe CSU who receivedomalizumab (150 mg every 2-4 weeks) between 2010 and 2011 → 10 patients (63%) had remission after the first injection; 4 patients (25%) required 2-6 treatments to achieve remission; 2 patients (12%) discontinued treatment after 2 injections; of the 14 patients who initially benefited, 4 remain asymptomatic >9
months after their last injection, 7 patients continue in remission with maintenance omalizumab, 3 patients became refractory and discontinued treatment.

- Omalizumab was an effective treatment for inducing and maintaining long-term remission for patients with severe CSU. Larger randomized trials are necessary to confirm these findings.

  - Drugs to prevent HAE attacks: 1) Attenuated androgens: low price; considerable dose-dependent side effects; contraindicated in children, pregnancy and breastfeeding. 2) C1INH replacement therapy (Cinryze, Viropharma): good safety profile; very expensive (highest annual cost of any drug in the US); reduce 50% of attacks. 3) Tranexamic acid.
  - Drugs to treat HAE attacks: 1) C1INH (Berinert, CSL Behring); 2) ecallantide (Kalbitor, Dyax): inhibitor of kallikrein; 3) icatibant (Firazyr, Shire): bradykinin receptor antagonist. For the 3 agents, many patients improve in <30 minutes, 75% of patients improve in <4 hours, complete alleviation is often achieved in 8-12 hours; none of the therapies completely control symptoms in every patient. Good safety profile for the 3 agents (3% risk of anaphylaxis with ecallantide).
  - 1983: the Orphan Drug Act (ODA) was declared to stimulate development of drugs for diseases that affect <200,000 individuals (7-year market exclusivity, development tax credits, less rigorous FDA approval process). In the decade before 1983 only 34 orphan drugs went on the market; between 1983 and 2009 FDA approved 275 orphan drugs for 337 orphan indications.
  - HAE affects approximately 6,000 individuals in the US (prevalence: 1/50,000) → all of the recently approved HAE treatments were developed under the auspices of the ODA program.

  - Mannose-binding lectin (MBL) activates complement by the lectin pathway, facilitating pathogen phagocytosis. It may also have an anti-tumorigenic role.
  - Mutations in MBL2 gene → low levels of MBL → susceptibility to diverse infections (bacterial, mycobacterial, viral, protozoal and fungal) and malignancies.
  - Authors report a 66-year-old man with a history of spindle cell tumor, pulmonary Mycobacterium avium infection, nasal aspergillus mycetoma and suspected strongyloidiasis. Immunologic evaluation demonstrated an undetectable MBL level of <0.5 ng/mL (normal >7.8 ng/mL).
  - Infections by Mycobacterium avium and Aspergillus suggest a possible role of MBL in augmenting adaptive cellular immune response.
  - Always suspect MBL deficiency in patients with recurrent or atypical infections in whom other studies of the immune system are normal.

- **MOSQUITO ALLERGY** (Crisp HC, Johnson KS. Ann Allergy Asthma Immunol 2013; 110: 65-69):
• **Mosquitoes:** class Insecta, order Diptera, family Culicidae; >3,500 species worldwide; need aquatic habitats; both sexes feed on plant juices for energy; females of most species require a blood-meal after copulation to complete egg development; 50-500 eggs are placed onto water surfaces or moist soil; Aedes and Culex are the most common genera in North America.

• **Mosquito saliva** contains >30 proteins that facilitate feeding (antiplatelet, anticoagulant and vasodilator properties); many of them are allergenic.

• **Typical reactions to mosquito bites:** 1) **Immediate reaction** (80% of bitten subjects): 2-10 mm wheals with surrounding erythema peaking in 20-30 minutes; correlates with saliva-specific IgE and IgG. 2) **Delayed reaction** (60% of individuals): 2-10 mm pruritic papules peaking at 24-36 hours and diminishing in several days; correlates with saliva-specific IgG and T cells.

• **Large local reactions** (2-5% of bitten subjects): 1) **Immediate:** erythematous pruritic swelling >3 cm occurring in minutes to hours at the site of a bite; correlates with saliva-specific IgE and IgG. 2) **Delayed:** papular, vesicular, blistering, bullous or ecchymotic, lesions that persist for days or weeks; correlates with saliva-specific IgG and T cells.

• **Skeeter syndrome:** large local reactions accompanied by fever; may mimic cellulitis; resolve in 3-10 days; correlates with saliva-specific IgG and IgG.

• **Anaphylactic reactions:** extremely rare; risk factors: high exposure, lack of acquired immunity (young children and immigrants).

• **Lymphoproliferative and hemophagocytic syndromes:** might occur in patients with Epstein-Barr virus (EBV)-associated lymphoproliferative diseases; hypothesis: repeated activation of saliva-specific CD4+ T cells, which induce reactivation of latent EBV in NK cells.

• **Natural history** of mosquito bite reactions in an individual progress through 5 stages: 1) no reaction (first exposure) → 2) delayed reactions only → 3) immediate reactions followed by delayed reactions at the same site → 4) immediate reactions only → 5) no reaction (desensitization, it may take 2-20 years).

• **Diagnosis** of mosquito allergy is mainly clinical. Patients with typical reactions should not be labeled as “allergic”; this term should be reserved for those with large local, atypical, or systemic reactions.

• In patients with a history of severe or atypical reactions, **diagnostic testing** might be helpful. Currently available tests (skin testing with whole-body extracts, in vitro detection of specific IgE) lack adequate sensitivity and specificity.

• **New approaches for diagnosis:** skin tests with standardized and recombinant allergens; mosquito bite testing (problems: trapping female insects, risk of eliciting severe reactions, risk of disease transmission; it may be considered in research to confirm clinical sensitivity).

• **Treatment:** avoidance (mosquito reduction, reduction of standing water, protective clothing, chemical repellants, mosquito netting, sleeping indoors); medication (prophylactic antihistamines, topical steroids, oral steroids, antipyretics for Skeeter syndrome, antibiotics if secondary bacterial infection occurs, epinephrine); immunotherapy (whole-body mosquito extracts are not standardized, recombinant allergens should be considered).
• N,N-diethyl-m-toluamide (DEET): the most effective insect repellant for skin or clothing; indicated for children >2 years old; appropriate concentrations between 10-30%, higher concentrations can cause systemic toxic effects, dermatitis or bullous eruptions.

• Permethrin 0.5% may be applied to clothes and bed nets 6 hours before wear to ↑ protection.


  • CVID: heterogeneous syndrome characterized mainly by hypogammaglobulinemia and impaired specific antibody responses; higher risk of infections, malignancy and autoimmunity.

  • Progressive multifocal leukoencephalopathy (PML): opportunistic demyelinating CNS disease caused by John Cunningham (JC) virus (polyoma group DNA virus); usually affects individuals with profound cellular immunosuppression.

  Authors report a 29-year-old woman with CVID and PML. Clinical history: recurrent sinopulmonary infections from 3 years old; thrombocytopenia and splenomegaly from 7 years old; splenectomy at 9 years old; initial diagnosis: selective IgA deficiency; meningitis at 15 and 18 years old; diagnosis of CVID at 18 years old; large palmar and plantar planar warts at 22 years old; 1 episode of left knee septic arthritis; PML diagnosed at 28 years old (dysarthria, ataxia, apraxia, radiographic abnormalities, positive PCR for JC virus in CSF).

• SHOULD EXHALED NITRIC OXIDE BE PART OF ROUTINE ASTHMA MANAGEMENT? (Jain, MD Peter Boggs, MD Myron Zitt, MD. Ann Allergy Asthma Immunol 2013; 110: 129-130):

  • Proposed utility of FeNO measurements: support diagnosis of asthma; support differential diagnosis; monitor airway inflammation; fine-tune ICS dosing. Its real value is controversial.


  • CU: 30% of patients are refractory to antihistamines; many patients use oral steroids. Immunomodulatory therapies may improve CU symptoms and decrease steroid use.

  Authors report 47 patients with antihistamine-refractory CU who received immunomodulatory therapies. 1st choice: hydroxychloroquine or sulfasalazine; 2nd choice: mycophenolate mofetil, cyclosporine or tacrolimus; 3rd choice: omalizumab → Age average: 44 years old; 69% of patients were female; 89% of patients were taking daily or frequent steroids.

  • Clinical benefit → cyclosporine: 88% of treated patients; sulfasalazine: 75%; tacrolimus: 60%; hydroxychloroquine: 56%; mycophenolate mofetil: 55%; omalizumab: 100% (only 3 patients).

  • Adverse events that required stopping therapy → hydroxychloroquine: 2 patients with drug eruptions; 1 patient with a mucosal reaction; sulfasalazine: 1 patient with gastrointestinal symptoms; cyclosporine: 1 patient with hypertension.

  • Cyclosporine is the only immunomodulatory therapy that has RCT data to support its use in CU.
• Omalizumab is being evaluated in a phase 3 clinical trial for treatment of CU.

• **WHEAT-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS (WDEIA) IN ELDERLY PATIENTS**

  • **Food-dependent exercise-induced-anaphylaxis** is caused by aerobic exercise within 2-4 hours after food ingestion; variable severity; usually occurs in adolescents and young adults.

  • Authors report 2 elderly patients (85-year-old woman and 79-year-old man) with WDEIA after mild physical activity. Diagnosis was confirmed by detection of specific IgE against recombinant omega-5 gliadin. Patients have remained asymptomatic by avoiding any significant physical activity for at least 3 hours after wheat ingestion.

  • The concept of exercise is not well defined for elderly patients. Proposed new terminology: “activity-dependent wheat allergy”.
JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:

  - WAS: X-linked disorder; mutation in the WAS gene; triad of thrombocytopenia, eczema, and susceptibility to infection. XLT: attenuated form of WAS with minimal or no immunodeficiency.
  - Autoimmune complications occur in 40-70% of WAS/XLT patients. Glomerulonephritis occur in 3.5-19% of patients. IgA nephropathy (IgAN) is very common.
  - Authors report 26 patients with WAS or XLT → 11 patients had autoimmune complications (IgAN, vasculitis, arthritis, colitis, autoimmune hemolytic anemia and thrombocytopenia); these patients had increased levels of: a) galactose-deficient IgA, and b) IgG-IgA circulating immune complexes, in an age-dependent manner.
  - Hypothesis: WAS mutation → aberrant glycosylation of IgA → increased immune-mediated glomerulonephritis. Mechanisms of aberrant glycosylation of IgA remain unclear.

  - Non–IgE-mediated GI food allergies: food protein–induced enterocolitis syndrome, food protein–induced proctocolitis, food protein–induced enteropathy; underlying mechanisms are not well defined, except for an important role of TNF-α; TH2 cells are thought not to be involved.
  - Authors detect antigen-specific TH2 cell responses in infants with non–IgE-mediated GI food allergies.

  - Authors present a 32-page comprehensive document about atopic dermatitis (51 Summary Statements), in behalf of the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI).
  - Atopic dermatitis: 10-20% of children, 1-3% of adults; pathogenic factors: atopy, defects in the skin barrier and humidity, bacterial and fungal colonization of the skin, dysregulated innate and adaptive responses, increased early Th2 and Th22 responses, autoreactivity, stress; management: trigger avoidance, measures to restore skin barrier function, antiinflammatory medication.

  - The main purpose of PID classification is to define the natural history and the most appropriate treatment for each PID.
Why PID classification is difficult? a) Heterogeneity (current IUIS classification lists 188 PIDs); b) Defects in the same gene can cause different clinical phenotypes; c) Defects in different genes can result in the same clinical or laboratory phenotype.

Defects in \textit{RAG1} and \textit{RAG2} can result in different clinical phenotypes → a) T-B-NK+ SCID; b) Omenn syndrome; c) Combined immune deficiency (CID) with CMV infection and Tγδ lymphocyte expansion; d) CID with cutaneous granulomatous lesions.

\textbf{Omenn syndrome} can result from defects in: \textit{RAG1}, \textit{RAG2}, \textit{DLCRE1C}, \textit{IL2RG}, \textit{IL7R}, \textit{ADA}, \textit{LIG4}, \textit{RMRP7} (cartilage-hair hypoplasia).

SCID can evolve into Omenn syndrome after antigenic triggering.

Defects in \textit{WAS} can result in different clinical phenotypes → a) Wiskott-Aldrich syndrome (loss-of-function mutations); b) X-linked thrombocytopenia (loss-of-function mutations); c) X-linked severe congenital neutropenia (gain-of-function mutations).

Defects in \textit{STAT1} can result in different clinical phenotypes → a) Autosomal dominant gain-of-function mutations: chronic mucocutaneous candidiasis, autoimmunity; b) Autosomal dominant loss-of-function mutations: susceptibility to mycobacterial and Salmonella infection; c) Autosomal recessive loss-of-function mutations: severe viral or mycobacterial disease.

New-generation and whole-exome \textit{sequencing} will help to detect novel defects in well-known genes and to discover new PID-causing genes.

Does it matter whether a gene defect results in SCID, leaky SCID, atypical SCID, profound CID, or late-onset CID? It matters only if the treatment approach will differ. Multicenter clinical trials are required to define the most appropriate treatment for each PID.


Authors report 4 brothers from a consanguineous family → severe eczema, milk and egg allergies, recurrent infections, intractable diarrhea, failure to thrive, lymphoma, severe T-cell lymphopenia. 2 patients underwent successful HSCT from a matched unrelated donor.

Genetic sequencing showed: 1) a mutation in \textit{CLEC7A} (C-type lectin domain family 7, member A), also known as dectin-1, associated with familiar CMC; b) a novel mutation in \textit{DOCK8} (dedicator of cytokinesis 8).

\textit{Exome sequencing} should be considered in patients with atypical presentations of PID to examine possible mutations in >1 locus.

Authors report a 32-yr-old woman with autoimmune hepatitis who had received immunosuppressive therapy with corticosteroids and azathioprine for 9 years → she presented with fever, abdominal lymphadenopathy and diarrhea → bone marrow, liver, lymph node and duodenum biopsies showed macrophages containing acid-fast bacilli → Mycobacterium genavense DNA was detected → laboratory analysis of patient’s cells showed defective IFN-γ production in response to IL-12, lack of IL-12Rβ1 expression and impaired STAT-4 phosphorylation after stimulation with IL-12 → genetic sequencing showed a composite heterozygous mutations of IL12RB1 gene.

IL-12Rβ1 deficiency: most patients present with isolated BCG infection; some patients present with infections caused by environmental mycobacteria, M tuberculosis, Salmonella, Klebsiella or Nocardia; incomplete clinical penetrance; environmental factors may trigger disseminated infections (e.g. subcutaneous injection of BCG, use of immunosuppressant drugs).

MSMD (Mendelian susceptibility to mycobacterial diseases) may present as disseminated mycobacterial infection in patients receiving immunosuppressive treatment.


Traffic-related air pollutants, such as diesel exhaust particles (DEP), contribute to pathogenesis of wheezing and asthma in early childhood.

Authors report a study in 92 asthmatic children → children with increased FOXP3 methylation were 2 times more likely to have asthma than children with lower FOXP3 methylation.

Chronic DEP exposure during childhood → FOXP3 methylation → reduced FOXP3 expression → increased risk for persistent wheezing and asthma.

New strategy for asthma prevention and treatment: upregulate FOXP3 → expand Treg cells.


Certain microbial exposure in early life → TLR activation → modulation of the immune system → less atopy and asthma.

Asthma has been associated with genetic polymorphisms in TLR2, TLR4, TLR7, TLR8, TLR9.

Authors evaluated the association between asthma and SNPs in 41 genes from TLR-mediated signaling cascades → asthma was associated with SNPs in >20 genes; association for atopic asthma was distinct from nonatopic asthma, only partially overlapping → different TLR signaling mechanisms might be involved in the pathogenesis of atopic and nonatopic asthma.

• New PIDs are being discovered at an ever-increasing rate. Authors review 19 novel PIDs that have been discovered after the release of the last IUIS classification report.

• Each new PID provides valuable insights into how our immune system normally works.

• PROPHYLACTIC THERAPY IN CHILDREN WITH HEREDITARY ANGIOEDEMA (HAE) (Farkas H, Csuka D, Zotter Z, Varga L, Füst G. J Allergy Clin Immunol 2013; 131: 579-582):

  HAE: recurrent attacks of angioedema without urticaria due to C1-inhibitor deficiency; 50% of cases initiate in childhood or adolescence; 50% of patients may experience a life-threatening attack; management: treat and prevent attacks; prophylaxis in children is difficult because of few suitable medications and low safety profile.

  Authors report their experience managing 48 pediatric patients (<18 yr old) with HAE, and present an algorithm for HAE prophylaxis in children.

  HAE prophylaxis in children: a) Antifibrinolytics: agents of choice; rarely contraindicated (e.g. thrombophilia). b) Anabolic androgens: usually contraindicated; they may be necessary in a proportion of cases; danazol appeared well tolerated at the lowest effective dose. c) Human plasma-derived C1-INH: good option; problem: cost.


  Asthma: chronic inflammation in the airways → release of cytokines and growth factors → remodeling.

  TGF-β1 levels in the airways are increased in asthma. Actions: regulatory, profibrotic.

  Authors show that TGFB1 SNPs are significantly associated with asthma severity, airway inflammation and remodeling.

• TICK-BORNE ENCEPHALITIS VIRUS VACCINE AS ADDITIONAL ALTERNATIVE NEOANTIGEN FOR THE CLINICAL IMMUNOLOGIST’S TOOLBOX (Seidel MG, Planitzer CB, Kreil TR, Förster-Waldl E. J Allergy Clin Immunol 2013; 131: 617):

  Substitution therapy with IgG provides antibodies against the majority of pathogens → how to test active antibody response in patients who receive regular IgG substitution therapy? → using neoantigens (antigens to which the general population is usually not exposed).

  Neoantigens: rabies virus vaccine; the nonlicensed artificial antigens bacteriophage 4X174 and keyhole limpet hemocyanin; tick-borne encephalitis virus (TBEV) vaccine.

  TBEV vaccine: licensed and easily available in most European countries; routine laboratory tests to quantify the vaccine response exist.

• ζ CHAIN–ASSOCIATED PROTEIN OF 70 KDA (ZAP70) DEFICIENCY IN HUMAN SUBJECTS IS ASSOCIATED WITH ABNORMALITIES OF THYMIC STROMAL CELLS (Poliani PL, Fontana E, Roifman CM, Notarangelo LD. J Allergy Clin Immunol 2013; 131: 597-600):
• **Thymic stromal cells:** cortical thymic epithelial cells (cTECs), medullary TECs (mTECs) and dendritic cells (DCs). cTECs → differentiation and positive selection of thymocytes. mTECs and DCs → negative selection of self-reactive T cells; generation of Treg cells.

• A subset of mTECs express AIRE (autoimmune regulator), a transcription factor that promotes expression of tissue-restricted antigens, important for negative selection of autoreactive T cells. Mature mTECs express TSLP and involucrin, important cytokines for DC function.

• 3 major thymic DCs: myeloid DCs, plasmacytoid DCs, Langerhans cells. Interaction between XCL1 (secreted by mTECs) and XCR1 (expressed in DCs) attract DCs to the deeper medulla.

• Cross-talk between thymocytes and mTECs is essential for mTEC maturation and immune tolerance induction → several SCID, including Omenn syndrome, are associated with ↓ differentiation of mTECs, ↓ expression of AIRE and ↓ thymic DCs.

• Authors evaluated the thymus of 2 infants with ZAP70 deficiency (recurrent infections, lymphadenopathy, small-sized thymic shadow, reduced CD8+ lymphs, impaired function of CD4+ lymphs) → ZAP70 deficiency was associated with: a) ↓ terminal differentiation of mTECs (minimal amounts of TLSP and involucrin); b) ↓ numbers of AIRE+ mTECs; c) ↓ medullary DCs; d) ↓ thymic FOXP3+ Treg cells → ZAP70 deficiency might predispose to autoimmunity (currently there is little clinical evidence, possibly due to the rarity of the disease or because most patients receive HSCT in infancy, before autoimmunity could develop).

• **Hypothesis:** ZAP70 deficiency → CD4+ T cells are unable to provide adequate signals to support terminal differentiation of mTECs.
PEDiATRIC ALLERGY AND IMMUNOLOGY:

A PROPOSED EXPLANATION FOR INCREASED RISK OF ACTIVE TUBERCULOSIS IN CHILDREN WITH ALLERgIC DISEASE (Eisenhut M. Pediatr Allergy Immunol 2013: 24: 98):

- A recent large study reported significant association between tuberculosis and allergic disease.

- Hypothesis: respiratory allergies → high IL-4 production in the airways → 1st mechanism: IL-4 enhances endocytosis via macrophage’s mannose receptor → mannose receptor binds mycobacterial lipoarabinomannan → increased entry of *M. tuberculosis* into macrophages. 2nd mechanism: IL-4 reduces nitric oxide synthase expression → reduced IFN-γ-induced nitric oxide → decreased intracellular killing of *M. tuberculosis*.

- IL-4 inhibitors (anti-IL-4, soluble IL-4 receptor) are being developed to treat asthma. They may be useful for tuberculosis.


- Authors report 7 patients (10-18 years old) from the IMPACT 1 study who received a single injection of pdC1-INH concentrate (Berinert®, CSL Behring) 20 U/kg for type I or II HAE attacks → Median time to onset of relief: 0.42 h; median time to complete resolution: 8.08; no patient had worsening of symptoms during the 0–4-h assessment period.

- Authors report 9 patients (10-18 years old) from the IMPACT 2 study who received a single injection of pdC1-INH concentrate (Berinert®, CSL Behring) 20 U/kg for type I or II HAE attacks → Median time to onset of relief: 0.49 h; median time to complete resolution: 14.1 h.

- Outcomes with pdC1-INH treatment of HAE attacks in children were similar to adult’s outcomes.

DESSENSITIZATION TO ANTIBIOTICS IN CHILDREN (Cernadas JR. Pediatr Allergy Immunol 2013: 24: 3–9):

- Drug hypersensitivity reactions can occur to almost all drugs. More common drugs: β-lactams, sulfanilamides, NSAIDs. Incidence in children: 0.75-4.5%.

- Individual with suspected drug hypersensitivity (child or adult) → skin tests (intradermal tests are difficult to perform in children); in vitro tests; drug challenges (may be performed in a proper hospital setting during diagnostic workup or delayed until the patient requires the drug).

- Individual with confirmed drug hypersensitivity (child or adult) → avoid the drug; give a safe and effective alternative drug → desensitize when there is no alternative treatment.

- Drug desensitization: induction of transient tolerance to a drug; tolerance can only be maintained by continuous drug administration; mainly performed in IgE-mediated reactions but also seems to work for non-IgE reactions; contraindicated in severe immunocytotoxic reactions, vasculitis or bullous skin diseases; mechanisms are not well known (IgE may be neutralized by the increasing dose of antigen; mast cells and basophils may be slowly degranulated).

- Desensitization protocols in children are similar to adult’s, differing only in the final dose.
• **Serum sickness-like illness** occurs in 0.06% of children receiving cephalor; possible mechanism: cytotoxic effect of the drug.

• **Amoxicillin** and **ampicillin** often induce rash in patients with EBV infection. Infections can induce an inflammatory state that activates T cells and predispose to drug reaction.

• **General rules for rapid drug desensitization:**
  1) be sure that the drug is irreplaceable;
  2) assume that it is a risky procedure;
  3) evaluate individual risk/benefit for the procedure, benefits must outweigh risks;
  4) get informed consent;
  5) be prepared to manage an acute hypersensitivity reaction;
  6) monitor the patient continuously;
  7) educate nurses and parents to recognize early signs of a hypersensitivity reaction;
  8) desensitization for severe reactions should be performed in ICU;
  9) follow available desensitization protocols, if they exist;
  10) initial dose depends on the patient’s history (usually 1/10,000; up to 1/1,000,000 when there was a history of anaphylaxis).

• **Desensitization to penicillin:** oral route seems to be safer (less prone to produce multivalent penicillin conjugates); mild reactions occur in 30–80% of patients; most procedures are completed with success.

• Patients with **cystic fibrosis**: high prevalence (up to 70%) of allergic reactions to antibiotics, especially β-lactams, in part because of frequent use. Many patients need desensitization procedures because of frequent requirement of specific antipseudomonal antibiotics; impaired lung function increases the procedure’s risk.

• **Tuberculosis (TBC) treatment** requires administration of multiple drugs simultaneously → hypersensitivity reactions occur in up to 5% of patients. Immediate and non-immediate reactions (mostly urticarial rashes) are seen with these drugs, predominantly with rifampicin.

• **Reaction to TBC treatment** → stop all drugs and reintroduce them one at a time, with a 4–5 days interval. In some circumstances (e.g. tuberculous meningitis) it is not possible to stop all drugs, so only the most probable causal drug(s) should be stopped.

• Both successful and unsuccessful desensitization outcomes should be published, to establish the most efficient and safer protocols.


• Hen’s egg allergy (HEA): 1–2% of young children; 4% of children outgrow HEA by the age of 4, 26% by the age of 8, 48% by the age of 12 and 68% by the age of 16; current treatment: avoidance (problems: significant dietary limitation, decreased quality of life, psychological problems), self-injectable epinephrine for severe allergy.

• Authors report a 6-month ‘in home’ protocol that successfully desensitized 8 out of 10 children (>4 years old) with moderate-severe IgE-mediated HEA.

• **Active group:** 8 children (80%) achieved daily intake of 25 ml; 1 child (10%) tolerated 2 ml/day; 1 child failed the desensitization. **Control group:** only 2 children (20%) could tolerate hen’s egg.

• Authors report 562 children who were patch tested with nickel sulphate → 26 children had a positive reaction at 12 and 18 months old → patch tests were repeated at 3 and 6 years old in 21 of those children → only 2 children had reproducible positive reactions.

• Repeated nickel patch tests did not cause sensitization in infants; positive reactions were probably of irritant or non-specific nature.

  - Nasal polyposis: 2–4% of the general population; 0.1% of children; symptoms: rhinorrhea, nasal congestion, loss of smell; might be associated with asthma and allergy; ↓ quality of life.
  - In the US, mometasone furoate nasal spray (MFNS) is approved to treat: 1) nasal polyposis in individuals ≥18 years old; 2) allergic rhinitis in individuals ≥2 years old.
  - Authors report 46 children (6–11 years old) and 81 teens (12–17 years old) with bilateral nasal polyps who received MFNS for 4 months → MFNS was safe and effective to treat nasal polyps, even at double the recommended pediatric dosage for allergic rhinitis.

  - Authors report a 6-month protocol that partially desensitized 9 out of 10 children (5-11 years old) with very severe IgE-mediated hen’s egg allergy (HEA), using raw HE emulsion.
  - Active group: 9 children (90%) achieved partial tolerance (at least 10 ml, but <40 ml of raw HE emulsion in a single dose); 1 child (10%) tolerated only 5 ml/day; side effects occurred in all children. Control group: the 10 children did not tolerate hen’s egg.

• When Should Adrenaline Be Given and by Whom? (Dreborg S. Pediatr Allergy Immunol 2013: 24: 97–98):
  - When should adrenaline be administered? At early symptoms of anaphylaxis (itching of the throat, soles, the whole body or hacking cough), especially when there is a probable trigger (e.g. drug, food, insect sting). The problem is to better define which early symptoms indicate anaphylaxis.
  - Who should be trained to administer adrenaline to children and adolescents? Patient (school children or adolescent), parents, teachers, school nurses and caregivers.