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- **CONTRIBUTION OF HIGHLY SENSITIVE DIAGNOSTIC METHODS TO THE DIAGNOSIS OF SYSTEMIC MASTOCYTOSIS (SM) IN THE ABSENCE OF SKIN LESIONS** (Alvarez-Twose I, Matito A, Sánchez-Muñoz L, Morgado JM, Orfao A, Escribano L. Allergy 2012; 67: 1190–1191);

- **CX3CL1 IN ALLERGIC DISEASES: NOT JUST A CHEMOTACTIC MOLECULE** (Julia V. Allergy 2012; 67: 1106–1110);

- **INTENSIVE EDUCATIONAL COURSE IN ALLERGY AND IMMUNOLOGY (A/I)** (Elizalde A, Perez EE, Silaroon P, Nguyen D, Lockey RF, Dorsey MJ. Allergy 2012; 67: 1085–1086);

- **SERUM BIOMARKERS ARE SIMILAR IN CHURG–STRAUSS SYNDROME (CSS) AND HYPEREOSINOPHILIC SYNDROME (HES)** (Khoury P, Zagallo P, Talai-Williams C, Santos CS, Dinerman E, Holland NC, Kilon AD. Allergy 2012; 67: 1149–1156);

- **THE COST-EFFECTIVENESS OF IMMUNOTHERAPY (IT) FOR RESPIRATORY ALLERGY: A REVIEW** (Simoens S. Allergy 2012; 67: 1087–1105);

- **ADHERENCE TO ENVIRONMENTAL CONTROL MEASURES** (Desai M, Oppenheimer J. Ann Allergy Asthma Immunol 2012; 109: 85–86);


- **FARMING-ASSOCIATED ENVIRONMENTAL EXPOSURES AND EFFECT ON ATOPIC DISEASES** (Poole JA. Ann Allergy Asthma Immunol 2012; 109: 93-98);

- **HEREDITARY ANGOEDEMA (HAE): IMPLICATIONS OF TREATING A RARE DISEASE** (Kalfus IN, Glen Gower R, Riedl M, Bernstein JA, Lumry WR, Frank MM. Ann Allergy Asthma Immunol 2012; 109: 150-151);

- **IMPROVING PATIENT ADHERENCE WITH ASTHMA SELF-MANAGEMENT PRACTICES: WHAT WORKS?** (Eakin MN, Rand CS. Ann Allergy Asthma Immunol 2012; 109: 90-92);

- **WHAT SHOULD DRIVE THE CHOICE OF ALLERGEN FOR IMMUNOTHERAPY (IT) IN POLYSSENSITIZED PATIENTS?** (Puccinelli P, Dell’Albani I, Frati F. Ann Allergy Asthma Immunol 2012; 109: 147-149);

- **WHAT WILL ALLERGEN IMMUNOTHERAPY LOOK LIKE IN THE FUTURE?** (Nelson HS. Ann Allergy Asthma Immunol 2012; 109: 87-89);

- **OMALIZUMAB IN CHRONIC URTICARIA (CU)** (Metz M, Maurer M. Curr Opin Allergy Clin Immunol 2012; 12: 406–411);

- **PROGRESS IN UNDERSTANDING HYPERSENSITIVITY DRUG REACTIONS: AN OVERVIEW** (Blanca M, Thong B. Curr Opin Allergy Clin Immunol 2012; 12: 337-340);


**ALLERGY:**

  - Worldwide heterogeneity in the prevalence of immediate reactions to β-lactams suggests a complex trait under environmental and genetic influences.
  - Total IgE, IgE against mites and IL4RA polymorphisms are related to increased prevalence of β-lactam allergy in South of Spain.

  - Indolent SM (ISM) without urticaria pigmentosa (UP): low MC burden; substantial proportion of cases lack bone marrow (BM) MC aggregates.
  - Methods to diagnose SM with no skin lesions: flow cytometry immunophenotyping for the identification of BMMC down to frequencies as low as $10^{-4}$ to $10^{-5}$; KIT mutation analysis of highly purified BMMC.
  - Investigation of KIT mutation in whole BM samples, specifically identifying D816V KIT mutation without investigating other exon 17 mutations, may lead to a lower rate of detection of mutated BMMC (false negative results).
  - Serum tryptase levels <20 μg/l do not exclude SM, cut-off should be lowered.

- **CX3CL1 IN ALLERGIC DISEASES: NOT JUST A CHEMOTACTIC MOLECULE** (Julia V. Allergy 2012; 67: 1106–1110):
  - >50% of children with AD develop asthma; 75% will suffer from allergic rhinitis.
  - CX3CL1 (fractalkine or neurotactin): chemokine that is upregulated in inflammatory diseases, including psoriasis, COPD, pulmonary hypertension, pulmonary fibrosis and allergic diseases.
  - Intestinal epithelial cells, alveolar cells, bronchial epithelial cells → CX3CL1 secretion → acts on CX3CR1, expressed in monocytes, NK cells and subsets of T cells → increase in intracellular calcium, actin rearrangement, and activation of proinflammatory pathways → cell survival, proliferation and migration.
  - Chemokines are well-known as chemoattractants, they can also ↑ survival.
• Local administration of CX3CL1 antagonist to mice → reduced AHR and airway inflammation. Effect of CX3CL1 antagonist in human asthma must be explored.

  - The A/I intensive education course (Boot Camp) program was implemented at the University of South Florida to facilitate fellows-in-training (FIT) education.
  - 1-day Boot Camp course significantly ↑ competency of 1st and 2nd year FIT.
  - Educational methods: (1) PPT presentations; (2) demonstration of procedures by faculty. Covered topics: anaphylaxis, spirometry, FENO determination, skin testing, prescribing and administering IT, asthma education, topical management of AD, food challenge, patch testing, antibiotic desensitization and challenge, treatment with IVIG and SCIG, and special immunology testing.

  - CSS and HES overlap considerably in clinical presentation.
  - Definitive diagnosis of CSS relies on the demonstration of vasculitis in tissue. Affected tissues may not be easily accessible for biopsy.
  - p-ANCA are associated with CSS, but they present in about only 50% of patients with biopsy-proven CSS.
  - American College of Rheumatology (ACR) criteria for CSS: (i) asthma, (ii) eosinophilia > 10%, (iii) mono- or polyneuropathy, (iv) migratory or transitory pulmonary infiltrates, (v) paranasal sinus abnormality, and (vi) extravascular eosinophils noted on a biopsy that includes an artery, arteriole or venule. In the setting of documented vasculitis, the presence of ≥4 ACR criteria had a sensitivity of 95% and specificity of 99.2% for CSS.
  - HES is defined by unexplained eosinophilia >1500/μL on 2 separate occasions at least 1 month apart and evidence of eosinophil-induced organ involvement.
  - Laboratory and clinical parameters were compared between subjects with biopsy-proven vasculitis (CSS), ≥4 ACR criteria (probable CSS), HES with asthma and/or sinusitis without other CSS-defining criteria (HESwAS), HES without asthma or sinusitis (HES), and normal controls.
  - There were no differences between eosinophilic groups with respect to age, gender or maintenance steroid dose. Serum CCL17, IL-8, and eotaxin levels were similar between eosinophilic groups but higher than healthy controls.
• Distinction between ANCA-negative CSS and PDGFR-negative HES with asthma and/or sinusitis can be very difficult in the absence of clear pathologic evidence of vasculitis.

• Of the 276 adults with eosinophils >1500/μl, 106 (38%) had a documented secondary cause of eosinophilia (i.e., drug hypersensitivity, helminth infection, myeloproliferative neoplasm) and were excluded from further study.

• **THE COST-EFFECTIVENESS OF IMMUNOTHERAPY (IT) FOR RESPIRATORY ALLERGY: A REVIEW (Simoens S. Allergy 2012; 67: 1087–1105):**

  • Evidence appears to support the cost-effectiveness of IT as compared with pharmacotherapy for allergic rhinoconjunctivitis, subcutaneous IT as compared with pharmacotherapy for allergic rhinitis and IT as compared with pharmacotherapy for allergic rhinitis and asthma.

  • 1 economic evaluation suggested that IT as compared with pharmacotherapy is unlikely to be cost-effective for asthma.

  • The questions of the cost-effectiveness of sublingual vs. subcutaneous IT and of the cost-effectiveness of IT for allergic conjunctivitis are not resolved yet.

  • The cost-effectiveness of IT depends on the duration of the clinical benefit following treatment cessation, and on the break-even point of cumulative costs between IT and pharmacotherapy.

  • There is a need for economic evaluations based on high-quality prospective and long-term clinical studies comparing IT with pharmacotherapy in real-life practice and comparing sublingual with subcutaneous IT.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

ANNALS OF ALLERGY AND CLINICAL IMMUNOLOGY:

  - To better control asthma and rhinitis we should: (1) educate about **environmental measures**, although uncertainty exists about their practicality, efficacy, and cost-effectiveness; (2) improve **adherence**.
  - Measures for **dander allergy**: (1) keep pets out of home; (2) keep pets out of the bedroom; (3) wash pets weekly; (4) get a room air purifier.
  - 2010 Cochrane Review: **chemical treatments** and **bedroom measures** may be of some benefit in reducing HDM-induced perennial allergic rhinitis symptoms.

  - Case report 1: 51-year-old woman; hives for 4 months, no response to anti-H1; myalgias, arthralgias and fever; positive ANA (1:160 speckled), anti-Ro, anti-La; IgG=2,640 mg/dL (normal: 844–1,912); good response to doxepin 10 mg/day.
  - Case report 2: 52-year-old woman; hives for 20 years; arthralgias, bone pain, fevers; IgM=391 mg/dL (normal: 40–230); good response to bid anti-H1.
  - **SS**: inflammatory disease with features of autoimmunity. IL-1 and IL-6 are implicated. Monoclonal IgM gammopathy is frequent, IgG gammopathy is rare. IgM deposits in skin → immune complexes → complement activation → hives. Histology is variable, from neutrophilic urticaria to spongiotic dermatitis.
  - **Therapies**: corticosteroids, anakinra, canakinumab.

- **FARMING-ASSOCIATED ENVIRONMENTAL EXPOSURES AND EFFECT ON ATOPIC DISEASES** (Poole JA. Ann Allergy Asthma Immunol 2012; 109: 93-98):
  - Children living on farms: OR for atopy was 0.25-0.5; protective effect may continue into adulthood. When exposure to farm animals was initiated as an adult, the risk of developing allergic sensitization increased.
  - Despite lower rates of IgE-mediated diseases, **respiratory tract disorders** represent a substantial health problem for the farming community.

  - Decisions regarding prophylaxis or on-demand therapy for HAE are **patient specific**, according to quality of life, frequency and severity of attacks. There are individual differences in response to therapy.
There are 7,000 orphan diseases and only 350 approved therapies.

The 1983 Orphan Drug Act grants time-limited market exclusivity, spurring clinical drug development. Investment in HAE therapies may exceed $1.5 billion. Without the ability to recover their investment, pharmaceutical companies would not develop drugs, and orphan diseases would go untreated.


- Adherence with controller therapies in asthma ranges from 30 to 70%.
- <50% of families with asthma follow prescribed environmental control measures; only 20% of families accept to remove pets; up to 55% of patients with asthma still have frequent exposure to nicotine.
- Every office visit physicians should review inhaler technique, medication treatment plans, adverse effects and adherence. To improve adherence physicians must first assess it.
- Physicians should not rely on clinical status to rate adherence. Verbal assessment is often inexact. Asthma diaries are useful to detect nonadherence. Electronic monitoring may help in difficult cases. Use of validated scores, such as the Asthma Control Test, is recommended.
- Barriers to adherence: (1) concerns and cost about medication; (2) difficulty fitting therapy into daily life; (3) bad physician-patient relationship.
- Educational materials and routine office visits may ↑ adherence to therapy.
- Information technology (IT) tools are increasingly being applied to change health behaviors and promote patient adherence: interactive telephone messaging systems, short message service (SMS) text messaging.


- Polysensitization is an obstacle to prescribe IT. 2 attitudes are dominant: (1) to renounce to IT or (2) to perform it by mixtures of all allergens giving a positive result to allergy tests. Both approaches are inappropriate, because the former has no real basis, whereas the latter was demonstrated to be ineffective.
- Use of component-resolved diagnosis, including ISAC, could improve the capacity of choosing allergens for IT.

• **IT benefits**: prevents new sensitizations in monosensitized individuals; prevents progression from rhinitis to asthma; provides persisting benefit for years after discontinuation of treatment.

• Despite these benefits, only few candidates receive IT. Principal reasons: concern about safety, dislike of repeated injections, inconvenience, cost.

• A problem with **SLIT** is the **very low adherence** during a 3-year treatment.

• Novel approaches: **epicutaneous and intralymphatic**. Advantages of intralymphatic: (1) only 3 injections; (2) very little discomfort; (3) very small amount of allergen extract, (4) inexpensive development program because current extracts are approved for injection.

• New approach: **fusion proteins** that consist of an allergen covalently bound to an immunoglobulin-derived molecule that can activate inhibitory receptors.
**CURRENT OPINION IN ALLERGY AND CLINICAL IMMUNOLOGY:**


  - Omalizumab binds to CH3 domain of ε chain, close to the binding site of IgE for FceRI and CD23 → specific for circulating free IgE, can’t bind to cell-bound IgE.

  - Approved in US (2003) to treat moderate-severe asthma in patients ≥12 years old; approved in Europe (2005) to treat severe allergic asthma in patients ≥6 years old. Potential mechanisms: ↓ free IgE levels (to less than 10% of baseline), downregulation in FceRI expression on basophils and mast cells.

  - Aim of treatment for urticaria: complete symptom relief.

  - Guidelines for CU therapy: (1<sup>st</sup> line) 2<sup>nd</sup>-generation anti-H1, 50% incomplete response; (2<sup>nd</sup> line) four-fold dose of anti-H1; (3<sup>rd</sup> line) add anti-LT, systemic steroids for exacerbations; (4<sup>th</sup> line) add ciclosporin A, omalizumab or others.

  - The underlying cause in CU is almost never an allergy. However, patients with chronic spontaneous urticaria (CSU) have on average higher total IgE levels than healthy controls; autoallergic mechanisms can be present in 50% of cases. In some patients with cold urticaria, urticaria factitia and solar urticaria, a transferable serum factor consistent with IgE may exist.

  - 2 multicenter RCT have shown excellent efficacy of omalizumab in CSU. Case series and reports show efficacy in inducible urticaria including cholinergic urticaria, urticaria factitia, solar, cold, heat and delayed pressure urticaria.

  - Omalizumab is an effective and well tolerated drug in antihistamine-resistant CU. Potential mechanism of action: removal of autoreactive IgE. Other diseases with potential efficacy: bullous pemphigoid.

  - 49 patients with CSU and IgE anti-thyroperoxidase → rapid relieve of wheals in 70.4% of omalizumab-treated versus 4.5% of placebo-treated patients. Doses were based on total IgE levels and body weight (as in asthma therapy); however, treatment response in CSU appears to be independent of total IgE.

  - Hives recur in most patients usually 4–8 weeks after last omalizumab injection.


  - It is of great importance not to diagnose wrongly a drug allergy in children. Diagnosis approach includes skin tests, in-vitro specific IgE, BAT and DPT.

  - Most frequent drugs involved in hypersensitivity among adults: NSAIDs.

  - Most frequent drugs involved in hypersensitivity among children: antibiotics (ATB), mainly β-lactams; then NSAIDs.
• The value of skin testing in children with **exanthematous reactions to β-lactams** is very limited, with lower sensitivity than in adults.

• **Approach to immediate allergic reactions to betalactams:** prick test → intradermal reaction (IDR) → drug provocation tests (DPT). Only few cases present positive in-vitro tests with negative in-vivo tests.

• As in adults, **clavulanic acid**, due to its increasing prescription in formulations associated with amoxicillin, is a molecule that must be considered in children.

• Patients may be allergic to specific **cephalosporins** with good tolerance to other betalactams.

• A very common clinical entity found in children is **facial angioedema induced by ibuprofen and other strong COX 1 inhibitors**, and positive skin tests to HDM.

• After the **1st episode** of reported reaction to NSAIDs, clinical history can’t fully confirm hypersensitivity; neither separate between intolerance and allergy.

• Patients may be allergic to the main **vaccine component** (viral protein or bacterial toxoids), or other components including gelatin or egg proteins.

• **Proton pump inhibitors** are increasingly reported to cause immediate and delayed hypersensitivity reactions. BAT can help to confirm diagnosis.

• Is there association between **mast cell activation syndrome** and drug-induced anaphylaxis? Only few studies associate severe perioperative events with mastocytosis. Drugs that induce **non-specific histamine release** (e.g. muscle relaxants or contrast media) can cause anaphylactic reactions in patients prone to release vasoactive mediators.

• **Hypersensitivity reactions during anaesthesia** can be immune (allergic) and non-immune-mediated (non-allergic hypersensitivity). Agents more frequently involved: neuromuscular blocking agents, β-lactams and NSAIDs.

• In patients with **cystic fibrosis**, the sensitivity of IDR for **non-immediate reactions to ATB** is low. Because it is not easy to find alternate ATB, confirmation of diagnosis is obligatory, so **DPT is often required**. Desensitization is necessary when allergy is confirmed. As most of reactions are exanthematous, no significant risks are taken with desensitization.

• Keratinocyte apoptosis in **severe drug reactions (NET, DRESS)** involve expression of perforin, Fas ligand and TNF.
NATURE REVIEWS IMMUNOLOGY:

  - **Autoinflammatory diseases**: unprovoked pathological activation of the innate immune system (stress-sensing pathways) in the absence of autoantibodies or autoreactive T cells.
  - **Subclinical signs** of autoinflammatory diseases (e.g. ↑ levels of acute-phase proteins or pro-inflammatory cytokines) can often be detected in the absence of symptoms.
  - Several autoinflammatory diseases are inherited in an autosomal dominant manner, owing to gain-of-function mutations in innate immune signalling proteins. Many of these mutations cause the proteins involved to misfold or form abnormal oligomers.
  - **NADPH oxidases**: plasma membrane- and phagosomal membrane-bound enzyme complexes that transfer electrons from NADPH to molecular oxygen, promoting the generation of the reactive oxygen species superoxide.
  - How diverse stimuli gain access to the cytoplasmic NLRP3 inflammasome and trigger its activation? Entering of PAMPs and DAMPs by pannexin 1 hemichannel; rupture of phagolysosomes; generation of ROS.
  - Macrophages from patients with CGD who are deficient in subunits of the NOX2 NADPH oxidase produce normal levels of IL-1β in response to LPS.
  - **Mitophagy**: the removal of damaged mitochondria by autophagy.
  - How do the NLRP3 mutations in patients with CAPS enhance inflammasome activation? Most of the 110 known disease-associated mutations in NLRP3 are concentrated in exon 3, which encodes the nucleotide-binding domain, suggesting that this domain has functional importance in the disease process.
  - The mutant TNFR1 in TRAPS seems to function as an unusual gain-of-function protein, enhancing inflammatory responses; it requires cooperation from the wild-type receptor. TNF blockade has partial efficacy, as TNF blockade would only affect extracellular TNF binding to wild-type TNFR1, not the intracellular effects of the mutant receptor.
  - **Colchicine**: an inhibitor of microtubule polymerization that has anti-inflammatory properties, possibly through blockade of neutrophil chemotaxis. Effective for gout and familial Mediterranean fever.
  - Mutant pyrin enhances inflammation and symptoms of FMF in a dominant manner that is highly dependent on gene dosage, although haploinsufficiency
or a dominant-negative mechanism that inhibits an unknown inflammatory suppressive function remains conceptually possible.
PEDIATRIC ALLERGY AND IMMUNOLOGY:

  - Prevalence of EoE: 1/1000 (the most common EGID).
  - Depression is significantly associated with non-adherence in patients with EGID. Always screen for depression in patients with EGID.

  - XLP: primary immunodeficiency, affects approximately 1/10^6 males.
  - XLP type 1 (SAP deficiency): extreme vulnerability to EBV. Major clinical phenotypes: fulminant infectious mononucleosis (FIM) or EBV-associated HLH (60%); lymphoproliferative disorder (30%); dysgammatglobulinemia (30%). Other phenotypes: vasculitis; aplastic anemia; pulmonary lymphoid granulomatosis. Patients with XLP often develop >1 phenotype over time.
  - We identified 33 patients from 21 families with XLP-1 in Japan.
  - 12 patients (35%) underwent HSCT → 11 of these (92%) survived.
  - 21 patients (65%) did not undergo HSCT → everyone died.
  - Optimal approach: early diagnosis (combination of flow cytometric assay and genetic analysis) → HSCT.

  - Mattress dust endotoxin exposure → significant increase in neonatal respiratory compliance; non-significant decrease in neonatal airway resistance. No associations between allergen exposure and neonatal lung function.

• **Gut microbiota:** Bifidobacteria and Lactobacillus sp are considered beneficial for human; staphylococci and clostridia are considered potentially pathogenic.

• **Allergic infants:** low numbers of Bifidobacterium/Lactobacilli; high levels of Clostridium, staphylococci and E coli. Hydrolyzed formula used to feed these infants is deprived of lactose.

• Adding lactose to extensively hydrolyzed formula → ↑ total fecal counts of Lactobacillus/Bifidobacteria, ↓ of Bacteroides/Clostridia → ↑ concentration of short chain fatty acids, especially acetic and butyric acids → health benefit.

• **SAMTER’S TRIAD AND EICOSANOID IMBALANCE IN CHILDREN WITH RECURRENT NASAL POLYPS (NP)** *(Olze H, Lau S, Förster U. Pediatr Allergy Immunol 2012; 23: 500)*:

  • Diagnosis of pediatric CRS → search for allergy, immunologic deficiencies, primary ciliary dyskinesia, cystic fibrosis.

  • Few reports describe pediatric or adolescent cases of NP + asthma + NSAID intolerance (Samter’s triad, aspirin-exacerbated respiratory disease/AERD). Proposed pathogenic mechanism: eicosanoid imbalance.

  • We report 3 cases of Samter’s triad in pediatric/adolescent patients (2 girls, 1 boy). To examine the balance between leukotrienes and prostaglandins, we used the in vitro functional eicosanoid test (FET), which has a sensitivity of 96% and specificity of 89%. Our patients had mild eicosanoid imbalance.