



# ΑΛΛΕΡΓΙΚΗ ΡΙΝΙΤΙΔΑ ΠΟΛΥΠΟΔΕΣ ΚΑΙ ΑΣΘΜΑ

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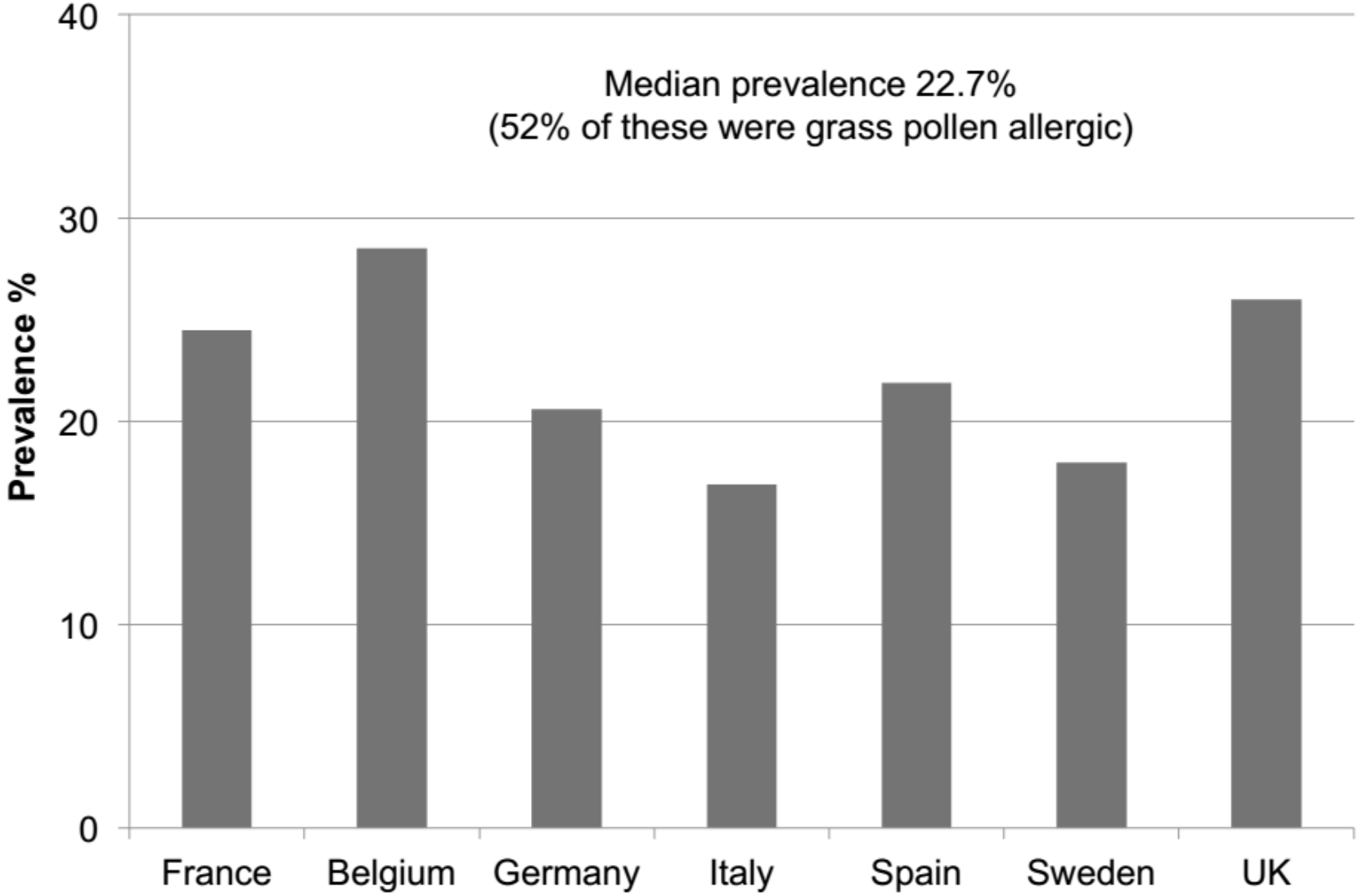
**19ο Πανελλήνιο Σεμινάριο Ρινολογίας**

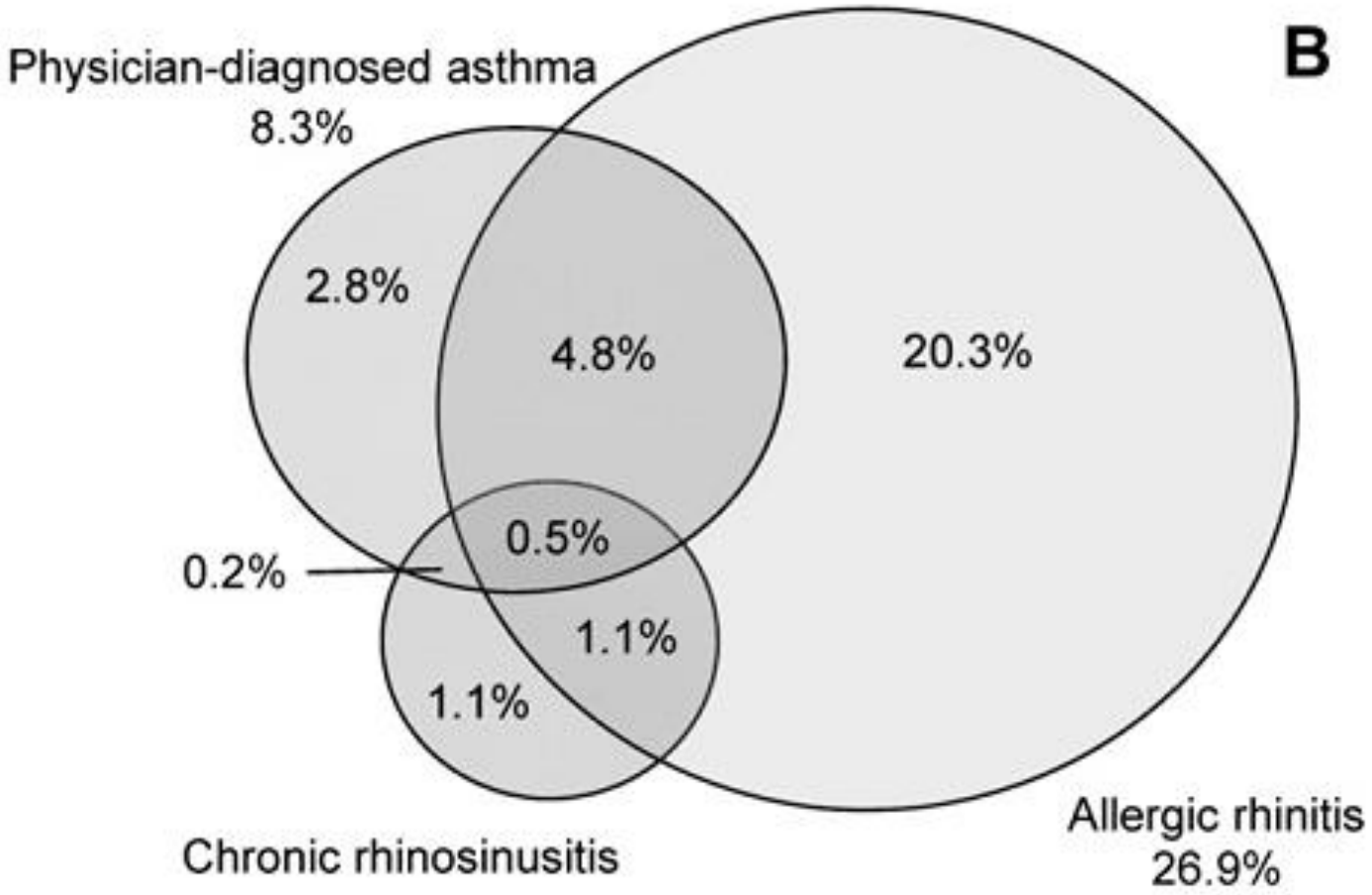
**Νοσοκομείο «Αττικόν»**

Αθήνα, 11-14 Απριλίου 2019

# Prevalence of allergic rhinitis confirmed by clinical examination in Europe




*Bauchau et al Eur Respir J. 2004 Nov;24(5):758-64Durham, Eur Respir J 2004*

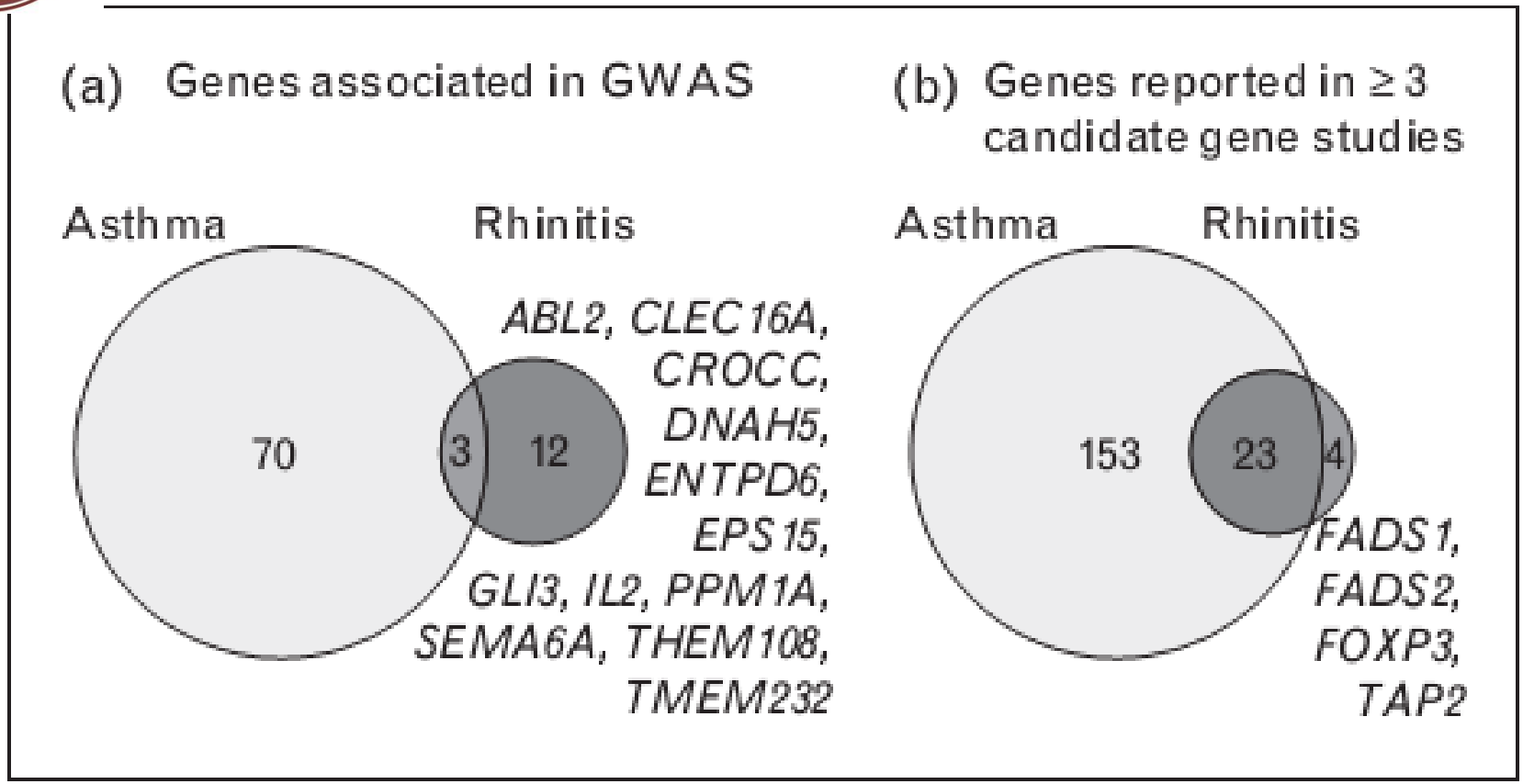



Συχνότητα ΑΡ στο ΑΣΘΜΑ : 63.9%
ΑΣΘΜΑ στην ΑΡ: 19.8%

ΧΡΚ στο ΑΣΘΜΑ : 8.4%
ΑΣΘΜΑ στη ΧΡΚ : 24.4%

Respiratory Medicine (2011) **105**, 1611–1621

# Genetic Links




a. LRRC32, genes of the HLA region, and TSLP

b. ACE, ADAM33, ADRB2, CD14, CFTR, CTLA4, CYP2D6, FLG, GATA3, HLA-DQB1, HLA-DRB1, IL4, IL4R, IL5, IL6, IL13, IL18, SCGB1A1, TAP1, TGFB1, TLR2, TLR4, and TNF.



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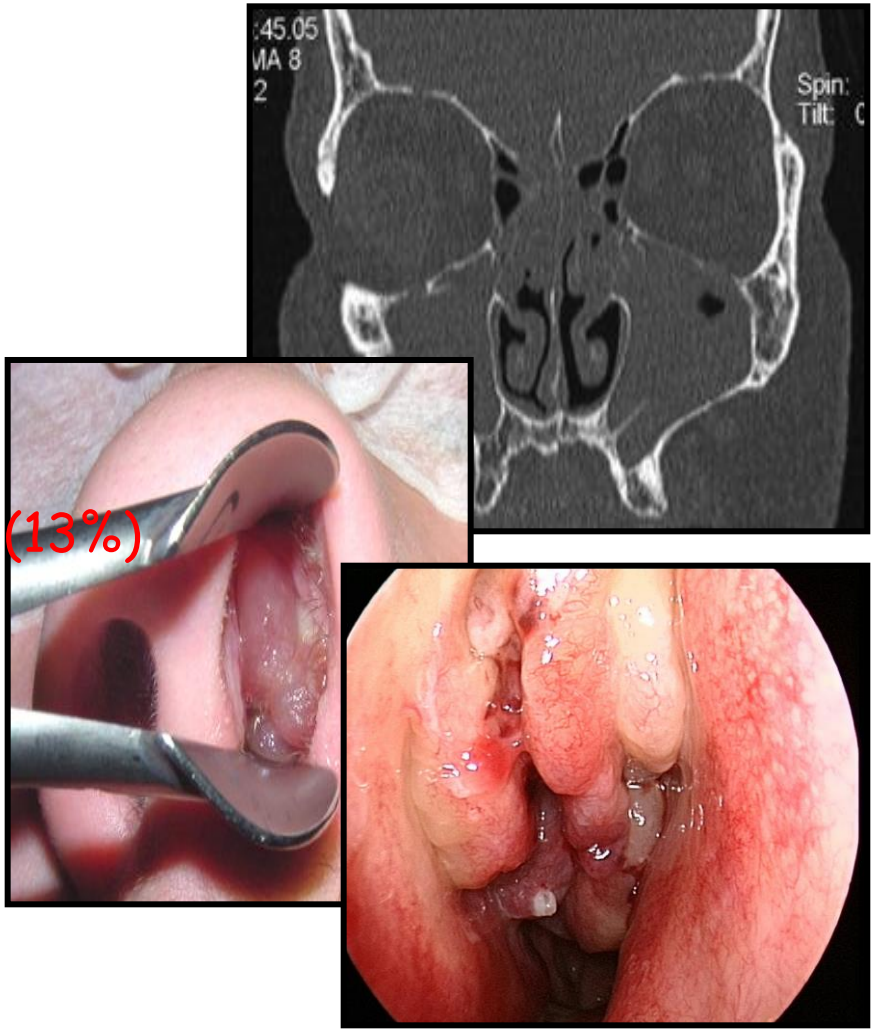
# Nasal polyposis

- Prevalence approx. 2- 4%
- Asthma in approx. 40-65%
- Aspirin sensitivity in 10-15%
- Polyps are more common in patients with non-allergic asthma (13%) than allergic asthma (5%)
- Mixed cellular infiltrate with prominent eosinophilia in 90%
- Inflammation with
  - local IgE production
  - increased IL-5, eotaxin,
  - cys-LTs and ECP



Clin Transl Allergy. 2017; 7: 17.

**Multi-morbidities of allergic rhinitis in adults: European Academy of Allergy and Clinical Immunology Task Force Report**

C. Cingi, P. Gevaert, R. Mösges, et al.

## Chronic rhinosinusitis with nasal polyps (CRSwNP)

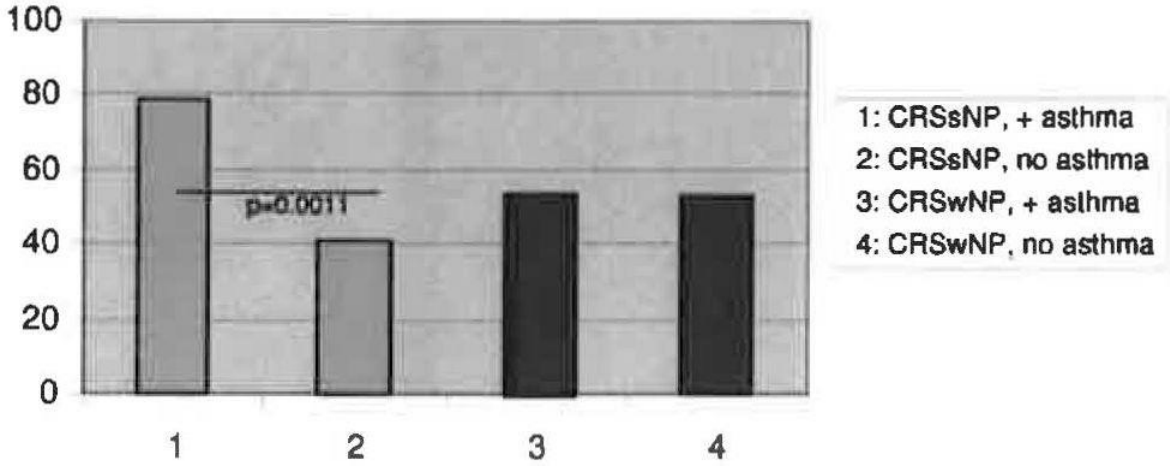
- **an allergic aetiology of NPs has been presumed, though never firmly demonstrated**.
- In NPs, the **level of IgE is independent of the atopic status** of the patient.
- The **local IgE in NPs** is the result of two types of IgE production: **systemic allergic IgE formation and a local polyclonal IgE formation**. Local polyclonal IgE correlates with the presence of Staphylococcus aureus enterotoxins (SAE).
- Finally, Gevaert et al. demonstrated that **antagonizing IgE by injections of omalizumab** is effective for **both allergic and nonallergic CRSwNP**. The later finding proves the relevance of local mucosal IgE.

**CRSwNP is an IgE mediated disease; however, the role of atopy is less clear**

Am J Rhinol. 2006 Nov-Dec;20(6):625-8.

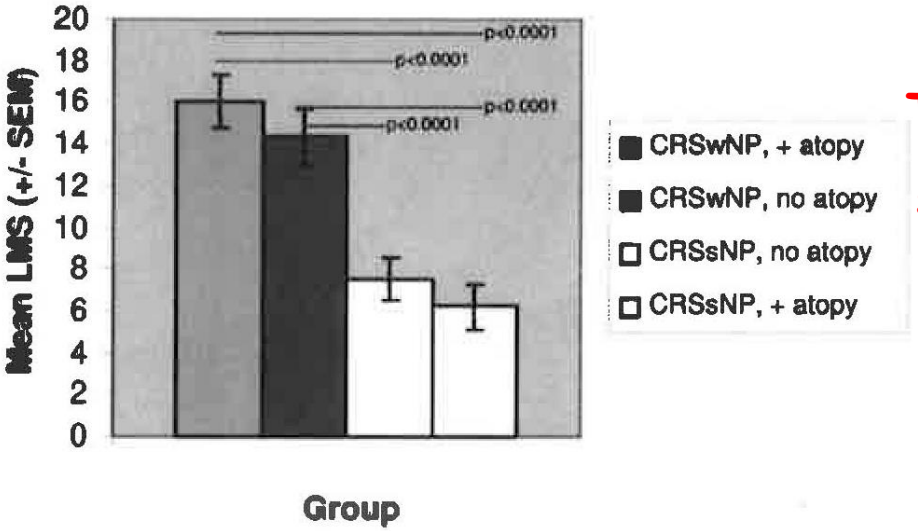
**The relationship between atopy and chronic rhinosinusitis.**

Robinson S, Douglas R, Wormald PJ.




Among CRS without nasal polyposis patients, atopy was more prevalent in those who had asthma (1 and 2).

Among CRS with nasal polyposis patients, atopy was similar between asthmatic and non asthmatic patients (3 and 4).




**These results suggest that atopic status has minimal impact on the severity of CRS.**

Mean Lund-MacKay score (LMS) was greater in polyp patients with and without atopy. Non polyp patients had lower mean LMS, regardless of atopic status.

Am J Rhinol Allergy. 2009 ; 23(2): 145–148. doi:10.2500/ajra.2009.23.3284.

**Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy**

Aaron N. Pearlman, Rakesh K. Chandra, Dennis Chang, et al.

- no significant difference between the mean Lund-Mackay score and the presence of atopy when comparing patients with CRSwNP and patients with CRSsNP.
- Similarly, Tan *et al.* found no difference among patients with atopy and with CRS and patients without atopy with CRS who were undergoing sinus surgery.

Eur Arch Otorhinolaryngol (2014) 271:733–741
DOI 10.1007/s00405-013-2626-6

RHINOLOGY

# Predictors of quality of life outcomes in chronic rhinosinusitis after sinus surgery

Michael Katotomichelakis · Efthimios Simopoulos · Gregory Tripsianis · Dimitrios Balatsouras · Gerasimos Danielides · Christos Kourousis · Miltos Livaditis · Vassilios Danielides

Eur Arch Otorhinolaryngol (2014) 271:733–741
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RHINOLOGY

# Predictors of quality of life outcomes in chronic rhinosinusitis after sinus surgery

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- Although all patients' QoL improved significantly after ESS, a 49.5–64.9 % of patients with CRS experienced clinically significant improvement (QOD: 56.8 %, BDI: 49.5 %, SF-36: 64.9 %).
- Clinical phenotypes,
- **CRS associated with anosmia or hyposmia,**
- **CRS associated with nasal polyps,**
- CRS associated with non- smoking habits, and
- in medium or high socio-economic status patients were significant predictors of better QoL outcomes;

Curr Allergy Asthma Rep (2014) 14:427
DOI 10.1007/s11882-014-0427-7

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

# Evidence-based Surgery for Chronic Rhinosinusitis with and without Nasal Polyps

Christos Georgalas · Marjolein Cornet · Gwijde Adriaensen · Susanne Reinartz · Carlijn Holland · Emmanuel Prokopakis · Wytske Fokkens

- Presence of Allergy:

• Data are contradictory

• Management of allergy in atopic patients preoperatively could improve overall outcome.


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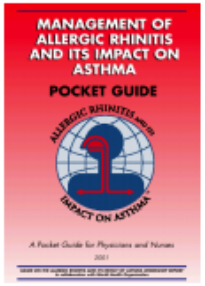
# ΑΛΛΕΡΓΙΚΗ ΡΙΝΙΤΙΔΑ ΚΑΙ ΑΣΘΜΑ

- Άσθμα: ορισμοί – βασικές γνώσεις
- Το μοντέλο του ενιαίου αεραγωγού
  - Επιδημιολογικά δεδομένα
  - Θεραπευτικές εφαρμογές
- Παθοφυσιολογικές αλληλεπιδράσεις ρινός - βρόγχων
- Σε ποιούς φαινότυπους άσθματος υπάρχει ρινίτιδα;

# Rhinitis is a risk factor for asthma

| Authors | Location | Number | Risk |
|---|---|---|---|
| Leynaert et al. | Europe | 90478 adults | 6.63 (OR) |
| Toren et al. | Sweden | 15813 adults | 5.40 (OR) |
| Guerra et al. | USA | 2350 | 3.21 (OR) |
| Plaschke et al. | Sweden | 1370 adults | 4.09 (OR) |
| Chatkin | Brazil | 494 children | 2.80 (RR) |

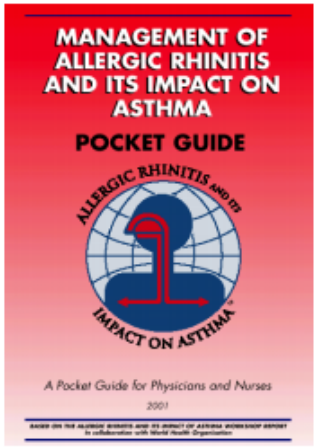



*Cruz et al, Allergy 2007: 62 (Suppl. 84): 1–41*

# Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA2LEN

- Allergic rhinitis is one of the multiple risk factors identified for asthma development.
- Patients with persistent AR should be evaluated for asthma.
- Patients with asthma should be properly evaluated for rhinitis.
- A combined strategy should be used to treat the upper and lower airways for better efficacy/safety ratio.

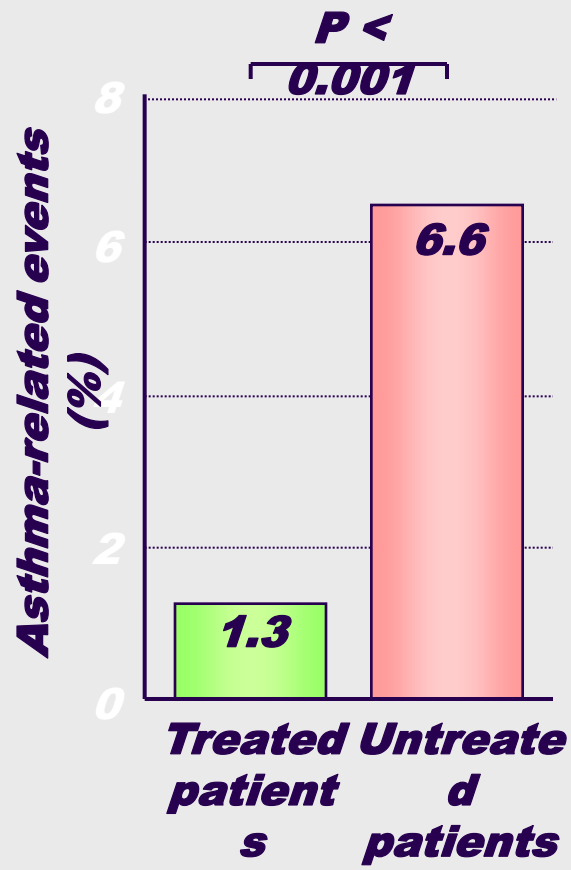
up to 50% of patients with allergic rhinitis have bronchial hyperreactivity (BHR)




*Cruz et al, Allergy 2007: 62 (Suppl. 84): 1–41*

# Allergic Rhinitis and its Association with Asthma

## *Asthma is improved by treating concomitant allergic rhinitis*




- ***Treatment of allergic rhinitis reduces asthma-related events 5-fold***

Crystal-Peters J et al J Allergy Clin Immunol 2002;109:57-62.

# ΑΛΛΕΡΓΙΚΗ ΡΙΝΙΤΙΔΑ ΚΑΙ ΑΣΘΜΑ

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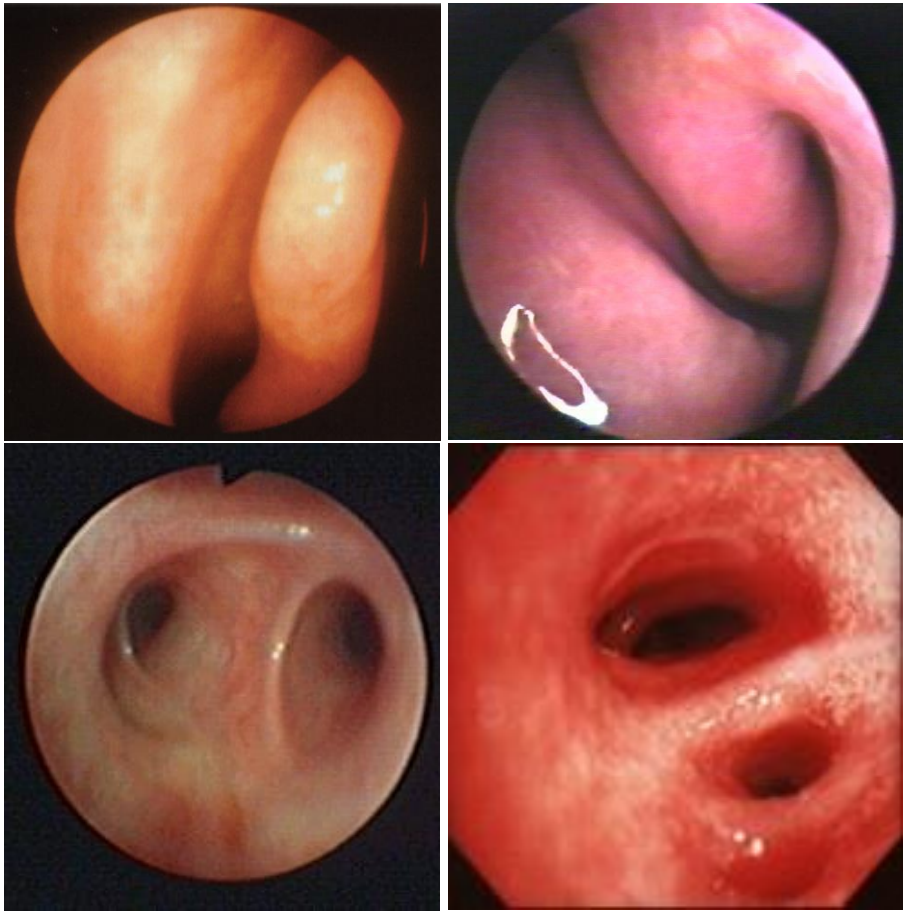
- Σε ποιούς φαινότυπους άσθματος υπάρχει ρινίτιδα;


Η επικοινωνία μεταξύ ανώτερων και κατώτερων αεραγωγών στην αναπνευστική αλλεργία είναι αμφίδρομη

# Μακροσκοπική εικόνα

Μύτη



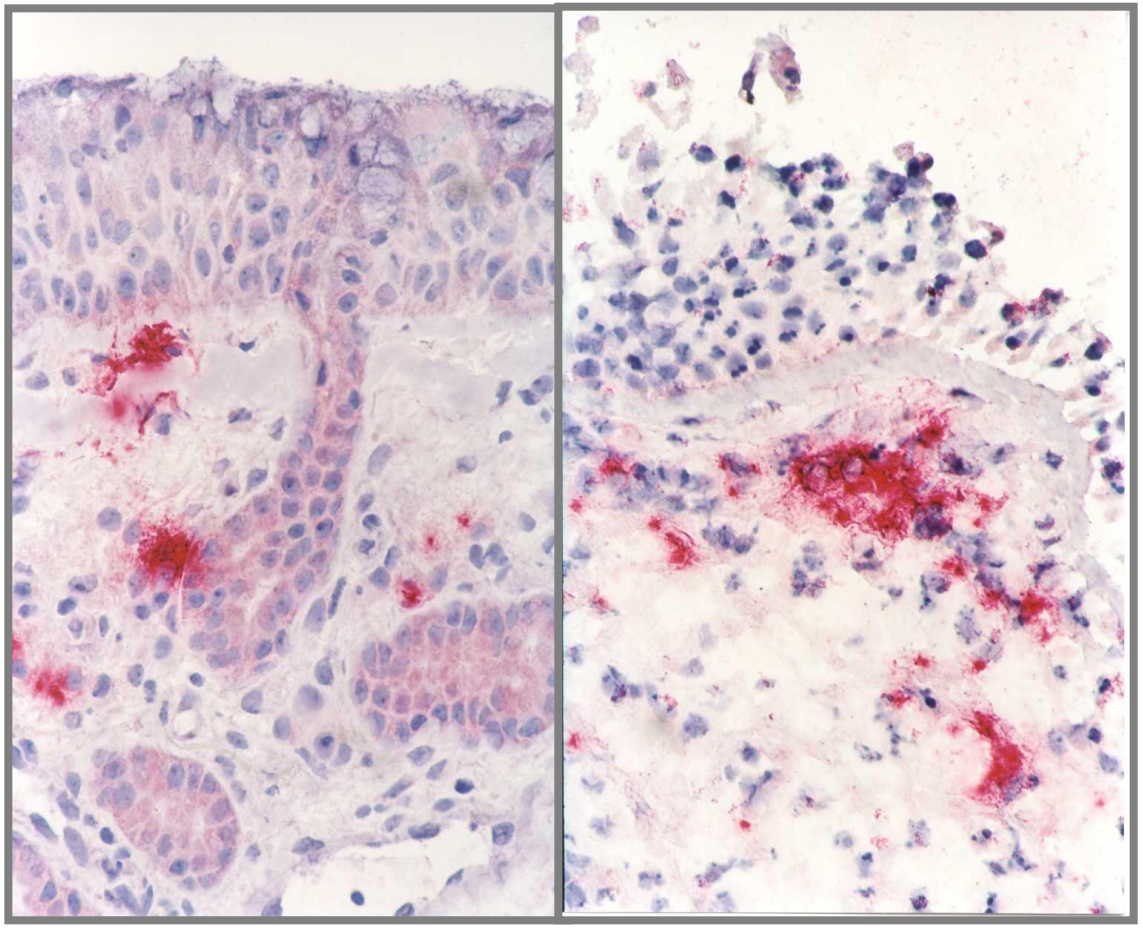
Ρινίτιδα

Πνεύμονες

Άσθμα

# Μικροσκοπική εικόνα

Ρινίτιδα



Άσθμα

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- Θεραπευτικές ιδιαιτερότητες

# Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision

**Recommendation 16:** We suggest oral leukotriene receptor antagonists in adults and children with seasonal allergic rhinitis (conditional recommendation | high quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence). In adults with perennial allergic rhinitis we suggest that clinicians do not administer and patients do not use oral leukotriene receptor antagonists (conditional recommendation | high quality evidence).

**Recommendation 17:** We suggest oral H1-antihistamines over oral leukotriene receptor antagonists in patients with seasonal allergic rhinitis (conditional recommendation | moderate quality evidence) and in preschool children with perennial allergic rhinitis (conditional recommendation | low quality evidence).

# Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision

## III. Treatment of asthma in patients with allergic rhinitis and asthma

**Recommendation 42:** In patients (both children and adults) with allergic rhinitis and asthma, we suggest clinicians do not administer and patients do not use oral H1-antihistamines for the treatment of asthma (conditional recommendation | very low quality evidence).

**Recommendation 44:** In patients with allergic rhinitis and asthma, we suggest that clinicians do not administer and patients do not use intranasal glucocorticosteroids for treatment of asthma (conditional recommendation | low quality evidence).

**Recommendation 45:** In patients with allergic rhinitis and asthma, we recommend inhaled glucocorticosteroids over oral leukotriene receptor antagonists as a single controlling medication for asthma (strong recommendation | moderate quality evidence).

# Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision

## III. Treatment of asthma in patients with allergic rhinitis and asthma

**Recommendation 46:** In patients with allergic rhinitis and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate quality evidence).

**Recommendation 47:** In patients with allergic rhinitis and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation | low quality evidence).

**Recommendation 48:** In patients with allergic rhinitis and asthma with a clear IgE-dependent allergic component, uncontrolled despite optimal pharmacologic treatment and appropriate allergen avoidance, we suggest monoclonal antibody against IgE for treatment of asthma (conditional recommendation | moderate quality evidence).

# Συμπεράσματα

- ✓ **Η αλλεργική ρινίτιδα συχνά προηγείται του άσθματος και αποτελεί παράγοντα κινδύνου για την εμφάνισή του**
- ✓ **Στη ρινίτιδα ή/και το άσθμα φλεγμαίνει όλο το αναπνευστικό σύστημα**
- ✓ **Υπάρχει αμφίδρομη σχέση μεταξύ ρινίτιδας και άσθματος**
- ✓ **Η συστηματική κυκλοφορία παίζει σημαντικό ρόλο σ' αυτή την αλληλεπίδραση**



# ΑΛΛΕΡΓΙΚΗ ΡΙΝΙΤΙΔΑ, ΠΟΛΥΠΟΔΕΣ ΚΑΙ ΑΣΘΜΑ

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- Αλλεργική ρινίτιδα και άσθμα
- **Πολύποδες και άσθμα**

Published in final edited form as:
*J Allergy Clin Immunol Pract*. 2016 ; 4(4): 639–642. doi:10.1016/j.jaip.2016.05.007.


# Chronic Rhinosinusitis Phenotypes: An Approach to Better Medical Care for Chronic Rhinosinusitis

Seong H. Cho, MD[a], Claus Bachert, MD, PhD[b,c], and Richard F. Lockey, MD[a]

## CRS phenotypes

| |
|---|
| 1. CRSsNP |
| 2. CRSwNP |
| 3. CRS with aspirin-exacerbated respiratory disease |
| 4. Allergic fungal sinusitis |
| 5. Infectious CRS |
| 6. CRS with cystic fibrosis |
| 7. Other CRS phenotypes |
| a. CRS with immune deficiencies such as common variable immunodeficiency and specific antibody deficiency |
| b. CRS with immotile cilia syndrome |
| c. CRS with anatomical abnormalities |
| d. Biomarker based (endotypes) |
| 1) Eosinophilic CRS vs noneosinophilic CRS |
| 2) Allergic CRS vs nonallergic CRS |
| 3) $T_H2$ high vs $T_H2$ low |
| 4) High IgE vs normal IgE |

Clinical reviews in allergy and immunology

# Endotype-driven care pathways in patients with chronic rhinosinusitis

Claus Bachert, MD, PhD,[a,b] Nan Zhang, MD, PhD,[a] Peter W. Hellings, MD,[c] and Jean Bousquet, MD, PhD[d] *Ghent and Leuven, Belgium, Stockholm, Sweden, and Montpellier, France*



## .....to Endotypes

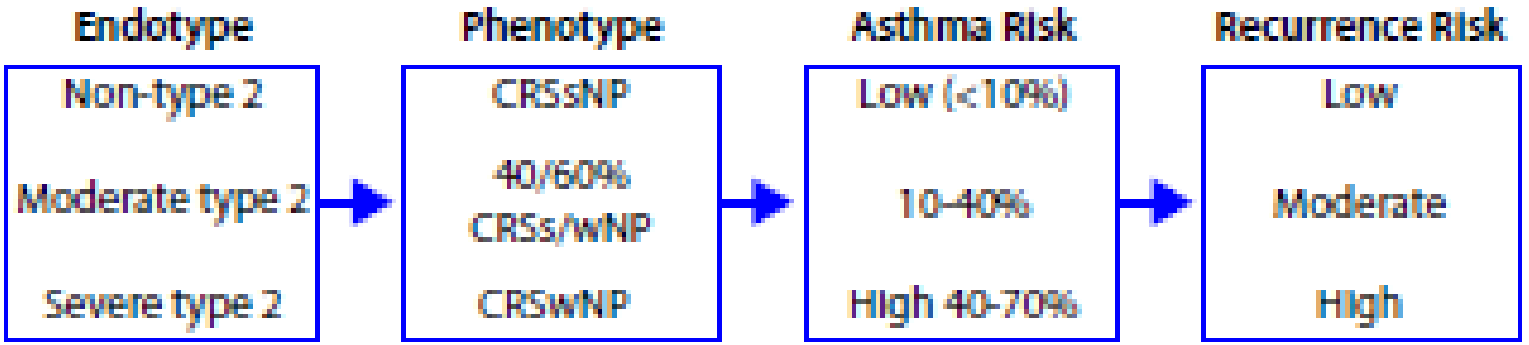



FIG 1. Endotypes of CRS and clinical consequences.

Defined 3 endotypes:
(1) non-type 2,
(2) moderate type 2, and
(3) severe type 2 immune reactions, based on significant up-regulations of cytokines and mediators in diseased versus healthy subjects or patients with severe versus moderate disease

# From Pheno…….. to Endotypes

BULGARIAN NATIONAL SOCIETY OF OTORHINOLARYNGOLOGY, HEAD AND NECK SURGERY

Rhinitis, sinusitis, and upper airway disease

## Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers

Peter Tomassen, MD,[a] Griet Vandeplas, MD,[a] Thibaut Van Zele, MD, PhD,[a] Lars-Olaf Cardell, MD, PhD,[b] Julia Arebro, MD,[b] Heidi Olze, MD, PhD,[c] Ulrike Förster-Ruhrmann, MD,[c] Marek L. Kowalski, MD, PhD,[d] Agnieszka Olszewska-Ziąber, MD,[d] Gabriele Holtappels,[a] Natalie De Ruyck,[a] Xiangdong Wang, MD, PhD,[e] Cornelis Van Drunen, PhD,[f] Joaquim Mullol, MD, PhD,[g] Peter Hellings, MD, PhD,[h] Valerie Hox, MD, PhD,[h] Elina Toskala, MD, PhD,[i] Glenis Scadding, MD,[j] Valerie Lund, MD,[j] Luo Zhang, MD, PhD,[e] Wytske Fokkens, MD, PhD,[f] and Claus Bachert, MD, PhD[a,b] *Ghent and Leuven, Belgium, Stockholm, Sweden, Berlin, Germany, Lodz, Poland, Beijing, China, Amsterdam, The Netherlands, Barcelona, Spain, Philadelphia, Pa, and London, United Kingdom*

# From Pheno…….. to Endotypes

BULGARIAN NATIONAL SOCIETY OF OTORHINOLARYNGOLOGY, HEAD AND NECK SURGERY

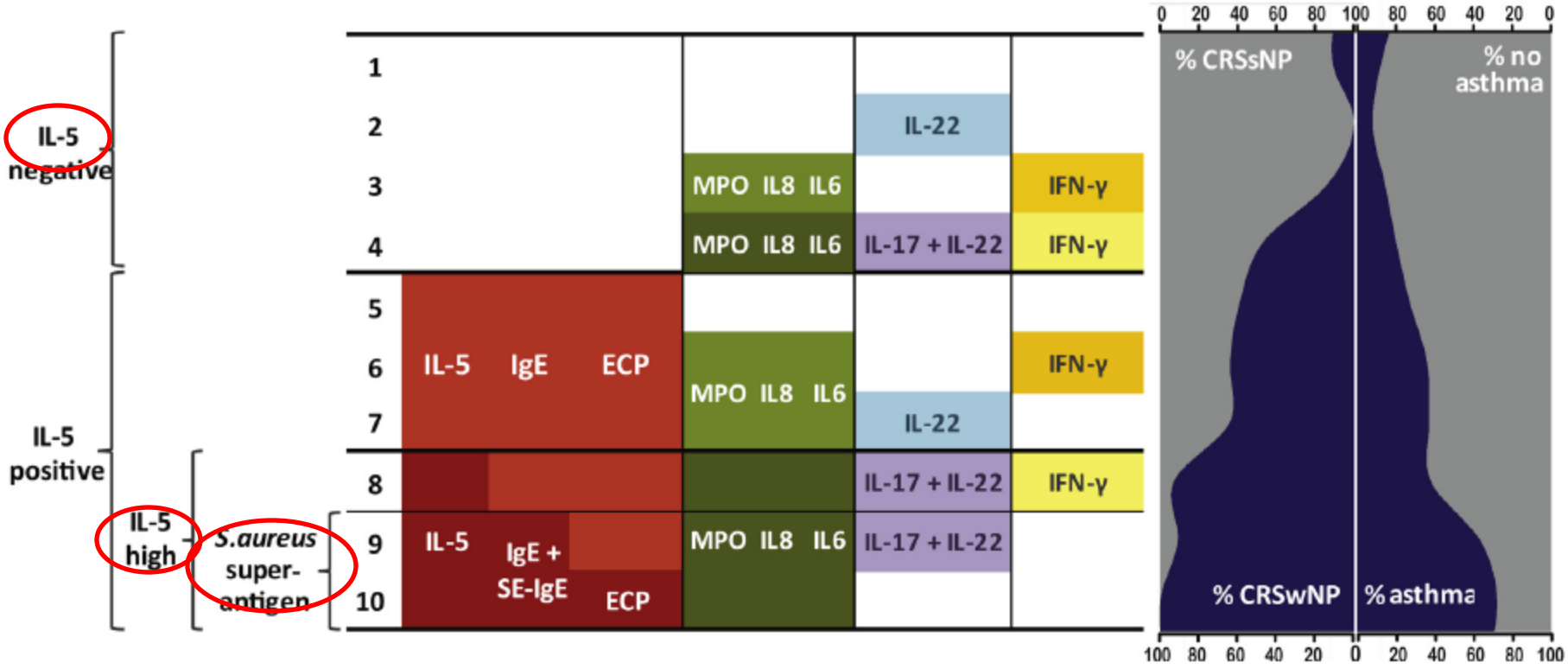



**FIG 4.** Summary graph. Simplified graphic depiction of the clusters and their characteristic cytokines, as well as the distribution of CRSsNP versus CRSwNP and asthma. For cytokines, white indicates no increased concentration, light colors indicate moderately increased concentrations, and dark colors indicate strongly increased concentrations. *Horizontal lines* indicate groups of clusters, as determined by IL-5, SE-IgE, and CRSwNP and asthma characteristics.

# Treatment options for chronic rhinosinusitis with nasal polyps.

Published in: Bauke Pauwels; Karin Jonstam; Claus Bachert; *Expert Review of Clinical Immunology* **2015,** 11, 349-361.

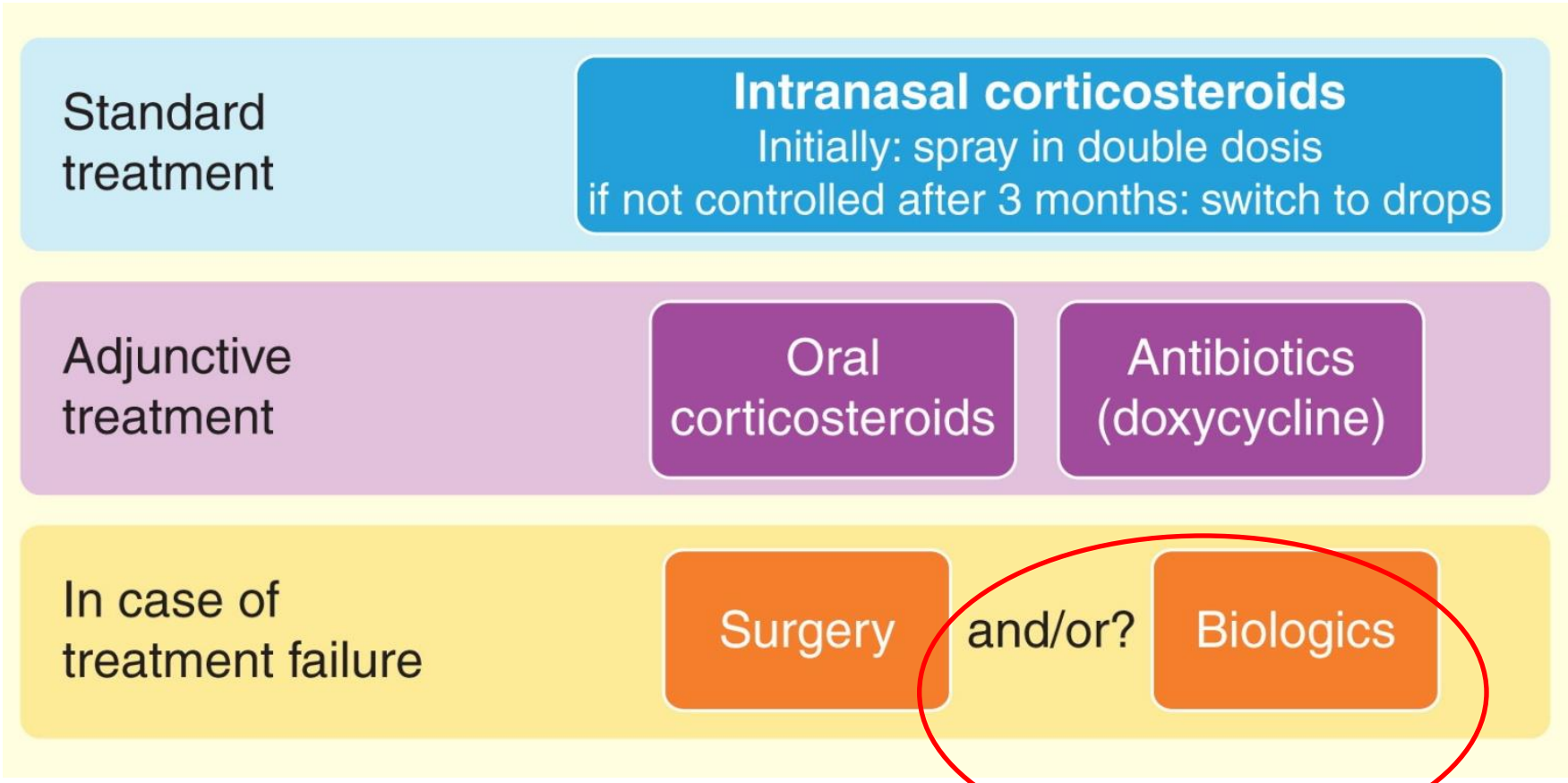



**TABLE I.** Reported studies with hmAbs in nasal polyposis

| Antagonist | Target | Year | Therapeutic effects | Limitations | Status of development |
|---|---|---|---|---|---|
| Omalizumab[39] | IgE | 2013 | Significant reduction of polyp and CT scores, improvement of symptoms of upper and lower airways and quality of life | No reduction of serum or nasal secretion mediators, frequent rhinopharyngitis | PoC |
| Mepolizumab[40] | IL-5 | 2011 | Significant reduction of polyp score, reduction of blood eosinophil count, as well as ECP and IL-5Rα levels, in serum | No significant improvement of symptoms, frequent rhinopharyngitis | Clinical trial, phase 3 |
| Reslizumab[41] | IL-5 | 2006 | Significant reduction of polyp score, reduction of blood eosinophil counts, as well as ECP levels, in serum | No significant improvement of symptoms | PoC |
| Dupilumab[42] | IL-4Rα | 2015 | Significant reduction of polyp and CT scores, improvement of smelling, symptoms, and quality of life (SNOT-22); improvement of pulmonary function ($FEV_1$) and asthma control test score (ACQ5) | Side effects include headache, rhinopharyngitis, and reaction at injection site | PoC |

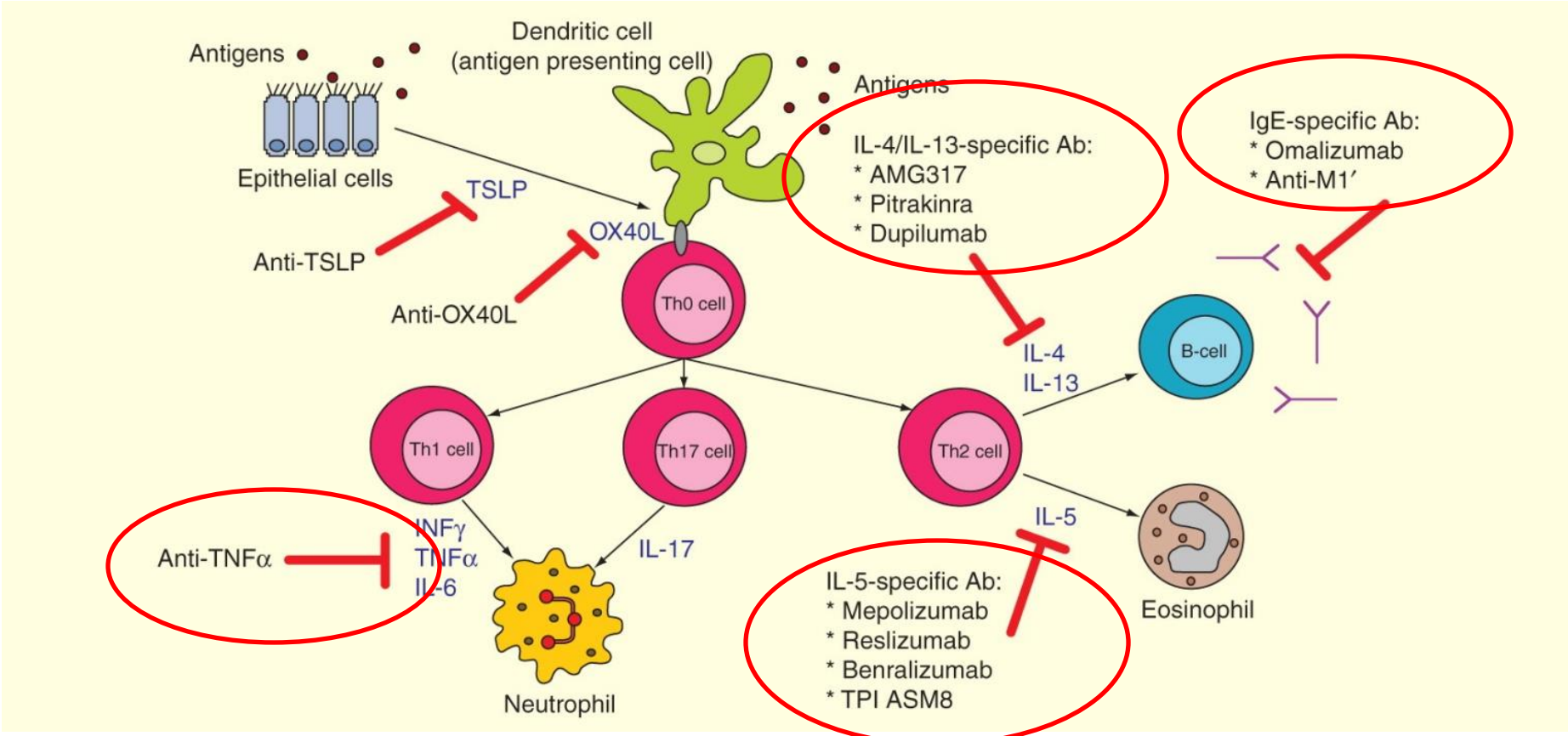
*ACQ5*, Five-item Asthma Control Questionnaire; *ECP*, eosinophil cationic protein; *IL4Rα*, IL-4 receptor α; *IL-5Rα*, IL-5 receptor α; *PoC*, proof of concept; *SNOT-22*, Sino-Nasal Outcome Test.

Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

## Current and future treatment options for adult chronic rhinosinusitis: Focus on nasal polyposis

Claus Bachert, MD, PhD,[a,b] Luo Zhang, MD,[c,d] and Phillippe Gevaert, MD[a] *Ghent, Belgium, Stockholm, Sweden, and Beijing, China*

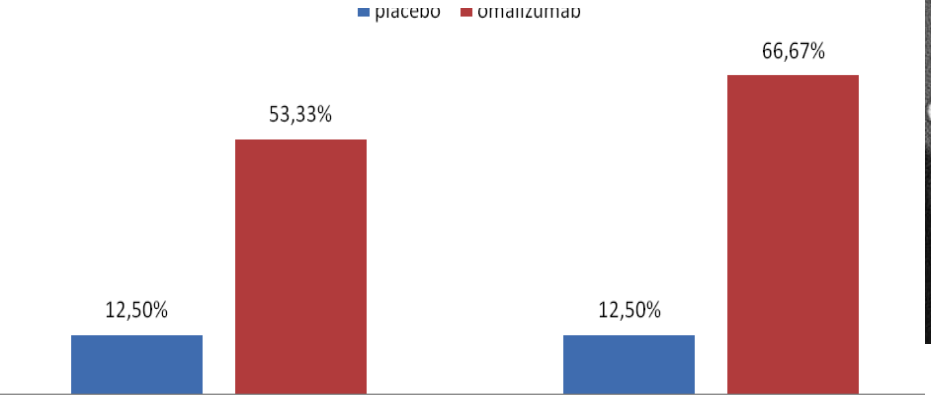


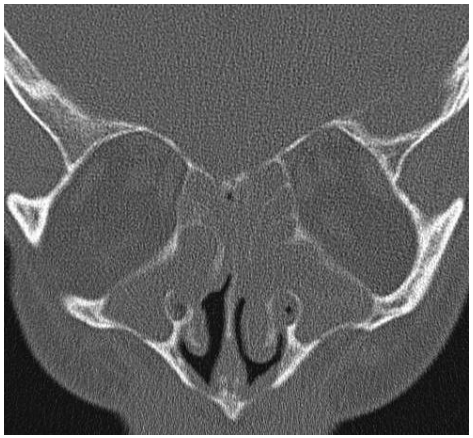

**Targets for monoclonal antibodies in chronic rhinosinusitis with nasal polyps.**

Published in: Bauke Pauwels; Karin Jonstam; Claus Bachert; *Expert Review of Clinical Immunology* **2015,** 11, 349-361.

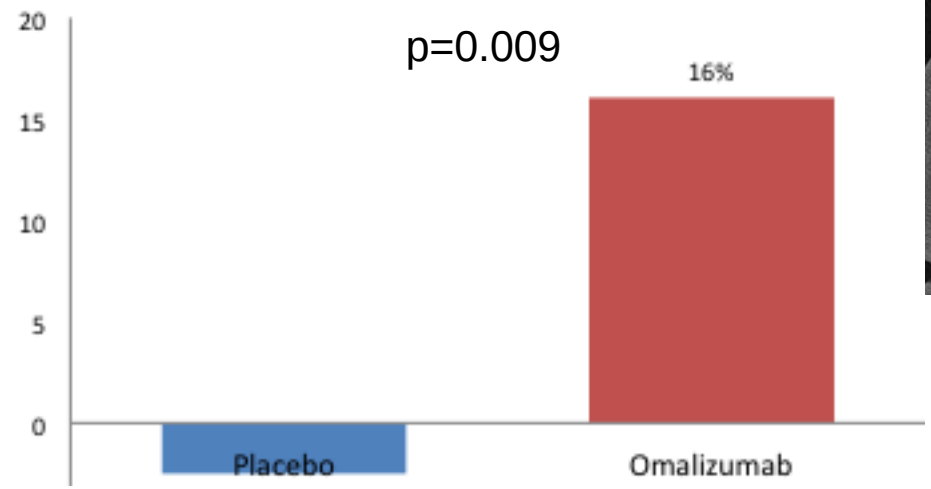
# Blinded CT-scan evaluation: baseline vs. 16 weeks

**Percentage patients with better CT-scan score by two independent observers**



**Mean Percentage improvement CT-scan**




Before treatment

After treatment (16w)

***Gevaert P et al. (JACI 2012)***

Clinical reviews in allergy and immunology

# Endotype-driven care pathways in patients with chronic rhinosinusitis

Claus Bachert, MD, PhD,[a,b] Nan Zhang, MD, PhD,[a] Peter W. Hellings, MD,[c] and Jean Bousquet, MD, PhD[d] *Ghent and Leuven, Belgium, Stockholm, Sweden, and Montpellier, France*

**TABLE I.** What to expect from biologics in the treatment of CRSwNP?

| | |
|---|---|
| Clinically | |
| Reduction of endoscopic nasal polyp score | D, M, O |
| Lund-Mackay CT scan score | D, O |
| Reduction of relevant nasal symptoms | D, M, O |
| Increase in smell (UPSIT and VAS) | D, M, O |
| Increase in quality of life (SNOT-22 and RSOM-31) | D, M, O |
| In asthmatic patients | |
| Increase in lung function ($FEV_1$ percent predicted) | D, O |
| Asthma control (ACQ and AQLQ) | D, O |
| Biomarker | |
| Reduction in blood eosinophil numbers | M |
| Reduction in serum IgE levels | D, O |
| Reduction in tissue eosinophil numbers | D, M |

*ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *D*, dupilumab; *M*, mepolizumab; *O*, omalizumab; *RSOM-31*, Rhinosinusitis Outcome Measure; *UPSIT*, University of Pennsylvania Smell Identification Test; *VAS*, visual analog scale.

**TABLE II.** Patient stratification for type 2 immune response

Biomarkers (larger clinical studies can modify the proposal)
- Blood eosinophil count >300/μL
- Total serum IgE level >150 kU/L
- Presence of serum SE-IgE
- Increased serum periostin level
- Lower airway biomarkers

Clinical
- Presence of comorbid late-onset asthma
- Recurrence after adequate sinus surgery


# ΣΑΣ ΕΥΧΑΡΙΣΤΩ


# ERS 2020

## June 21-25, 2020
## Thessaloniki, Greece

21st Congress of the International
Rhinologic Society
in addition to
28th Congress of European
Rhinologic Society &
37th International Symposiumof Infection
and Allergy of the Nose (ERS-ISIAN)