General considerations:

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

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

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

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April 2013 – content:

- **BASOPHILS UNLIMITED** (Gibbs BF, Nilsson GP. Allergy 2013; 68: 553–554).


SUCCESSFUL DESENSITIZATION PROTOCOL FOR PYRIDOSTIGMINE HYPERSENSITIVITY IN A PATIENT WITH MYASTHENIA GRAVIS (Aung T, Yoder Dowden A. Ann Allergy Asthma Immunol 2013; 110: 308).

SUCCESSFUL INTRAVAGINAL GRADED CHALLENGE AFTER A SYSTEMIC REACTION WITH SKIN PRICK TESTING TO SEMINAL FLUID (Baker TW, Ghosh D, Bernstein JA. Ann Allergy Asthma Immunol 2013; 110: 301-303).


HOST-MICROBIAL INTERACTIONS IN PATIENTS WITH CHRONIC RHINOSINUSITIS (Hamilos DL. J Allergy Clin Immunol 2013; 131: 1263-1264).

ALLERGY:

- **BASOPHILS UNLIMITED** (Gibbs BF, Nilsson GP. Allergy 2013; 68: 553–554):
  - Basophils: <1% of blood leukocytes; exacerbate IgE-mediated allergies; other functions are unclear (allergy initiation, antigen presentation, defence against ectoparasites).
  - It has been difficult to obtain sufficient basophils in vitro for research (in contrast to mast cells).
  - Gurzeler et al. describe how to generate “near-unlimited” mouse basophils by immortalizing myeloid progenitors with the transcription factor Hoxb8 in the presence of IL-3 and tamoxifen.
  - Human basophils: inhibitory FcγRIIB predominate; high CCR3 expression; absence of protease-activated receptors (PAR). Mouse basophils: stimulatory FcγRIIIA predominate; no CCR3 expression; presence of PAR; higher capacity to take up, process and present antigens.

  - Commercial dander extracts are routinely used for in vitro and in vivo diagnosis of dog allergy. However, there are patients with dog allergy who have negative tests to dog dander extracts.
  - Authors show that dog saliva has a greater number and diversity of allergenic proteins compared to dog dander. Allergenic proteins in dog saliva vary among dog breeds.
  - Dog saliva extracts may improve diagnostics of dog allergy.
  - Dog dander extracts might be contaminated with mite allergens → false positive SPT results.

  - Diagnosis of IgE-mediated occupational allergies: detailed clinical history, SPT, in vitro tests, specific inhalation challenge.
  - SPT: cheap and effective method to diagnose allergic diseases. Quality of SPT solution is essential for reliable results.
  - Authors from an EAACI Task Force analyzed 30 commercial SPT solutions containing occupational allergens (wheat and rye flour, soy, cow hair/dander, storage mites, natural rubber latex) → Conclusions: (i) SPT solutions had variable protein and antigen content; (iii) protein content alone did not fully reflect the quality of a SPT solution; (iv) antigen content should be increased in SPT solutions with low sensitivity; (v) SPT should be performed in duplicate; (vi) small wheal sizes may be relevant; (vii) SPT solutions from different manufacturers should be used in parallel; (viii) SPT with occupational allergens should be standardized.

• Human basophils release TNF-α after IgE-dependent activation → TNF-α stimulates MMP-9 release from monocytes → MMP-9 promotes tissue remodeling.

• IMPACT OF INTRANASAL CORTICOSTEROIDS (INS) ON ASTHMA OUTCOMES IN ALLERGIC RHINITIS (AR): A META-ANALYSIS (Lohia S, Schlosser RJ, Soler ZM. Allergy 2013; 68: 569–579):
  - Up to 80% of asthmatics have AR; up to 40% of patients with AR have asthma. AR may complicate asthma management
  - INS include: (i) INS sprays that deliver medication mainly to nasal mucosa; (ii) nasally inhaled corticosteroids that deliver medication to both nasal and lower airway respiratory epithelium.
  - This meta-analysis shows that INS significantly improved asthma outcomes in patients suffering from both AR and asthma.
  - ‘Unified airway’ concept: inflammation in the upper or lower airways affects each other.

  - AERD or Samter's triad: intolerance to NSAIDs, nasal polyposis and severe asthma. Aspirin desensitization is currently the only causal therapy. Optimal dose to maintain desensitization and avoid side effects is controversial; some authors recommend ≥325 mg twice daily; however, even doses of 325 mg/day are associated with a considerable risk of GI bleeding.
  - Authors show that aspirin desensitization with a maintenance dose of 100 mg/day prevented nasal polyp relapse, ↑ QoL, ↓ clinical complaints and was safe in patients with AERD.

  - About 200 patients with Schnitzler syndrome have been reported in the world. Male/female ratio: 1.76. Mean age of symptom onset: 51.6 yrs.
  - Schnitzler syndrome is probably a paradigm of acquired diseases involving auto-inflammatory mechanisms.
  - When to suspect Schnitzler’s syndrome? Adult patients with: (i) Chronic/recurrent urticarial rash: painful, no pruritic; poor response to antihistamines. (ii) Signs of systemic inflammation: probably mediated by IL-1β; fever, bone, muscle and joint pain, enlarged lymph nodes; poor response to NSAIDs. (iii) Monoclonal IgM or IgG gammopathy.
  - How to diagnose Schnitzler’s syndrome? Major criteria: (i) recurrent urticarial rash, (ii) monoclonal IgM or IgG gammopathy. Minor criteria: (i) recurrent fever, (ii) objective signs of abnormal bone remodeling, (iii) ↑ CRP level or ↑ WBC, (iv) neutrophilic infiltrate on skin biopsy.
  - Definite diagnosis: (i) 2 major criteria, including monoclonal IgM gammopathy, and 2 minor criteria; or (ii) 2 major criteria, including monoclonal IgG gammopathy, and 3 minor criteria.
• Probable diagnosis: (i) 2 major criteria, including monoclonal IgM gammopathy, and 1 minor criterion; or (ii) 2 major criteria, including monoclonal IgG gammopathy, and 2 minor criteria.

• These criteria should be considered provisional until prospective validation. There is no confirmative test at present.

• Patients with all signs of Schnitzler syndrome except the rash should be diagnosed as Schnitzler-like syndrome.

• Differential diagnosis: adult-onset Still’s disease (initial pharyngitis, ↑ transaminases, very high ferritin), urticarial vasculitis (skin biopsy shows vasculitis with fibrinoid necrosis of small vessel walls; complement consumption, anti-C1q antibodies) SLE, chronic spontaneous urticaria, autoinflammatory syndromes (usual present at young age, unusual monoclonal paraprotein), monoclonal gammopathy of unknown significance (MGUS).

• How to treat Schnitzler’s syndrome? Depends on severity; always balance risk/benefit ratio. (i) Avoid exacerbating factors. (ii) Colchicine (1–2 mg/d): 25% of patients respond (6-month therapeutic trial); good option for mild cases; ingest during a meal; be careful with drug interactions (e.g. with macrolides). (iii) NSAIDs: for short course treatments during exacerbations, especially of joint and bone pain. (iv) Anakinra (IL-1R antagonist) 100 mg/d SC: 1st line therapy in severe cases; symptoms usually recur as soon as therapy is stopped; taper to the lowest possible dose; controversial use in pregnancy. (v) Longer-acting IL-1 inhibitors: canakinumab or rilonacept. (vi) Tocilizumab (anti-IL-6) could be considered as an alternative.

• Low recommended therapeutic options: hydroxychloroquine, pefloxacin, thalidomide.

• How to follow-up a patient with Schnitzler’s syndrome? Clinical evaluation, CBC and CRP every 3 months. There is long-term risk of AA amyloidosis and overt lymphoproliferation (15-20% of patients). Serum amyloid A (SAA) protein may be useful for monitoring.

• All patients with Schnitzler’s or Schnitzler’s-like syndrome should be registered in the Schnitzler syndrome database (www.schnitzlersyndrome.com).


  • HHV-6 reactivation occurs in >60% of cases of drug-induced hypersensitivity syndrome (DIHS); it is associated with unfavorable outcomes. Mechanisms remain unknown.

  • Authors show the following mechanism: DIHS → HMGB-1 is released from damaged skin → HMGB-1 attracts monomyeloid precursors harboring HHV-6 to the skin → HHV-6 infects and replicates in skin-resident CD4+ T cells → HHV-6 reactivation → flaring of symptoms.
ANNALS OF ASTHMA, ALLERGY & IMMUNOLOGY:

  - Authors present a clinical vignette of a 30-yr-old woman with AFRS: headache, bilateral nasal obstruction and drainage; bilateral nasal polyposis; blood eosinophilia; IgE: 3,025 IU; ↑ sIgE to A fumigatus, C albicans, A alternata, Curvularia lunata; CT and MRI suggestive of AFRS with polyposis involving orbits and brain.
  - **AFRS**: noninvasive form of CRS; 5 -10% of CRS; more frequent in humid and warm regions.
  - **Pathophysiology**: entry of fungal spores in the sinuses → fungal growth → sIgE production to fungal allergens → eosinophil attraction and activation → tissue inflammation and damage.
  - **Typical presentation**: immunocompetent atopic young adult or adolescent with difficult-to-treat sinusitis and nasal polyposis.
  - **Diagnostic criteria** (Bent and Kuhn, 1994): 1) nasal polyposis; 2) ‘allergic mucin’ (eosinophil-rich thick secretions with Charcot-Leyden crystals and fungal elements) without fungal invasion of the paranasal tissues; 3) CT findings suggestive of CRS; 4) fungi detection by histology or culture; 5) sIgE to fungal allergens.
  - **Minor criteria**: history of asthma; unilateral disease; bone erosion; peripheral eosinophilia.
  - **Causal fungi**: depends on the geographic region; main genus: Bipolaris, Exserohilum, Curvularia, Alternaria, Aspergillus, etc.
  - **Complications**: secondary bacterial infections, extension beyond the sinuses walls (bone destruction, orbit and brain compression).
  - **Management**: team approach (allergist, ORL, etc.); functional endoscopic sinus surgery (removal of the fungi and secretions); steroids for at least 3 months (intranasal and systemic); consider antifungal drugs and fungal immunotherapy.

  - Common oat (Avena sativa): tolerable cereal for most patients with celiac disease (allergy to gluten); non-IgE-mediated reactions to oat have been reported.
  - Authors report the case of a 7-yr-old boy with IgE-mediated allergy to oats: cough, pruritus and wheezing within 30 min after oat ingestion; no history of food or respiratory allergies; diagnosis was confirmed by sIgE detection (ImmunoCAP), SPT and immunoblot (several oat proteins reacted with patient’s IgE, including a 12S seed storage protein); patient tolerated other cereals.

• Immediate hypersensitivity reactions to RCM: immunologic (IgE-mediated) or nonimmunologic mechanisms (changes in osmolarity and ion concentration → direct activation of mast cells or basophils; activation of complement system; activation of bradykinin-induced contact system).

• Mild immediate reactions to RCM: (i) ionic RCM: 3.8-12.7% of procedures; (ii) nonionic RCM: 0.7-3.1% of procedures.

• Severe immediate reactions to RCM: (i) ionic RCM: 0.1-0.4% of procedures; (ii) nonionic RCM: 0.02-0.04% of procedures.

• Authors performed intradermal tests (1/10 diluted) with nonionic RCM in 1048 subjects prior to RCM-enhanced computer tomography → RCM skin testing did not fully predict hypersensitivity reactions.

• Author’s recommendations: (i) subjects with a history of reaction (especially severe) to a RCM should be skin tested; (ii) positive skin tests may indicate an immunologic mechanism and should not be ignored even in patients with a history of mild immediate reaction; selection of an alternative RCM (by negative skin tests) would be better than only premedication use; (iii) skin tests should be performed several days before CT to detect immediate and delayed reactions.

• EFFICACY AND SAFETY OF ORAL DESENSITIZATION IN CHILDREN WITH COW’S MILK ALLERGY (CMA) ACCORDING TO THEIR SERUM SPECIFIC IGE LEVEL (García-Ara C, Pedrosa M, Belver MT, Martín-Muñoz MF, Quirce S, Boyano-Martínez T. Ann Allergy Asthma Immunol 2013; 110: 290–294):

• CMA: 80% of patients outgrow it by 5 yrs of age; patients who do not reach tolerance at 5 yrs old have poor tolerance prognosis; current treatment: avoidance (↓ QoL, does not prevent accidental exposure), epinephrine autoinjectors; specific oral immunotherapy (SOTI) is a valuable, but risky, option.

• Authors attempted SOTI in 36 children (4-13 yrs old) with CMA → 33 patients were successfully desensitized (100% of patients with sIgE <3.5 kU/L; 88% of patients with sIgE ≥3.5 kU/L); patients with sIgE <3.5 kU/L reached tolerance earlier and had less/milder adverse effects; only 1 child in the control group (19 children) reached tolerance during the study period.


• SLE: systemic autoimmune disease; variable clinical presentation; women/men = 9/1.

• Pathogenic factors: (i) ↑ TH17 responses and IL-17 production; (ii) ↓ IL-2 expression (estrogen ↓ expression of CREM-α and IL-2); (iii) ↓ Treg responses; (iv) ↓ immunity against EBV; (v) ↑ oxidative stress; (vi) autoantibodies against nuclear and cytoplasmic antigens → immune complex formation → deposition of immune complexes into tissues → inflammation (activation of leukocytes through Fcy receptors, stimulation of TLR7 and TLR9, ↑ type 1 IFN production).

• Diagnosis: fluorescent ANA (95% sensitivity, 70% specificity); ELISA ANA (80-90% sensitivity, more specificity than fluorescent ANA); anti-dsDNA (25% sensitivity, 95% specificity).

• Antiphospholipid antibodies: present in many patients with SLE; ↑ risk for venous and arterial thrombosis, thrombotic microangiopathy, recurrent fetal loss; may result in false-positive VDRL.
• **Treatment** depends on severity: (i) corticosteroids; (ii) immunosuppressants; (iii) biologic therapies targeting B cells (rituximab, belimumab, atacicept).

• **Fasting** → ↓ leptin → ↓ inflammation → beneficial effects in autoimmunity.


  • **DRESS**: severe immune reaction typically 2-4 wks after initiation of culprit drug; paradoxical worsening of symptoms after stopping culprit drug; mortality rate: 10%; **pathogenesis**: detoxification defects, slow acetylation processes, reactivation of human herpes viruses; **treatment**: corticosteroids, immunosuppressants.

  • Authors report the case of a 75-yr-old man with bacterial endocarditis complicated by vancomycin-induced DRESS syndrome (severe erythematous macular rash, eosinophilia, liver and renal dysfunction, RegisSCAR score=7) → **successful therapy** was completed with IV methylprednisolone (at moderate dose to avoid progression of endocarditis), high-dose IVIG (antiinflammatory effect, protective effect against infections), IV N-acetylcysteine (antioxidant properties), oral hydroxyzine, oral ranitidine, oral montelukast and IV gentamicin → 3 months after DRESS onset, **patch tests with vancomycin** were positive at 48 and 72 hours; HLA phenotyping was positive for HLA-B*1503.

  • How to treat a patient who presents a severe allergic reaction to an antibiotic prescribed for an active infection? → It is necessary to attenuate the immune response without exacerbating the ongoing infection → It represents a clinical challenge.


  • **NSAID hypersensitivity**: (i) **Intolerance**: pharmacologic mechanism (COX inhibition); cross-reactivity; urticaria/angioedema (U/AE) is the most frequent reaction. (ii) **Allergy**: IgE or T-cell mediated; selective reactivity; less frequent.

  • **Traditional management of intolerance to NSAIDs**: (i) avoidance of COX-1 inhibitors; (ii) use of selective COX-2 inhibitors as alternative drugs; (iii) desensitization to aspirin (effective but requires continuous therapy; tolerance disappears within 2 to 5 days after NSAID interruption).

  • Authors performed a NSAID challenge in 65 patients with a reported history of NSAID-induced U/AE → 59 patients (90%) tolerated the challenge; 6 patients presented U/AE → these 6 patients were challenged again (using the same NSAID) after receiving premedication with antihistamine (desloratadine 5 mg) ± leukotriene antagonist (montelukast 10 mg) → 5 patients tolerated the challenge, 1 patient presented urticaria despite premedication.

  • NSAID-induced U/AE may be prevented by premedication with antihistamines ± leukotriene antagonists.

• **SUCCESSFUL DESENSITIZATION PROTOCOL FOR PYRIDOSTIGMINE HYPERSENSITIVITY IN A PATIENT WITH MYASTHENIA GRAVIS** (Aung T, Yoder Dowden A. Ann Allergy Asthma Immunol 2013; 110: 308):
• **Myasthenia gravis (MG):** autoantibodies against acetylcholine (Ach) receptors → dysfunction of the neuromuscular junction → muscle weakness, fatigability. **Therapy:** (i) **symptomatic therapy:** acetylcholinesterase inhibitors (eg. pyridostigmine: ↓ degradation of Ach at the neuromuscular junction, provides short-term relief); (ii) **disease-modifying therapy:** prednisone, thymectomy.

• Authors report the case of a 43-yr-old man with MG and hypersensitivity to pyridostigmine (pruritus, urticarial rash, dysphonia) → **successful desensitization** was performed with a 2.5-hour, 6-dose protocol (1st reported successful desensitization to pyridostigmine in the literature) → patient has continued therapy with pyridostigmine 60 mg tid, with no further allergic reaction.

**SUCCESSFUL INTRAVAGINAL GRADED CHALLENGE AFTER A SYSTEMIC REACTION WITH SKIN PRICK TESTING TO SEMINAL FLUID** (Baker TW, Ghosh D, Bernstein JA. Ann Allergy Asthma Immunol 2013; 110: 301-303):

• **Seminal plasma hypersensitivity (SPH):** local (vaginal burning, pain and swelling) or systemic (urticaria, angioedema, bronchospasm, anaphylaxis) immediate reactions after contact with seminal fluid. **Treatment:** (i) intravaginal graded challenge; (ii) subcutaneous desensitization using relevant fractionated seminal plasma proteins.

• Authors report the case of a 37-yr old woman with SPH (vaginal itching and wheals, labial swelling and severe GI cramping within minutes of exposure to seminal fluid) confirmed by: (i) a **positive SPT** (local and systemic reaction: local wheal, vaginal pruritus, GI cramping, hives) to her husband’s fresh undiluted semen; (ii) a **positive Western blot** (patient’s specific IgE bound to prostate specific antigen) → with the patient’s consent, a **successful vaginal desensitization** was performed (patient received premedication with prednisone, cetirizine and montelukast) → patient was instructed to have unprotected intercourse ≥2 times per wk to maintain tolerance → patient has had uneventful unprotected intercourse (without premedication) for 12 wks.

• **Author’s commentaries:** (i) This is the 1st reported case of a systemic reaction to a SPT with semen. (ii) SPT is usually safe, but may be risky: a retrospective study reported 30 systemic reactions per 100,000 SPTs; an asthmatic patient died after food SPT. (iii) Nobody with SPH has died from an allergic reaction while undergoing seminal plasma desensitization.

**SUCCESSFUL RAPID DESENSITIZATION TO HYDROCHLOROTHIAZIDE** (Li J, Fernando SL. Ann Allergy Asthma Immunol 2013; 110: 307-308):

• Authors report the case of a 20-yr-old patient with congenital nephrogenic diabetes insipidus and delayed hypersensitivity to hydrochlorothiazide (severe pruritic bullous eruptions; histology suggestive of drug-induced lichenoid bullous dermatosis; positive patch test) → **successful desensitization** was performed with a 105-minute, 8-dose protocol → patient has tolerated hydrochlorothiazide 25 mg/day for 4 yrs, with no further allergic reaction.

**TARGETING THE SMALL AIRWAYS ASTHMA PHENOTYPE: IF WE CAN REACH IT, SHOULD WE TREAT IT?** (Lipworth B. Ann Allergy Asthma Immunol 2013; 110: 233-239):

• Conventional inhaled asthma therapy does not reach small airways (<2 mm in caliber) appropriately → patients with **small-airway asthma phenotype** might not respond to conventional ICS ± LABA → **extrafine particle (<2 µm)** ICS ± LABA may improve treatment of small airways disease without increasing systemic adverse effects.
• **Small-airway asthma phenotype**: associated with poorer disease control; preserved FEV\textsubscript{1} (reflects large and medium airways); ↓ forced midexpiratory flow (FEF\textsubscript{25-75%}); ↑ peripheral airway resistance (body plethysmography, impulse oscillometry, etc.).

• **How to assess small airway dysfunction?** Spirometry, impulse oscillometry, body plethysmography, nitrogen washout, HRCT with or without challenge, exhaled nitric oxide.

• **Density of glucocorticoid receptors** is similar in the large and small airways. **Density of β2-adrenoceptor** is higher in small airways → **extrafine β-agonist particles** may improve outcomes.

• Currently licensed **extrafine LABA formulations**: HFA-formoterol, HFA-beclomethasone-formoterol (MMAD = 1.5 µm; 66% deposits in large airways; 34% deposits in small airways).

• **Spacers** ↓ oropharyngeal deposition of ICS → ↓ gut bioavailability.

• **Ciclesonide**: prodrug that is converted in the lung to its active metabolite des-ciclesonide. Des-ciclesonide has 99% plasma protein binding—free drug is low → reduced adverse effects.

• We should try to achieve the **lowest effective maintenance dose** of ICS in every patient → adverse effects will decrease.
PEARLS IN ALLERGY AND IMMUNOLOGY

JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY:

• ALLERGEN IMMUNOTHERAPY (AIT): MUCH MORE THAN A SHOT IN THE DARK (Apter AJ. J Allergy Clin Immunol 2013; 131: 1092-1093):
  • Allergic rhinitis (AR): high prevalence; high costs to healthcare systems; ↓ QoL; ↓ productivity.
  • AIT: only therapy that can modify AR’s natural history; prevents new sensitizations.
  • Hankin et al: subcutaneous AIT significantly ↓ total healthcare costs in patients with AR. Cost reductions are observed within 3 months of starting AIT.
  • AIT may be beneficial by: (i) direct benefit on the disease; (ii) increased medical supervision.
  • An important obstacle for AIT is adherence.

  • I strongly suggest reading this 25-page article. Authors discuss: (i) the mechanisms of generation, maturation, activation and recruitment of B cells and plasma cells; (ii) the importance of B cells on respiratory diseases.

• EMERGENCY TREATMENT FOR ζ CHAIN–ASSOCIATED PROTEIN OF 70 KDA (ZAP70) DEFICIENCY (Hong-Diep Kim V, Murguia L, Schechter T, Grunebaum E, Roifman CM. J Allergy Clin Immunol 2013; 131: 1233-1235):
  • TCR stimulation → recruitment of ZAP70 → binding of ZAP70 to CD3ζ → conformational change in ZAP70 → ↑ ZAP70 catalytic activity → phosphorylation of signal transduction proteins (SLP-76, Cbl, Vav, etc.) → T-cell activation.
  • ZAP70 deficiency: severe opportunistic infections, autoimmunity, malignancy; ↓ CD8 T-cells, dysfunctional CD4 T-cells, normal number of B and NK cells; HSCT is the only curative therapy.
  • Authors report the case of a patient with ZAP70 deficiency (recurrent respiratory infections since 4 m of age; failure to thrive; ↓ IgG; ↓ CD8+ T cells; ↓ TREC levels; ↓ T-cell proliferation to PHA; normal T-cell proliferation to PMA and ionomycin; g.24417G>A mutation in ZAP70).
  • Patient’s clinical condition was very poor at 9 m of age → a related HLA-matched (10/10) HSCT was performed without delay and without conditioning → clinical condition markedly improved, except of periodic skin GvHD → 10 months after HSCT the patient presented graft failure → at 24 m of age a 2nd HSCT (same donor) was performed with full myeloablative conditioning → excellent clinical and laboratory response for 2 yrs after the 2nd HSCT (good thriving, normal T cell proliferation, normal TREC levels, normal immunoglobulin levels).
  • Profound T-cell immunodeficiency is a medical emergency → HSCT should be performed as early as possible. If conditions for a HSCT are not optimal, donor bone marrow can be infused as an urgent measure with a transient but lifesaving effect. Then a 2nd more definitive HSCT can be performed under ideal circumstances.
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  DNA ligase 4 deficiency: DNA repair disorder; variable T-cell and B-cell immunodeficiency; hematologic malignancies (EBV-associated B-cell lymphomas, T-cell leukemia/lymphomas, myelodysplasia), radiosensitivity, microcephaly, developmental delay, cytopenias.

  Authors report the case of a patient with DNA ligase 4 mutation (combined immunodeficiency, bronchiectasis, lymphopenia, anemia, thrombocytopenia, learning difficulties) who presented at 23 yrs of age with an EBV-independent diffuse large B-cell lymphoma (bilateral nasopharyngeal masses with extensive cervical lymphadenopathy) → treatment: dexamethasone, rituximab, low-dose cyclophosphamide, lomustine; there was no suitable donor for HSCT → patient died.

  HSCT for DNA ligase 4 deficiency → immunocompetent T cells → (i) recovery from immunodeficiency; (ii) improved immunity to malignancies.


  Fusarium sp: saprophytic fungi widely distributed in soil and plants; can cause invasive or disseminated infection in immunocompromised subjects.

  Cutaneous fusariosis: papulopustular lesions with abscesses, ulcerations or necrosis. Most immunocompetent patients with cutaneous fusariosis respond well to antifungal therapy.

  Authors report the case of a 7-yr-old girl with cutaneous fusariosis by Fusarium solani for >6 yrs (see photographs in the article), recalcitrant to therapy (fluconazol, itraconazole, terbinafine, amphotericin B, voriconazole, thymopentin) → CBC, lymphocyte subsets and immunoglobulin levels were normal → exome sequencing: missense mutation c.604A>G (p.M202V) in STAT1. This mutation has been reported in patients with CMC and autoimmunity; intriguingly, the patient had no history of Candida infections.

  STAT1 is an important molecule for interferons signalling. (i) Complete AR STAT1 deficiency → life-threatening intracellular bacterial and viral diseases; (ii) partial AR STAT1 deficiency → milder intracellular bacterial and viral diseases; (iii) AD STAT1 deficiency (dominant negative effect) → MSMD; (iv) AD gain-of-function STAT1 mutation → defective production of TH17 cells → CMC and autoimmunity.

  STAT1 gain-of-function mutations may result in susceptibility to infections by Fusarium sp.

  To author’s knowledge, this is the 1st report of cutaneous fungal infections other than candidiasis related to STAT1 mutation.


  Adenylate kinase (AK): protein that regulates intracellular levels of ADP and maintains mitochondrial membrane potential. AK1 is cytoplasmic, AK2 is mitochondrial. Most tissues
express AK1 and AK2; neutrophils, T cells and cells of the stria vascularis in the inner ear only express AK2.

- **Reticular dysgenesis (RD):** AR form of SCID caused by AK2 deficiency; ↓ T cells, severe congenital neutropenia, sensorineural deafness.

- Several genetic defects associated with SCID → residual development of oligoclonal T cells that expand and infiltrate tissues (skin, gut, liver, etc.) → Omenn syndrome (OS).

- Authors report the case of a patient with RD (consanguineous parents; neonatal lymphopenia and neutropenia, ↓ IgA, ↓ IgM, lack of thymic shadow, low T-cell proliferation to mitogens, ↓ TREC; profound hearing loss; ↓ AK2 protein levels in T cells; c.524 G>A mutation in AK2) who developed OS at 8 wks of age (desquamative erythroderma, pachydermia, diarrhea, generalized lymphadenopathy, ↑ T-cell count with oligoclonal repertoire; maternal engraftment and somatic reversion in T cells was ruled out) → patient improved with methylprednisolone and ciclosporin, and underwent a 9/10 HLA-A mismatched unrelated HSCT at 3 m of age → patient developed VODI, multiorgan dysfunction and acute GvHD, which caused death.

- This is the 1st reported case of OS in a patient with RD. Some AK2 mutations may result in residual T-cell development, oligoclonal expansion and OS.


  - T-cell receptor excision circles (TRECs): most accepted method for neonatal screening of SCID; low rate of false-positive results; SCID confirmation by flow citometry can take some wks.

  - Authors used flow citometry (anti-CD3/CD4/CD45) to analyze lymphocyte populations in cord blood (CB) from newborns → they incidentally identified a case of SCID (lymphocyte percentage: 5.9%, complete absence of T-cells; subsequent flow analysis revealed a T-B+NK-phenotype; genetic studies: JAK3 mutation) → patient underwent a CB HSCT.

  - This is the 1st reported SCID detection by flow cytometry of lymphocytes in freshly collected CB.

  - Advantages of flow cytometry for SCID newborn screening: earlier results than TRECs; allows identification of other PIDs (eg. B cell defects, neutropenia); more available than TRECs in many countries. **Limitations:** CB collection in unspecialized centers; transport of fresh CB samples to reference centers; false-negative results (maternal engraftment or oligoclonal cells); possibly higher costs; flow citometry is not useful to screen other diseases.

- **HOST-MICROBIAL INTERACTIONS IN PATIENTS WITH CHRONIC RHINOSINUSITIS (CRS)** (Hamilos DL. J Allergy Clin Immunol 2013; 131: 1263-1264):

  - **Biofilm:** ecological structure formed by bacteria and glycocalyx (sugary macromolecular substance) attached to mucosal surfaces; ↑ bacterial survival and resistance to ATB; bacteria within biofilm are in a “sessile” state, free-floating bacteria are in a “motile” or “planktonic” state; **diagnosis:** electron microscopy, confocal scanning laser microscopy (samples can be imaged without fixation or dehydration, specific microbes can be identified with fluorescent markers).

  - **Microbial community:** all culturable and nonculturable bacteria living and interacting in an environment.
\textbf{Nasal and sinus secretions} contain many antimicrobial peptides/proteins: lysozyme, SLPI, C3, serum amyloid A, ficolins, collectins, defensins, cathelicidins, lactoferrin.

Sinonasal epithelial cells express from TLR1 to TLR10. TLR stimulation \(\rightarrow\) activation of innate and adaptive immunity. TLR2 recognize gram (+) and (-) bacteria, and fungi. TLR4 recognize gram (-) bacteria.

\textit{Activation of bitter taste receptors} \(\rightarrow\) \(\uparrow\) NO production and ciliary beat frequency in sinus epithelial cells. TAS2R38 variant is associated with \(\downarrow\) ciliary beat frequency and bacterial CRS.

\textbf{IL-22}: essential guardian of immunity against extracellular bacteria in the lung and gut mucosa; stimulates production of antibacterial proteins; \(\uparrow\) epithelial renewal and goblet cell restitution.

\textbf{TH17 cells} produce IL-22, IL-17A and IL-17F. \textbf{TH22 cells} produce IL-22 but not IL-17.

No specific defects in IL-17A or IL-22 signaling have been identified in patients with CRS.

CRS: \(\uparrow\) susceptibility to bacterial and viral respiratory infections; \(\uparrow\) fungal colonization; prevalence of bacterial biofilm is ~56% (associated with more severe disease); CRS might be associated with \(\downarrow\) epithelial barrier function (\(\downarrow\) mucosal hydration, \(\uparrow\) microbe penetration); CRS might be associated to \(\downarrow\) TLR function or signalling.

\textbf{Active CRS} \(\rightarrow\) \(\downarrow\) mucociliary clearance, which usually normalizes after clearance of infection and restoration of sinus ostial patency.

\textbf{Refractory CRS}: inadequate response to surgery, ATB, saline rinses and topical steroids; 72-80\% of cases have positive bacterial cultures, mainly for S aureus and P aeruginosa.

\textbf{Recalcitrant CRS}: recurrent nasal polyps after polyp surgery.

CRS with nasal polyposis (CRSwNP) is associated to: pathologic Th2 responses, eosinophilic inflammation, \(\downarrow\) innate immunity (eg. \(\downarrow\) antimicrobial peptides), \(\uparrow\) colonization by S aureus (role of superantigens?) and fungi (particularly Alternaria sp).

CRS without nasal polyposis (CRSsNP): predominant neutrophilic inflammation.

\textbf{Allergic fungal rhinosinusitis}: allergic mucin, sIgE to fungi, fungal detection in sinus samples.

\textbf{Primary ciliary dyskinesia} \(\rightarrow\) \(\downarrow\) mucociliary clearance \(\rightarrow\) CRS.


\(\uparrow\) IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 \(\rightarrow\) signalling by receptors containing the common \(\gamma\) chain (\(\gamma c\)) \(\rightarrow\) activation of the cytoplasmic tyrosine kinase JAK3 \(\rightarrow\) T-cell and NK-cell development (among other functions).

Defects in JAK3 \(\rightarrow\) SCID, typically T-B+NK- phenotype.
Authors report the case of a patient with **JAK3-deficient leaky SCID** diagnosed at 27 m of age (pneumonia with good response to ATB; mouth ulcers; 2 episodes of severe diarrhea; low weight and height; lack of thymic tissue; lymphopenia; ↓ CD3+ T cells; ↓ CD4+CD45RA+ naive T cells; no proliferative response to mitogens; very weak positive response to vaccine antigens; normal numbers of B and NK cells; normal immunoglobulins; positive IgG to some vaccine antigens; homozygous R117C missense mutation in exon 3 of JAK3; JAK protein was present, but dysfunctional) → HSCT from his mother 9 m after diagnosis → chimerism analysis 4 yrs after HSCT: 85% donor’s NK cells; 100% donor’s T and B cells.

At diagnosis, patient had an expanded unusual **CD56-CD16+KIR+NKG2C+ NK cell subset** (61% of NK cells; control group: 10.7% of NK cells), without evidence of active viral infection. This expanded subset has been previously described in **HIV patients** and in a patient with SCID (CD3ε deficiency) during a CMV infection.

**NKG2C** expression in NK cells has been associated with lysis of CMV-infected cells. The absence of CMV DNA in this patient could be the result of successful CMV control by NK cells.