July 2013

General considerations:

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

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

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

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PEARLS IN ALLERGY AND IMMUNOLOGY

July 2013 – content:


- **ANAPHYLAXIS TO GOLD TEQUILA** (Coons BD, White K. Ann Allergy Asthma Immunol 2013; 111: 70–71).

- **EOSINOPHILIC ESOPHAGITIS TO UNSUSPECTED RARE FOOD ALLERGEN** (Mane SK, Jordan PA, Bahna SL. Ann Allergy Asthma Immunol 2013; 111: 64–65).


- **MAST CELL ACTIVATION SYNDROMES** (Jung Lee M, Akin C. Ann Allergy Asthma Immunol 2013; 111: 5–8).


- **RAPID DESENSITIZATION TO DOXYCYCLINE** (Fernando SL, Hudson BJ. Ann Allergy Asthma Immunol 2013; 111: 73–74).
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- **WHEN TO SUSPECT AND WORK UP ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS** (Greenberger PA. Ann Allergy Asthma Immunol 2013; 111: 1–4).


- **DIAGNOSTIC, FUNCTIONAL, AND THERAPEUTIC ROLES OF MICRORNA IN ALLERGIC DISEASES** (Lu TX, Rothenberg ME. J Allergy Clin Immunol 2013; 132: 3-13).


- **WHAT IS AN “EOSINOPHILIC PHENOTYPE” OF ASTHMA?** (Nair P. J Allergy Clin Immunol 2013; 132: 81-83).
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- Which is the ideal term for immunotherapy of allergic diseases? EAACI-AAAAI consensus → ‘Allergen immunotherapy’ (AIT): therapy of an allergic disease with an allergen-containing product. ‘Non-allergen immunotherapy’: therapy of an allergic disease with a product that does not contain allergen but modulates the immune system (eg. anti-IgE, anti-IL-13, anti-TSLP).


- Pitfalls of the term ‘specific immunotherapy’: (i) ‘immunotherapy’ is a broad term (manipulation of the immune system to prevent or treat diseases), which includes immunizations, mAbs, immunosuppressants, etc; (ii) ‘specific’ is an unclear term (eg. specific disease, specific allergen, specific patient); (ii) ‘specific immunotherapy’ is also used outside the allergy field (eg. oncology); (iv) an immunotherapy product may contain more than one allergen.

- Pitfall of the term ‘allergen-specific immunotherapy’: this term may imply that ‘non-allergen-specific immunotherapy’ or ‘allergen-non-specific immunotherapy’ also exist.

ALLERGIC INFLAMMATION: FOCUS ON EOSINOPHILS (Simon H-U. Allergy 2013; 68: 823–824):

- Eosinophils are usually ↑ in allergic diseases (atopic dermatitis, asthma, CRS, EoE) → inhibition of eosinophils can benefit patients with allergies.

- Novel information about eosinophils (including current issue of Allergy): (i) eosinophils can generate different functional subsets in vivo; (ii) eosinophils can produce extracellular DNA-containing traps able to kill bacteria; (iii) obesity may ↑ airway eosinophilia; (iv) CRTH2 antagonists may improve allergic rhinitis and EoE; (v) ↓ blood eosinophil numbers does not necessarily indicate ↓ eosinophilic inflammation; (vi) dietary therapy can reverse esophageal subepithelial fibrosis in patients with EoE; (vii) adult patients with EoE are frequently sensitized to C albicans (benefit from antifungal therapy?); (viii) morphological changes in eosinophils correlate with severity of asthma exacerbations in children; (ix) retinoic acids ↑ expression of eotaxin receptors (mediate eosinophil attraction).


- Authors present a 9-page position paper about desensitization in patients with delayed drug hypersensitivity reactions. I strongly suggest reading the entire document.

FREQUENT SENSITIZATION TO CANDIDA ALBICANS AND PROFILINS IN ADULT EOSINOPHILIC ESOPHAGITIS (EoE) (Simon D, Straumann A, Dahinden C, Simon H-U. Allergy 2013; 68: 945–948):

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• **EoE:** infiltration of eosinophils into esophageal mucosa → chronic inflammation → esophageal dysfunction; frequent association with respiratory and skin allergic diseases.

• **IgE-mediated reactions to microbes** (eg. S. aureus, C. albicans) are often associated with atopic diseases.

• Authors studied 35 patients (17–65 yrs old) with EoE → (i) 43% of patients had sIgE to C. albicans (ImmunoCAP); (ii) 83% of patients had sIgE to aeroallergens; 80% to pollens; 23% to food-specific allergens; 69% to cross-reactive allergens [eg. 40% to profilins, 37% to PR10 proteins] (ImmunoCAP-ISAC); (iii) dysphagia after rice and/or bread ingestion was associated with sensitization to cross-reactive allergens.

• **Author’s commentaries:** (i) EoE → use of swallowed steroids → ↑ Candida colonization and infection of the oral cavity and esophagus → production of sIgE to C. albicans; (ii) C. albicans may have a pathogenic role in adult EoE (eg. ↑ IL-5 production) → possible benefit from antifungal therapy; (iii) adults with EoE: high frequency of IgE to food-specific allergen components (eg. egg or milk).


  • Authors report the outcomes of 189 desensitization procedures to antineoplastic agents (oxaliplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide, rituximab) in 23 patients (mean age: 56 yrs) → (i) the novel desensitization protocol lasted ~4 hrs and ↓ exposure risks to hazardous drugs; (ii) sensitization candidates were carefully elected by anamnesis, skin testing, risk assessment and graded challenge; (iii) 188 desensitizations were successful (1 patient revoked consent after a breakthrough reaction); (iv) 177 (94%) desensitizations had no breakthrough reactions; 4 desensitizations had moderate/severe reactions; no deaths; (v) 11 desensitized patients had a reaction during their 1st desensitization (premedication [montelukast + acetylsalicylic acid] was useful to complete 2nd desensitizations, except for one oxaliplatin-reactive patient who needed additional steps); (vi) specific IgE to oxaliplatin (ImmunoCAP) had 54% sensitivity (0.10 UI/l cutoff point) and 100% specificity in 10 oxaliplatin-reactive patients; (vii) 2 patients had positive skin tests to paclitaxel.

  • **Author’s commentaries:** (i) Desensitization Programs are of great utility in reference hospitals; (ii) premedication with acetylsalicylic acid and montelukast may improve desensitization tolerability; (iii) skin testing with taxanes could be a useful risk marker for desensitization.


  • CRSwNP: chronic inflammation of the nasal and paranasal mucosa with polyps formation; TH2/eosinophilic environment; clinical manifestations: nasal congestion, rhinorrhea, facial pain/pressure, hyposmia; therapy: corticosteroids (topical, systemic), nasal irrigation, surgery.
• **Resveratrol**: 1st extracted from Cassia quinquangulata Rich (a nonedible Peruvian legume); ubiquitous in nature; found in few foods (mainly in grape); **reported mechanisms**: ↓ cyclooxygenase, antioxidant, antifibrogenic; **reported beneficial effects**: cancer prevention, cardioprotection, life extension; no significant genotoxicity or carcinogenicity (animal safety studies); nephrotoxicity may occur at very high doses (2000–3000 mg/kg/day).

• Authors studied the effects of resveratrol in a murine model of eosinophilic CRSwNP → resveratrol had several beneficial effects: (i) ↓ eosinophilic inflammation and subepithelial fibrosis (similar potency to triamcinolone acetonide); (ii) ↓ expression of IL-4, IL-5, prostaglandin D synthase and leukotriene C4 synthase genes; (iii) ↓ production of 5-lipoxygenase.

• **Author’s commentaries**: (i) resveratrol may be useful to prevent eosinophilic CRSwNP; (ii) should we promote grape consuming in patients at risk to develop CRSwNP? (iii) is resveratrol helpful for other eosinophilic and fibrotic diseases?


  • Authors analyzed 333 cases (300 in adults, 33 in children, age range: 1-85 yrs old) of severe drug-induced anaphylaxis collected by the Allergy Vigilance Network from 2002 to 2010 → (i) reactions were classified as anaphylactic shock (76.6%), severe systemic reactions (10.5%), acute laryngeal edema (9%), severe bronchospasm (2.1%) and death (1.8%); (ii) deaths were linked to the use of suxamethonium (2 cases), amoxicillin (2 cases, one occurred in fetus), hydroxycobalamin (1 case) and ACE inhibitor (1 case); (iii) 81.1% of cases were ambulatory anaphylaxis; (iv) 18.9% of cases occurred during general anesthesia; (v) 84 drugs were incriminated: antibiotics (49.6%, mainly beta-lactams), muscle relaxants, latex and anesthetics (15%), NSAIDs (10.2%), acetaminophen (3.9%), iodinated or MRI contrast media (4.2%), immunotherapy and vaccines (3.9%), other drugs (13%); (vi) routes of administration: oral (58.5%), intravenous (28.8%), subcutaneous (5.7%), intramuscular (2.4%), skin application (4.2%), intra-articular (one case); (vii) time to anaphylaxis onset: 7 min (IV infusion), 10 min (IM injection), 16 min (SC injection), 28 min (oral intake), 29 min (skin application); (viii) diagnosis of drug hypersensitivity could be established in 79.2% of cases by a 3-step diagnostic approach (72.9% by skin tests, 2.4% by in vitro tests, 3.9% by oral challenges); (ix) 4 of 4 reactions to diclofenac were suggestive of IgE-dependent anaphylaxis; (x) 46.2% of reactions to acetaminophen were suggestive of IgE-dependent anaphylaxis.

  • **Author’s commentaries**: (i) limitations of the study: patients with negative skin tests may not have been reported, specificity of skin tests to many drugs (nonirritating concentrations) is not well defined; (ii) IgE-detection tests and oral challenges may be underused in patients with a history of drug anaphylaxis; (iii) oral challenges are important to assess ADRs to NSAIDs (nonimmune hypersensitivity is more frequent than IgE-mediated allergy); (iv) benefit–risk of oral challenges must be carefully weighed in anaphylactic patients; (v) oral challenges must be performed in hospital settings by trained allergists; (vi) factors that may ↑ anaphylaxis severity: β-blockers, ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, exercise, alcohol.

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- **Eosinophil deficiency** has been reported in the following conditions: (i) eosinophil deficiency associated with immunodeficiency and thymoma (several reported patients, unclear mechanisms for eosinopenia); (ii) eosinophil deficiency and dysgammaglobulinemia (1 reported patient in a 1977 book); (iii) eosinophil and basophil deficiency (3 patients reported in 1977, 1983 and 1988); (iv) allergic diseases (very few cases reported); (v) use of eosinophil-depleting therapies; (vi) use of corticosteroids; (vii) serious organic illnesses.

- **Eosinophil-depleting mAbs** (anti-IL-5 [mepolizumab, reslizumab], anti-IL-5Rα [benralizumab, also depletes basophils]): therapeutic options in patients with eosinophilic diseases (hypereosinophilic syndrome [HES], eosinophilic esophagitis, severe eosinophilic asthma); no significant side effects (eg. patients with HES who have received mepolizumab for 6 yrs).

- ↓ eosinophils in mice and humans → no significant deleterious effect on health (apparently) → what would happen if human patients lacking eosinophils are exposed to helminths?

- Eosinophils seem to have contributory, but not essential, roles in several physiological events.

- **ANAPHYLAXIS TO GOLD TEQUILA** (Coons BD, White K. Ann Allergy Asthma Immunol 2013; 111: 70–71):
  - **Tequila**: Mexican liquor from distilled blue agave plant; categories: (i) blanco (“white”): clear tequila with little to no aging; (ii) reposado (“rested”) or añejo (“aged”: tequilas aged in oak barrels for months to yrs (aging process causes the golden color of Gold tequila).
  - Authors report the case of a 47-yr-old woman (personal history: tree pollen-induced allergic rhinitis) with several allergic reactions (urticaria, angioedema, anaphylaxis) to gold tequila (no reported reactions to other alcoholic drinks; patient tolerates blanco tequila and beer) → diagnosis: positive SPT (3-mm wheal, body itching and erythema, shortness of breath) to a lyophilized extract of gold tequila (liquid gold tequila was not used because it produced a 3-mm wheal in one control); immunoblot analysis was technically unsuccessful.
  - Author’s commentaries: (i) the type of reaction and the positive SPT suggest an IgE-mediated allergy to gold tequila; (ii) 1st reported case of anaphylaxis to distilled liquor (there are previous reports of anaphylaxis to beer and wine); (iii) why the patient reacted to gold tequila but tolerated blanco tequila? Hypothesis: contamination of gold tequila with oak allergens during aging in oak barrels (patient had oak allergy).

- **EOSINOPHILIC ESOPHAGITIS (EoE) TO UNSUSPECTED RARE FOOD ALLERGEN** (Mane SK, Jordan PA, Bahna SL. Ann Allergy Asthma Immunol 2013; 111: 64–65):
  - **EoE**: immune reaction to food or respiratory allergens in the esophagus (common causal foods in children: milk, egg, soy, wheat, beef, chicken; common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg → chronic eosinophilic inflammation → abdominal pain, vomiting, dysphagia, food impaction, heartburn, cough, choking (often misdiagnosed as GERD).
  - **Diagnosis of EoE**: (i) clinical history, (ii) esophageal endoscopy and biopsy (≥15 eos per high-power field), (iii) allergy tests (SPT, in vitro slgE detection, patch test) with food and respiratory allergens, (iv) food avoidance and reintroduction.
  - **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) swallowed corticosteroids.
Authors report the case of a 58-yr-old man with garlic-induced EoE → (i) clinical history: 15-yr history of nausea, dyspepsia and dysphagia (treated as GERD with partial improvement); frequent eating of garlic-containing foods; (ii) 1st endoscopy: distal esophageal inflammation; (iii) 2nd endoscopy: apparent healthy mucosa; (iv) biopsy: esophagitis with ↑ eosinophils (>60/hpf in 1st endoscopy; 0–17/hpf in 2nd endoscopy); (v) laboratory: ↑ IgE (499 KU/L), ↑ blood eosinophils (650/μL); (vi) allergy tests: positive SPT to garlic and cottonseed extracts (among 44 tested allergens); (vii) successful treatment: avoidance of garlic, swallowed viscous budesonide.

Author’s commentaries: (i) EoE can be induced by ‘rare’ foods (eg. pea, mustard, carrot, almonds, string beans, pork, broccoli, rye, corn, garlic); (ii) EoE may be misdiagnosed as GERD for many years; (iii) clinical history may not be sufficient to detect/suspect causal foods in some patients with EoE; (iv) allergy testing can be decisive in the diagnostic approach of EoE (as in this case); (v) when EoE is suspected, an apparent normal esophageal mucosa in endoscopy should not deter biopsy; (vi) the six-food elimination diet may not help patients with EoE induced by ‘rare’ foods; (vii) allergy testing to a limited number of foods may not identify the culprit food in some patients with EoE; (viii) be careful with spice-induced allergic diseases.

IMMUNOGLOBULIN G4-RELATED DISEASE (IgG4-RD) PRESENTING AS AN ETHMOID AND MAXILLARY MASS (Hu EK, Parrish Ch, Wrobel B, Deshpande V, Stone JH. Ann Allergy Asthma Immunol 2013; 111: 64–65):

IgG4: 5% of total IgG; antinflammatory properties (negligible binding to C1q and Fcγ receptors; exchangeable heavy chains [“Fab arm exchange”] that prevents cross-linking of antigen).

IgG4 autoantibodies have pathogenic roles in certain autoimmune disorders (eg. pemphigus vulgaris: IgG4 against desmoglein; idiopathic membranous glomerulonephritis: IgG4 against the PLA-2 receptor).

IgG4-RD: multi-organ fibroinflammatory disease (tumefactive lesions rich in T cells and IgG4-positive plasma cells); unclear pathogenesis; can affect almost every organ; usually presents in middle-aged to elderly men; common clinical manifestations: autoimmune pancreatitis, sialadenitis, orbital disease (typically affecting lacrimal gland); 30% of patients have normal serum IgG4 concentrations; frequent allergies and eosinophilia.

Authors report the case of a 50-yr-old man with IgG4-RD presenting as an ethmoid and maxillary mass → (i) clinical history: recurrent sinusitis refractory to corticosteroids and antibiotics; (ii) sinus CT: complete opacification of all left sinuses; (iii) MRI: contrast-enhancing mass in the left ethmoid and maxillary sinuses; (iv) endoscopic sinus surgery: severe mucosal inflammation in left sinuses (ethmoid, maxillary and frontal); (v) histology: intense IgG4-positive plasma cell infiltrate with focal areas of fibrosis in a storiform pattern; (vi) laboratory: normal IgM, IgA, IgE, IgG subclasses → successful treatment: rituximab 1 g (2 doses 2 wks apart); symptom-free 8 months after treatment.

MAST CELL ACTIVATION SYNDROMES (Jung Lee M, Akin C. Ann Allergy Asthma Immunol 2013; 111: 5–8):

Authors present a clinical vignette about a 50-yr-old woman with monoclonal mast cell activation syndrome (MMAS) → (i) clinical manifestations: recurrent flushing, abdominal cramps, diarrhea, fatigue, hypotension that required epinephrine; (ii) laboratory: basal tryptase = 7 ng/mL, tryptase during hypotension = 18 ng/mL; (iii) bone marrow aspirate and biopsy:
scattered mast cells without significant clustering, ~20% of mast cells had elongated morphologic findings, aberrant CD25 expression on mast cells; (iv) genetic analysis: D816V point mutation in c-kit; (v) treatment: H1 and H2 blockers twice daily, cromolyn sodium.

• **Mast cell activation diseases (MCAD):** diseases characterized by recurrent signs and symptoms (flushing, abdominal cramps, hypotension, predisposition to anaphylaxis after hymenoptera sting) and ↑ laboratory markers (serum tryptase levels, urinary N-methylhistamine, PGD2, or 11-β-prostaglandin F2) of mast cell mediator release.

• **3 categories of MCAD (2010 classification):** (i) primary (clonal): systemic mastocytosis (SM), MMAS; (ii) secondary (nonclonal): allergic diseases, chronic urticaria, chronic inflammatory diseases, neoplasms, etc.; (iii) idiopathic (unknown whether clonal or nonclonal): idiopathic mast cell activation syndrome, idiopathic anaphylaxis. *Clonal disorders:* inherent defects in mast cells and their progenitors (eg. activating c-kit mutations).

• **MMAS:** pathogenesis: genetic defects of mast cells → mast cell hyperfunction and expression of activation/clonal markers (eg. c-kit mutations, CD25 expression); difference from SM: no urticaria pigmentosa (UP), basal tryptase is often normal; difference from MCAS: anaphylaxis is more common than urticaria/angioedema; *life expectancy:* similar to general population.

• **Idiopathic MCAS:** diagnostic criteria: (i) recurrent signs and symptoms of mast cell activation, (ii) positive laboratory markers of mast cell activation, (iii) improvement with therapies targeting mast cell mediators; difference from SM: no UP; differences from MMAS: no clonality, urticaria/angioedema is more common than anaphylaxis; *life expectancy:* similar to general population.

• **UP** should point to a diagnosis of **SM** or **cutaneous mastocytosis** rather than other MCAD.

• **Management of MCAD:** (i) non sedating H1-antihistamines (up to 2-4 times the usual dose), (ii) 1st generation H1-antihistamines (especially for breakthrough symptoms); (iii) H2-antihistamines (bid, especially for abdominal symptoms); (iv) mast cell stabilizers (ketotifen 1-2 mg bid, cromolyn sodium 200 mg qid); (v) montelukast (10 mg/day); (vi) aspirin in NSAID-tolerant patients (start with 81 mg/d, ↑ dose gradually up to 325 mg bid); (vii) autoinjectable epinephrine; (viii) venom immunotherapy for patients with IgE-mediated allergy to hymenoptera sting.

• **MULTIFUNCTIONAL ACRYLATES AS POSSIBLE SENSITIZERS IN ELECTROCARDIOGRAM ELECTRODE ALLERGY** (Núñez-Acevedo B, González-Fernández MT, Mayela Juangorena M, Vidal C. Ann Allergy Asthma Immunol 2013; 111: 77–78):

• Authors report the case of a 64-yr-old woman with allergy to multifunctional acrylates → (i) clinical history: circular erythematous eczematous lesions at the sites where ECG electrodes had been applied for several hours during shoulder surgery; (ii) patch testing: positive reaction to acrylate-containing ECG electrodes, positive reaction to multifunctional acrylates.

• **Electrode allergy:** several causal allergens, including acrylates (in the adhesive or gel part of electrodes); protective factors: presence of a methyl group, greater size of the ester group; *risk factor:* higher number of unsaturated groups in the monomer; *acrylate-free electrodes* do exist.

• Authors performed a RCT in 548 patients (≥ 12 yrs old) with PAR to evaluate the ocular safety of FFNS (110 µg once daily) used continuously for ≥ 2 yrs → (i) 367 patients received FFNS (199 completed the study); (ii) 181 patients received placebo (104 completed the study); (iii) compared to placebo, FFNS did not affect ocular safety (measured by monitoring of lens opacification, intraocular pressure, visual acuity and funduscopic horizontal cup-to-disc ratio).

• Author’s commentary: (i) patients with long-term use of intranasal corticosteroids should have regular ophthalmic monitoring.

• RAPID DESSENSITIZATION TO DOXYCYCLINE (Fernando SL, Hudson BJ. Ann Allergy Asthma Immunol 2013; 111: 73–74):

  • Tetracyclines (tetracycline, doxycycline, minocycline): common core structure, different side chains → IgE-mediated reactions may be class or drug specific.

  • Anaphylaxis to tetracyclines: rare drug reactions; unclear mechanisms.

  • Authors report the case of a 48-yr-old woman with Q fever and anaphylaxis minutes after doxycycline intake (urticaria, facial angioedema, throat constriction, hoarseness, dyspnea, wheezing) → the infection did not respond to alternative antibiotics → a successful intravenous desensitization to doxycycline was done (4-hr protocol, 4 months after the anaphylactic episode) → patient could tolerate treatment with oral doxycycline (100 mg bid for several wks).

  • Author’s commentaries: (i) 1st published report of anaphylaxis to oral doxycycline and successful desensitization to a tetracycline; (ii) skin or in vitro sIgE testing to doxycycline are not standardized; (ii) oral desensitization was not performed because oral formulations of doxycycline were not sufficiently soluble to prepare very low drug concentrations.

• THE NEBULOUS DIAGNOSIS OF TYPE III HEREDITARY ANGIOEDEMA (HAE) (Fernando SL. Ann Allergy Asthma Immunol 2013; 111: 65–66):

  • Type III HAE: angioedema without urticaria, normal C1-inh level and function, positive family history, more frequent in women (estrogen is a frequent trigger of attacks), frequent mutations in the factor XII gene (pathogenic role is controversial).

  • Non-histaminergic idiopathic AE: diagnosis of exclusion → histamine-resistant angioedema, normal C1-inh levels and function, no family history, no mutations in the factor XII gene.

• WHEN TO SUSPECT AND WORK UP ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA) (Greenberger PA. Ann Allergy Asthma Immunol 2013; 111: 1–4):

  • ABPA: hypersensitivity to Aspergillus fumigatus in the lower airways; affects up to 2.5% of adults with severe asthma; complications: uncontrolled asthma, recurrent pneumonias, bronchiectasis, lung fibrosis, ↓ lung function, respiratory failure.

  • It is very important to diagnose ABPA before bronchiectasis or fibrosis occurs.

  • Conditions where ABPA prevalence may be increased: severe asthma, hyper-IgE syndrome, CGD, cystic fibrosis, family history of ABPA.

  • When to suspect ABPA? (i) severe asthma with expectoration of mucous plugs; (ii) pulmonary infiltrates (especially in upper or middle lobe); (iii) perihilar mucous plugging; (iv) lobar or lung
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collapse; (v) central bronchiectasis (inner 2/3 of lung fields); (vi) blood eosinophils ≥8%; (vii) total IgE >417 kU/L (take the sample before starting systemic corticosteroids); (viii) positive skin tests (SPT, IDR) to A fumigatus; (ix) ↑ sIgE and IgG (precipitating antibodies) to A fumigatus; (x) A fumigatus in sputum culture; (xi) suggestive histology (allergic mucin, fungal hyphae, bronchi with mucoid impaction, bronchocentric granulomatosis); (xii) major improvement with prednisone (↓ infiltrates, ↓ total IgE); (xiii) concurrent allergic fungal rhinosinusitis.

- Patients with severe asthma should be screened for ABPA.
- Difficulties to diagnose ABPA: (i) no pathognomonic test; (ii) infiltrates can be relatively silent; (iii) bronchiectasis may not produce any sputum.
- Frequent diagnostic mistakes: (i) to exclude ABPA when precipitating antibodies to A fumigatus are not detected; (ii) to exclude ABPA when skin testing to A fumigatus is negative; (iii) to exclude ABPA when total IgE is <417 kU/L (IgE may ↓ during remission stage or prednisone-dependent asthma stage); (iv) to exclude ABPA when bronchiectasis are not present (seropositive ABPA).
- Differential diagnosis of ABPA: severe asthma with fungal sensitization (SAFS), cystic fibrosis, bronchopulmonary infections.
- Skin testing (SPT, IDR) with A fumigatus: highly sensitive screening test for ABPA.
- Serum IgE and/or IgG antibodies to A fumigatus: highly specific tests for ABPA.
- Controversial aspects: (i) best diagnostic and therapeutic approach for ABPA, (ii) efficacy of allergen immunotherapy with A fumigatus, (iii) efficacy of omalizumab.

**ACTIVATION OF GROUP 2 INNATE LYMPHOID CELLS: A NEW ROLE FOR CYSTEINYL LEUKOTRIENES** (Barrett NA, Boyce JA. J Allergy Clin Immunol 2013; 132: 214-216):

- Innate lymphoid cells: (i) group 1 (ILC1s): produce TH1 cytokines; (ii) group 2 (ILC2s): produce TH2 cytokines (IL-5, IL-13) after stimulation with IL-25, IL-33 or TSLP; (iii) group 3 (ILC3s): produce TH17 cytokines (IL-17, IL-22).
- Sources of TH2 cytokines: (i) TH2 cells (adaptive immunity); (ii) ILC2s (innate immunity).
- Cysteinyl leukotrienes (CysLTs): LTC4, LTD4, LTE4; ↑ inflammation (vascular leakage, mucus secretion, eosinophil attraction, bronchoconstriction, activation of TH2-inducing dendritic cells); pathogenic role in allergic diseases, especially in aspirin-exacerbated respiratory disease.
- CysLTs receptors: (i) CysLT1R: high-affinity receptor for LTD4; (ii) CysLT2R: low-affinity receptor for LTC4 and LTD4; (iii) CysLT3R: binding preference for LTE4.
- Hypothesis: airway exposure to allergens → production of CysLTs by airway-resident innate immune cells → stimulation of CysLT receptors in ILC2s → production of TH2-cytokines (IL-4, IL-5, IL-13) by ILC2s → TH2 inflammation (independent of adaptive immunity).
- Important observations: (i) CysLTs induced and amplified TH2 responses independent of adaptive immunity; (ii) LTD4 also induced IL-4 production from ILC2s; (iii) effects of LTE4 (the
most stable and abundant CysLT) were resistant to montelukast (CysLT1R antagonist) (hypothesis: LTE4 action through P2Y12 purinergic receptor and CysLT3R).

**ASTHMA IN THE REAL WORLD** (O’Byrne PM. J Allergy Clin Immunol 2013; 132: 214-216):

- **Reasons for uncontrolled asthma:** (i) severe disease (5-10% of patients); (ii) poor adherence to treatment.
- **Limitations of phase III trials:** study conditions are optimal, subjects with poor adherence to treatment are usually excluded → efficacy appears to be greater.
- **How to measure ‘real-world’ effectiveness?** (i) “pragmatic” studies; (ii) revision of data from administrative databases.
- **“Pragmatic” studies:** performed after product approval; no blinding; no randomization; no efforts to optimize adherence; confounding factors can easily influence the results.
- A previous pragmatic study (N Engl J Med 2011; 364: 1695-707) showed that LTRA were equivalent to ICS as first-line controller therapy and to LABA as add-on therapy in asthma → hypothesis: although ICS have more efficacy than LTRA, adherence to LTRA might be greater.
- Sadatsafavi et al (J Allergy Clin Immunol 2013; 132: 63-69) performed a real-life administrative-based study in asthmatic patients (12-45 yrs old) who received ICS and required a step up in therapy → (i) ICS/LABA were more effective than ICS/LTRA; (ii) adherence to ICS/LABA was greater compared to ICS/LTRA; (iii) long-term adherence to both treatments was very low.


- **CVID:** heterogeneous group of immunodeficiencies → defective antibody responses + susceptibility to infections, autoimmunity and neoplasms.
- **DC:** 7 genetic defects (DKC1 [X-linked]; NOP10, TCAB1 and NHP2 [autosomal recessive]; TERT, TERC and TINF2 [autosomal dominant]) → shortened or dysfunctional telomeres → bone marrow failure, susceptibility to infections, accelerated aging, malignancy, short stature, microcephaly, abnormal skin pigmentation, nail dystrophy, mucosal leukoplakia, pulmonary fibrosis, dental abnormalities, esophageal strictures.
- Authors report the case of a male patient with dyskeratosis congenita who initially presented as CVID → (i) clinical manifestations of CVID (from 4 months of age): recurrent infections (otitis, sinusitis, pneumonia, oral thrush), hepatosplenomegaly, bronchiectasis, ↓ IgG, ↓ IgA, ↓ IgM, inverted CD4/CD8 ratio, ↓ antibody response to bacteriophage ΦX174; (ii) clinical manifestations of DC (from 5 yrs of age): denuded tongue epithelium, white cobble-stoned palmar epithelium, nail dystrophy, leukoplakia, gingivitis, dental fistulas, esophageal strictures, diarrhea (marked apoptosis of colonic crypt cells), ↓ B cells, ↓ NK cells, severe anemia; (iii) diagnosis of DC (at 21 yrs of age): ↓ telomere length, ↓ dyskerin protein levels, mutation in exon 15 of the DKC1 gene (c.1512_1514 dupGAA) → poor response to IVIG and antibiotic prophylaxis → unsuccessful HSCT (patient died due to bacterial [Pseudomonas aeruginosa] and fungal [Rhizopus zygomycetes] pneumonia/sepsis 18 days after HSCT).
• **DIAGNOSTIC, FUNCTIONAL, AND THERAPEUTIC ROLES OF MICRORNA IN ALLERGIC DISEASES** (Lu TX, Rothenberg ME. J Allergy Clin Immunol 2013; 132: 3-13):

  • **MicroRNAs (miRNAs):** short (19-25 nucleotides) ssRNA molecules that target mRNA and regulate gene/protein expression; detectable in body fluids; more stable than mRNA; **functions:** regulation of many cell processes (proliferation, differentiation, apoptosis), including normal and pathologic immune responses (eg. allergic inflammation); **importance:** (i) pathogenic role in diseases, (ii) potential disease biomarkers (diagnosis, classification, prognosis), (iii) potential therapeutic targets (mi-RNA mimics or inhibitors).

  • A single miRNA can target hundreds of genes; single genes are regulated by multiple miRNAs.

  • Importance of miRNA in allergic diseases: (i) pathogenic roles (eg. miRNAs can regulate proliferation, differentiation, function and survival of T cells [TH1 vs TH2], mast cells, eosinophils, basophils, etc.); (ii) diagnostic/prognostic biomarkers (eg. an esophageal miRNA profile could distinguish EoE from noneosinophilic forms of esophagitis); (iii) therapeutic targets (eg. gene KO strategies, anti-miRNA–based therapies).


  • **IgE-mediated allergy to penicillin:** common drug allergy; hapten-carrier mechanism; **major allergen:** benzylpenicilloyl determinant; **diagnosis:** clinical history, specific IgE detection by skin tests or *in vitro* tests, drug challenge.

  • **False-negative diagnosis** of drug allergy can lead to severe reactions after subsequent exposure.

  • **False-positive diagnosis** of drug allergy can lead to unnecessary avoidance.

  • Authors studied the sera of 46 patients with suspected IgE-mediated penicillin allergy and positive specific IgE to penicillin V and/or penicillin G (ImmunoCAP) → 26% of the patients had specific IgE to PEA (phenylethylamine with a benzyl group), which is not clinically relevant.

  • **Author’s commentaries:** (i) patients with positive ImmunoCAP to penicillin may actually have clinically-irrelevant specific IgE to PEA; (iii) this diagnostic pitfall may also occur with other assays that detect specific IgE to penicillin.


  • **Mastocytosis:** clonal expansion of mast cells (MCs) due to activating KIT mutations; **clinical manifestations:** pruritus, urticaria pigmentosa, flushing, anaphylaxis, headache, diarrhea, osteoporosis; **best characterized marker of MC burden:** serum tryptase (useful to diagnose and monitor disease); **other biomarkers:** serum soluble KIT, soluble CD25, IL-6, IL-13, carboxypeptidase A, several neuropeptides, urinary histamine metabolites.

  • **Benign subtypes** (eg. cutaneous mastocytosis [CM], indolent systemic mastocytosis [ISM]) → **treatment:** avoidance of MC activation triggers, H1 antihistamines.
- **Advanced subtypes** (e.g., aggressive systemic mastocytosis, MC leukemia) → treatment: IFN-α, cladribine, inhibitors of KIT signalling.

- **IL-31**: pathogenic role in inflammatory skin diseases (atopic dermatitis, chronic spontaneous urticaria, allergic contact dermatitis, prurigo nodularis, primary cutaneous lymphomas).

- Authors studied sera and tissues (skin, bone marrow) from patients (1-82 yrs old) with different subtypes of mastocytosis → (i) patients with mastocytosis had ↑ serum IL-31 levels compared to healthy controls; (ii) IL-31 levels correlated with disease severity, tryptase levels and % of bone marrow infiltration; (iii) MCs in skin and bone marrow were able to produce IL-31.

- Author’s commentary: serum IL-31 is a potential diagnostic and prognostic biomarker in patients with mastocytosis.

- **SEVERE PHENOTYPE OF SEVERE COMBINED IMMUNODEFICIENCY (SCID) CAUSED BY ADENOSINE DEAMINASE (ADA) DEFICIENCY IN A PATIENT WITH A HOMOZYGOUS MUTATION DUE TO UNIPARENTAL DISOMY** (Geelen J, Pfundt R, Meijer J, Verheijen FW, van Kuilenburg ABP, Warris A, Marcelis C. J Allergy Clin Immunol 2013; 132: 222-223):

  - **ADA deficiency**: mutations in the ADA gene (chromosome 20q13.12) → ↑ concentrations of toxic metabolites → autosomal recessive form of SCID (T-B-NK-) → life-threatening infections, chronic diarrhea, failure to thrive, autoimmune, neurologic abnormalities.

  - Authors report a patient with ADA-SCID due to uniparental (paternal) disomy of chromosome 20, which included the mutated ADA gene → (i) clinical manifestations: dysmorphic facies (broad nasal tip, epicanthal folds, large low-set ears, microretrognathia), neurologic defects (microcephaly, hypotonia, absent reflexes, blindness, deafness, abnormal breathing pattern), erythroderma, thermolability, recurrent infections (urinary tract infection by Klebsiella sp, multiple paronychia, recurrent cellulitis), death at 30 yrs of age; (ii) laboratory: ↓ B cells, ↓ T cells, ↓ NK cells, ↓ IgG, ↓ IgA, ↓ IgM, ↓ ADA activity in erythrocytes; (iii) genetic analysis of the patient: homozygosity for a 5-bp deletion (c.956_960delAAGAG) in exon 10 of the ADA gene; (iv) genetic analysis of the patient’s parents: healthy father was heterozygous for the mutation; healthy mother had wild type ADA genes.

  - Why was the patient homozygous for the ADA mutation? → Because of paternal disomy of chromosome 20 (2 chromosomes of paternal origin), which included the mutated ADA gene → the patient received two mutated ADA genes from his father.

  - Mode of inheritance is important for genetic counseling (e.g. recurrence risk of uniparental disomy without chromosomal disturbances in parents: <1%; recurrence risk of an autosomal recessive disease when both patients are carriers of the mutation: 25%).

- **WHAT IS AN “EOSINOPHILIC PHENOTYPE” OF ASTHMA?** (Nair P. J Allergy Clin Immunol 2013; 132: 81-83):

  - Evidence that argue against a pathogenic role of eosinophils in asthma: (i) in murine models of asthma, airway hyperresponsiveness could be induced without eosinophils; (ii) in early studies, anti-IL-5 (eosinophil-targeting therapy) did not ↑ asthma outcomes despite decreasing airway and blood eosinophils (limitation: patients were not identified to have eosinophil-driven disease).
• **Evidence that supports a pathogenic role of eosinophils in asthma:** (i) activated eosinophils can be detected in airway lumen and tissue of patients with active asthma; (ii) eosinophils ↑ when asthma is uncontrolled and ↓ when asthma is controlled; (iii) in recent studies, anti-IL-5 improved asthma outcomes in patients with consistently elevated sputum eosinophil counts.

• **Methods to identify “eosinophilic phenotype” of asthma:** (i) sputum eosinophil counts: difficult to perform in routine clinical practice; (ii) blood eosinophil counts: inexpensive, widely available, poor sensitivity and specificity, increased values might correlate with asthma severity and might predict response to anti-IL-5 therapy; (iii) other methods: FENO, serum periostin levels.

• **Hastie et al (J Allergy Clin Immunol 2013; 132: 72-80)** → poor correlation between blood eosinophil counts and sputum eosinophil counts.

• **Conclusions:** (i) it might be prudent not to rely on eosinophil or neutrophil blood counts to guide asthma therapy; (ii) currently, sputum eosinophil counts seem to be the most accurate and clinically relevant method to predict an “eosinophilic phenotype” of asthma.